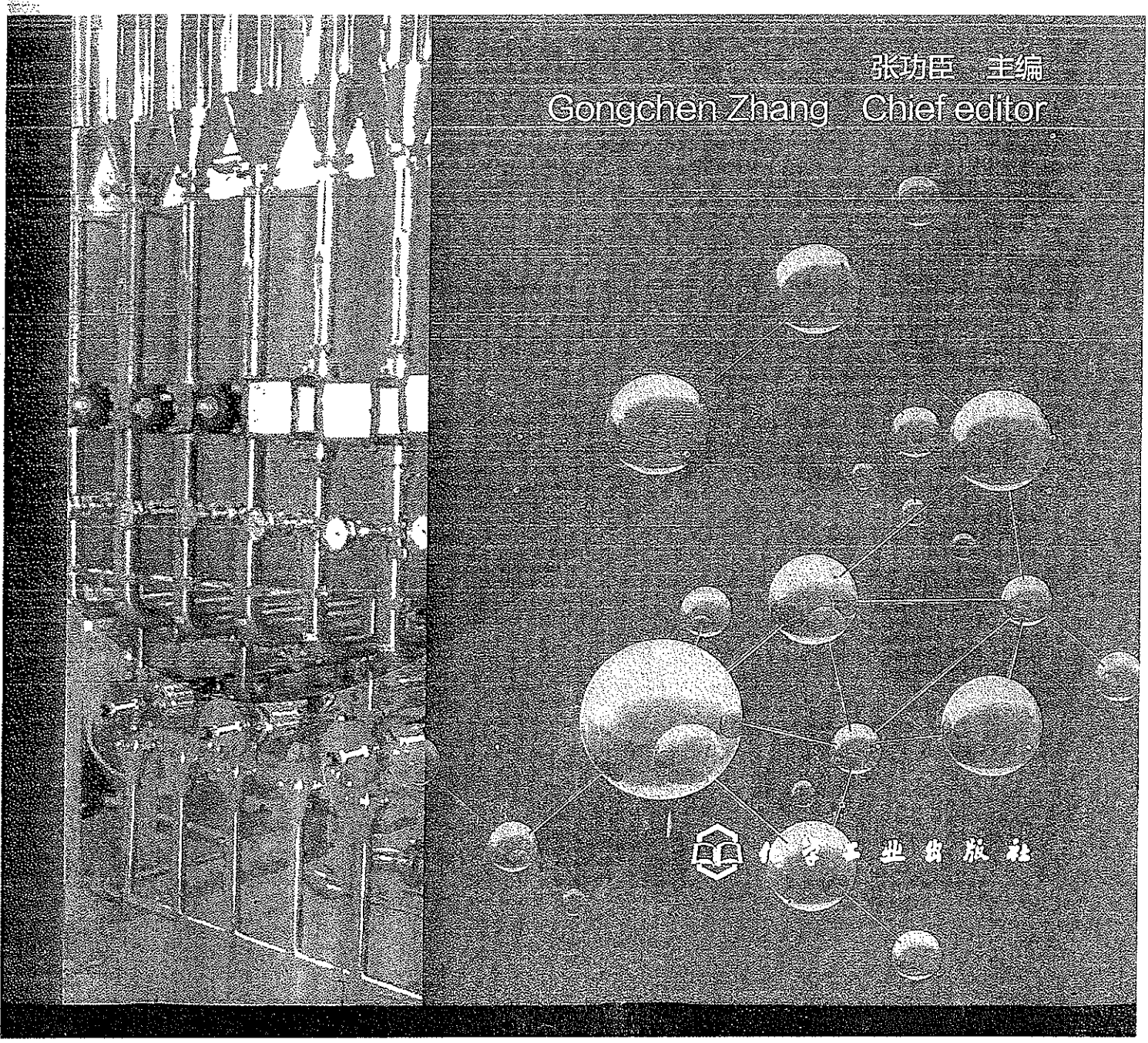
Pharmaceutical Water Systems

制药用水系统 英文版



张功臣 主编
Gongchen Zhang Chief editor

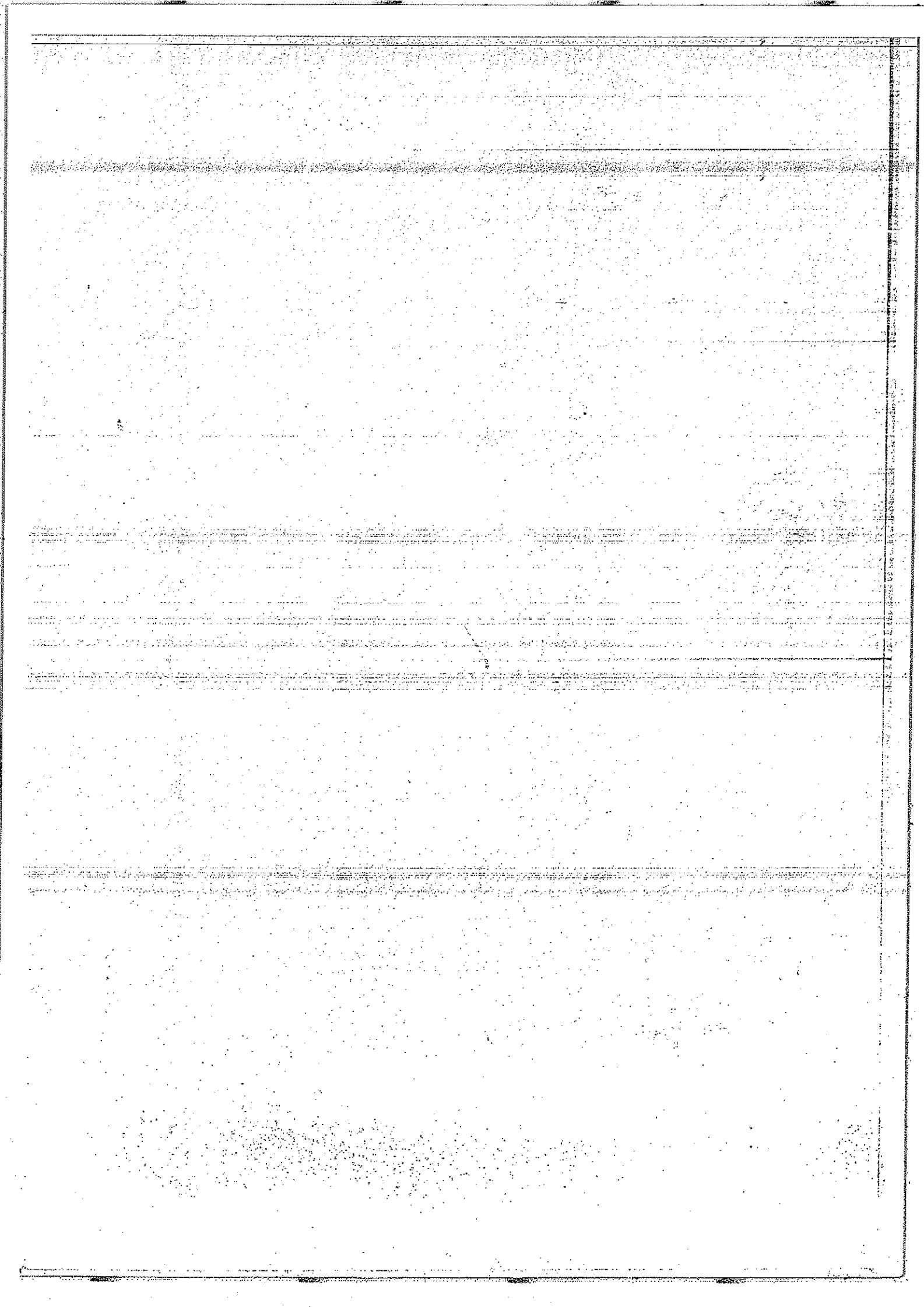
化学工业出版社

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北京



本书为英文版，结合多年工程实践实验，对制药用水系统进行了深入的总结和归纳。

本书大量采用实际工程案例和图片，结合ISPE及ASME BPE的理论经验，力求真实、形象、准确地介绍制药用水系统的基本概念和设计思路。本书基于“质量源于设计、预防微生物污染与预防颗粒物污染”的理念，重点介绍了制药用水系统的设计、安装、调试以及验证的基本原理与具体实践。本书还提供了制药用水系统组成材料的质量控制标准，以保证制药用水系统能稳定地为制药生产提供所需的制药用水和纯蒸汽。

本书适用于制药行业从事研究、设计、生产制药用水系统的技术人员，也可供制药工程相关专业高校师生阅读参考。

This book uses a large number of actual engineering cases and photos, and combines that with the theoretical experience of the International Society for Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers Bioprocessing Equipment (ASME BPE) to introduce the basic concepts and design approaches of pharmaceutical water systems in a vivid and accurate manner. This book is based on the concepts of the "quality by design, prevention of microbial contamination and particles contamination" to introduce the rationale of design, installation, commissioning and validation of pharmaceutical water systems. It also provides the readers with the quality control specifications for materials used in a Pharmaceutical Water Systems to ensure it can provide the pharmaceutical water and pure steam required for pharmaceutical production stably.

This book is of particular relevance to technicians who are engaged in researching, designing and manufacturing clean stainless steel fluid process systems. At the same time, it can be used as reference material for majors related to pharmaceutical engineering etc.

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Preface

Pharmaceutical water systems are an important subject in the *Good Manufacturing Practice*. Compared with developed countries. With gradual development of design, installation and validation activities, the pharmaceutical water systems are becoming the leading element in new or renovated projects of the modern pharmaceutical industry. All pharmaceutical enterprises will make the design, installation and validation activities the key of drug quality assurance, and realize that pharmaceutical water systems with reliable quality can provide competitive advantages of consistent quality assurance and cost savings for the enterprises.

For the pharmaceutical industry, pharmaceutical water systems is very important not only due to compliance requirements of regulations and product quality in the pharmaceutical industry, but also for the development of science and technology, and the benefits of cutting edge knowhow on drug quality improvement and risk control. With the continuous technological development of environmental protection, energy conservation and process safety in world, the design concepts and quality standards of pharmaceutical water systems have changed accordingly; this requires the pharmaceutical enterprises to adapt to the new requirements of the water generation equipment and storage and distribution systems. The original purpose for writing this book was to promote the understanding of the continuously improved quality requirements of pharmaceutical water systems, and the challenges faced by product manufacturing companies in pharmaceutical industry at present.

As a direct practitioner of design, installation and validation of pharmaceutical fluid process systems in the pharmaceutical industry, the author of this book has a rich technical expertise and practical experience with respect to pharmaceutical water systems, with 1000^{+} success project cases. The book provides an overview of the practical methods used in the day to day purified water systems, water for injection systems and pharmaceutical steam systems operations. These methods comply with advanced international advanced GMP regulations and guidelines and standardized applications of relevant content, including current innovative methods such as risk assessment concepts and GEP management. The book is an excellent reference text for pharmaceutical water systems, and a must read for those seeking to improve the level of design and validation activities in the pharmaceutical industry.

The author

January, 2017 in Shanghai, China

Foreword

Pharmaceutical Water Systems is a practical reference text that will facilitate a comprehensive understanding of pharmaceutical water systems; it provides clear explanations of pharmaceutical technologies, chemical principles, physical chemistry, pharmacopoeia, the Good Manufacturing Practice and relevant scientific theory and engineering technology. This book uses practical examples of unit operation, cleaning technology and microbiology to demonstrate the basic characteristics of pharmaceutical water systems in a comprehensive and vivid manner.

The Good Manufacturing Practice (2010 *Revision*) was formally issued and implemented in the Chinese mainland on March 1st, 2011. Many advanced design concepts and process analytical technologies are promoted in the pharmaceutical industry. The author published *Pharmaceutical Water Systems* (*First Edition in Chinese*) in 2012; it was widely accepted by the industry, and provided a comprehensive theory summary and practical experience insights for pharmaceutical enterprises and institutions of higher education.

After five years, the author edited and compiled *Pharmaceutical Water Systems* (*First Edition in English*) using a more comprehensive and in depth approach with successful system operation examples chosen from thousands of actual pharmaceutical water systems. This book introduces new and innovative technological concepts, including WFI generation with the purification method, online microorganism detecting technology, design and practice of WFI systems at normal temperature, residual chlorine removal technology with UV radiation, rouge remediation and prevention, etc. It is expected that this book will help practitioners in the pharmaceutical industry acquire a deeper and more visual understanding of pharmaceutical water systems, and promote the popularization of design, manufacturing and validation ability of pharmaceutical water systems in the industry.

The *Pharmaceutical Water Systems* has 13 chapters; Chapter 1 to Chapter 3 are mainly covering laws and regulations, design concepts and unit operation; Chapter 4 to Chapter 7 introduce the concept of quality by design as the starting point for a pharmaceutical water systems of high quality, including purified water generation systems, WFI generation systems, storage and distribution systems and pure steam systems; Chapter 8 takes the prevention of microbial contamination as starting port to systematically describe sanitation and sterilization technologies, and make detailed analyses and summaries of various sanitation/sterilization measures; Chapter 9 and Chapter 10 take the prevention of particles contamination as the starting point of a description of the hazards of rouge formation and derouging measures, and propose reasonable suggestions for maintenance of pharmaceutical water systems; Chapter 11 covers the principle of quality control with emphasis on the importance of welding, pickling and passivation; Chapter 12 and Chapter 13 are describing the process an-

alytical technology, commissioning and qualification methods of pharmaceutical water systems from the perspective of automatic control technology and validation.

This book uses a large number of actual engineering cases and photos, and combines that with the theoretical experience of the International Society for Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers Bioprocessing Equipment (ASME BPE) to introduce the basic concepts and design approaches of pharmaceutical water systems in a vivid and accurate manner. This book is based on the concepts of the "quality by design, prevention of microbial contamination and particles contamination" to introduce the rationale of design, installation, commissioning and validation of pharmaceutical water systems. It also provides the readers with the quality control specifications for materials used in a pharmaceutical water systems to ensure it can provide the pharmaceutical water and pure steam required for pharmaceutical production stably.

The author thanks Gordon Farquharson, ISPE senior lecturer, for his support and encouragement. Mr Gordon Farquharson devotes his enthusiasm to the transfer of scientific knowledge of water and steam systems promoting the development of the pharmaceutical industry. At the same time, the compilation of this book has been assisted by Dr Anthony Bevilacqua, head of R&D at Mettler Toledo, he is serving on USP Chemical Analysis Expert Committee and the ISPE Critical Utilities COP Steering Committee, and has made great contributions to the development of pharmacopoeia water. It is expected that this book will not only help the operators involved in the use and maintenance of pharmaceutical water, but also meet the requirements of in-depth understanding of pharmaceutical water systems by technicians who work on the design, installation, commissioning, validation and management of pharmaceutical water systems.

This book is authored by Gongchen Zhang. Relevant regulatory authorities, biopharmaceutical enterprises, institutes of higher education, engineering consulting companies and brand suppliers participated in the writing and proofreading of this book. All participant units and authors have exerted great efforts to the compilation of *Pharmaceutical Water Systems*. The author thanks the following writers and entities who have participated in the compilation of this book.

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This book is translated by professional translation team. All participant translators have exerted great efforts to the compilation of *Pharmaceutical Water Systems*. The author thanks the following translators who have participated in the compilation of this book.

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This book is of particular relevance to technicians who are engaged in researching, designing and manufacturing clean stainless steel fluid process systems, as well as the technical, production and engineering maintenance personnel from the pharmaceutical, chemical, daily chemicals manufacturing and semiconductor industry. At the same time, it can be used as reference material for majors related to materials chemistry, metal anticorrosion, pharmaceutical engineering, pharmaceutical preparation, bioengineering, etc. in institutes of higher education. Due to the limitation of knowledge level of the author and urgent time, the inappropriateness and error may exist in the book. The author will appreciate comments and suggestions from the readers regarding this book.

Gong Chen Zhang

Biography

Gongchen Zhang, Chinese senior GMP compliance and engineering design consultant expert, has over 19 years of practical experience and many patents in the pharmaceutical industry. He graduated in pharmaceutical engineering and chemical & biological engineering from Wuhan Engineering University and Huazhong University of Science and Technology of China. He is the training lecturer for the course "Water and Steam Systems" offered by the International Society for Pharmaceutical Engineering (ISPE), and the writer of GB 50913—2013 *Design Specification of Pharmaceutical Process Water Systems*. He mainly works on the design and R&D of pharmaceutical clean liquid process systems (pharmaceutical water systems, pharmaceutical process liquid preparation systems, CIP/SIP systems). He strongly supported the concept of Water Loop SKID and the pharmaceutical water systems Turn-key project in pharmaceutical industry (the typical cases such as Sinopharm Group, Boehringer Ingelheim, ReckittBenckiser, P&G, Novozymes, Apptec, Innovent, Tasly, Hualan, Kanghong etc.), and was involved in the research and implementation of many innovative design concepts such as Biopharmaceutical USP/DSP/Preparation processes with batch control systems (including antibody, insulin, vaccine and blood products), intelligent LVP preparation systems (the biggest 316L preparation tank volume is 35000L), intelligent fat emulsion injection (LVP/SVP) process preparation systems (the typical cases such as Kanglaite fat emulsion injection), and intelligent suppository and ointment process preparation systems (the typical cases such as Mayinglong suppository and ointment). He also had important contributions to the development of many innovative design concepts such as WFI systems with superheated water sterilization, heat storage/bypass circulation at normal temperature (the typical cases such as Innovent antibody and Protgen insulin), WFI storage and circulation at 4 degree temperature (the typical cases such as Blood Products), scientific derouging and passivation (the typical cases such as P&G and Lily), generation of high purity water or WFI with the purification method, applications of water electrolysis ozone sanitation, subloop cold point of use cooling modularization, etc. The author participated in the editing of the *Chemical Engineering Cartography* which is a teaching material for major of pharmaceutical engineering in national institutes of higher education involved in the 12th Five-Year Plan of the Ministry of Health, and the national standard GB 50913—2013 *Design Specification of Pharmaceutical Process Water Systems*; he supervised the editing and publishing of books such as *Pharmaceutical Water System*, *Pharmaceutical Fluid Process Manual*, and *Pharmaceutical Derouging Process Manual*, and participated in the editing of books such as *Pharmaceutical Engineering Process Design*, *Pharmaceutical Preparation Process Equipment* and *Engineering Design*, *Microbial Control in Pharmaceutical Cleanrooms*, *Pharmaceutical Process Validation Manual*, and *Compilation of EU GMP/GDP Regulations*.

Abbreviations

Abbreviations	English
AHU	Air Handing Unit
AOAC	Association of Official Analytical Chemists
AMV	Analytical Method Validation
API	Active Pharmaceutical Ingredient
ASME	American Society of Mechanical Engineers
ASME BPE	American Society of Mechanical Engineers Bioprocessing Equipment
ASTM	American Society for Testing and Materials
BD	Bowie-Dick
BI	Biological Indicator
BMS	Building Management System
CAPA	Corrective and Preventative Action
CCA	Component Criticality Assessment
CCP	Critical Control Point
CD	Cycle Development
CEHT	Clean Equipment Hold Time
CFR	Code for Federal Regulations
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CHO	Chinese Hamster Ovary
CIP	Clean in Place
ChP	Chinese Pharmacopeia
C_p/C_{pk}	Process Capability Index
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSV	Computer System Validation
CVP	Cleaning Validation Plan

cont

Abbreviations	English
DCS	Distributed Control System
DDS	Detailed Design Specification
DEHT	Dirty Equipment Hold Time
DNA	Deoxyribonucleic Acid
DoE	Design of Experiment
DOP	Dioctyl Phthalate(or Equivalent,Dispersed Oil Particulate)
DQ	Design Qualification
DS	Design Specification
ED_{50}	50% Effective Dose
EDI	Electrodeionization Deionization (US Filter)
EHS	Environment Health Safety
ELISA	Enzyme-linked Immuno Sorbent Assay
EMA	European Medicines Agency
EMS	Environmental Monitoring System
EP	European Pharmacopoeia
EPA	Environmental Protection Agency
ERP	Enterprise Resource Planning
ETOP	Engineering Turnover Packages
EU	European Union
FAT	Factory Acceptance Testing
FDA	Food and Drug Administration
FDS	Functional Design Specification
FMEA	Failure Modes and Effects Analysis
FS	Function Specification
FTA	Fault Tree Analysis
FQCP	Field Quality Control Plan
GAMP	Good Automated Manufacturing Practice
GDP	Good Document Practice
GEP	Good Engineering Practice

cont

Abbreviations	English
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GxP	Good x Practice
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard and Operability Analysis
HDS	Hardware Design Specification
HEPA	High Efficiency Particulate Air
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HMI	Human Machine Interface
HPLC	High Performance Liquid Chromatography
HVAC	Heating, Ventilation, and Air Conditioning
I/O	Input and Output
IC_{50}	The Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Electro technical Commission
IQ	Installation Qualification
ISO	International Standards Organization
ISPE	International Society for Pharmaceutical Engineering
IUPAC	International Union of Pure and Applied Chemistry
LIMS	Laboratory Information Management System
LOD	Limit of Detection
LOQ	Limit of Quantizatity
MB/L	Methylene Blue
MCB	Master Cell Bank
MES	Manufacturing Execution System
MTDD	Minimum Treatment Daily Dosage
OOS	Out of Specification

cont

Abbreviations	English
OQ	Operational Qualification
OSD	Oral Solid Dosage
P&ID	Piping and Instrumentation Diagrams
PAO	Poly-alpha-olefin
PAT	Process Analytical Technology
PBS	Phosphate Buffer Saline
PCB	Primary Cell Bank
PCR	Polymerase Chain Reaction
PDA	Parenteral Drug Association
PDI	Pre-delivery Inspection
PEP	Project Execution Plan
PFD	Process Flow Diagram
PHA	Preliminary Hazard Analysis
PIC/S	Pharmaceutical Inspiration Convention and Pharmaceutical Inspection Co-operation Scheme
PLC	Programmable Logic Controller
PM	Project Managemnet
PP	Polypropylene
PPE	Personal Protective Equipment
PPQ	Process Performance Qualification
PQ	Performance Qualification
PS	Pure Steam
PTFE	Polytetrafluoroethylene
PV	Process Validation
PVC	Polyvinyl Chloride
PVP	Process Validation Plan
PW	Purified Water
QA	Quality Assurance
QbD	Quality by Design

cont

Abbreviations	English
QC	Quality Control
QMS	Quality Management System
QPP	Quality and Project Plan
QRM	Quality Risk Management
RA	Risk Assessment
RABS	Restricted Access Barrier System
RH	Relative Humidity
RNA	Ribonucleic Acid
RO	Reverse Osmosis
RPN	Risk Priority Number
RSD	Relative Standard Deviation
RTM	Requirements Traceability Matrix
RTP	Rapid Transfer Port
SAL	Sterility Assurance Level
SAT	Site Acceptance Testing
SCADA	Supervisory Control and Data Acquisition
SCR	Source Code Review
SDA-PAGE	Sodium Dodecyl Sulfate-polyacrylamide gel
SDI	Silt Density Index
SDS	Software Design Specification
SFDA	State Food and Drug Administration
SIA	System Impact Assessment
SIP	Sterilize In Place
SME	Subject Matter Expert
SMS	Software Module Specifications
SMT	Software Module Test
SOP	Standard Operating Procedure
SV	Sindbis Virus
TM	Traceability Matrix

cont

Abbreviations	English
TOC	Total Organic Carbon
TR	Technical Report
UAF	Unidirectional Airflow
UCL	Upper Confidence Limit
UPS	Uninterruptable Power Supply
URB	User Requirements Brief
URS	User Requirements Specification
USP	United States Pharmacopoeia
UV	Ultraviolet Light
VHP	Vaporized Hydrogen Peroxide
VMP	Validation Master Plan
VP	Validation Plan
VSR	Validation Summary Report
VSV	Vesicular Stomatitis Virus
WCB	Working Cell Bank
WFI	Water for Injection
WHO	World Health Organization
WIP	Wetting in Place

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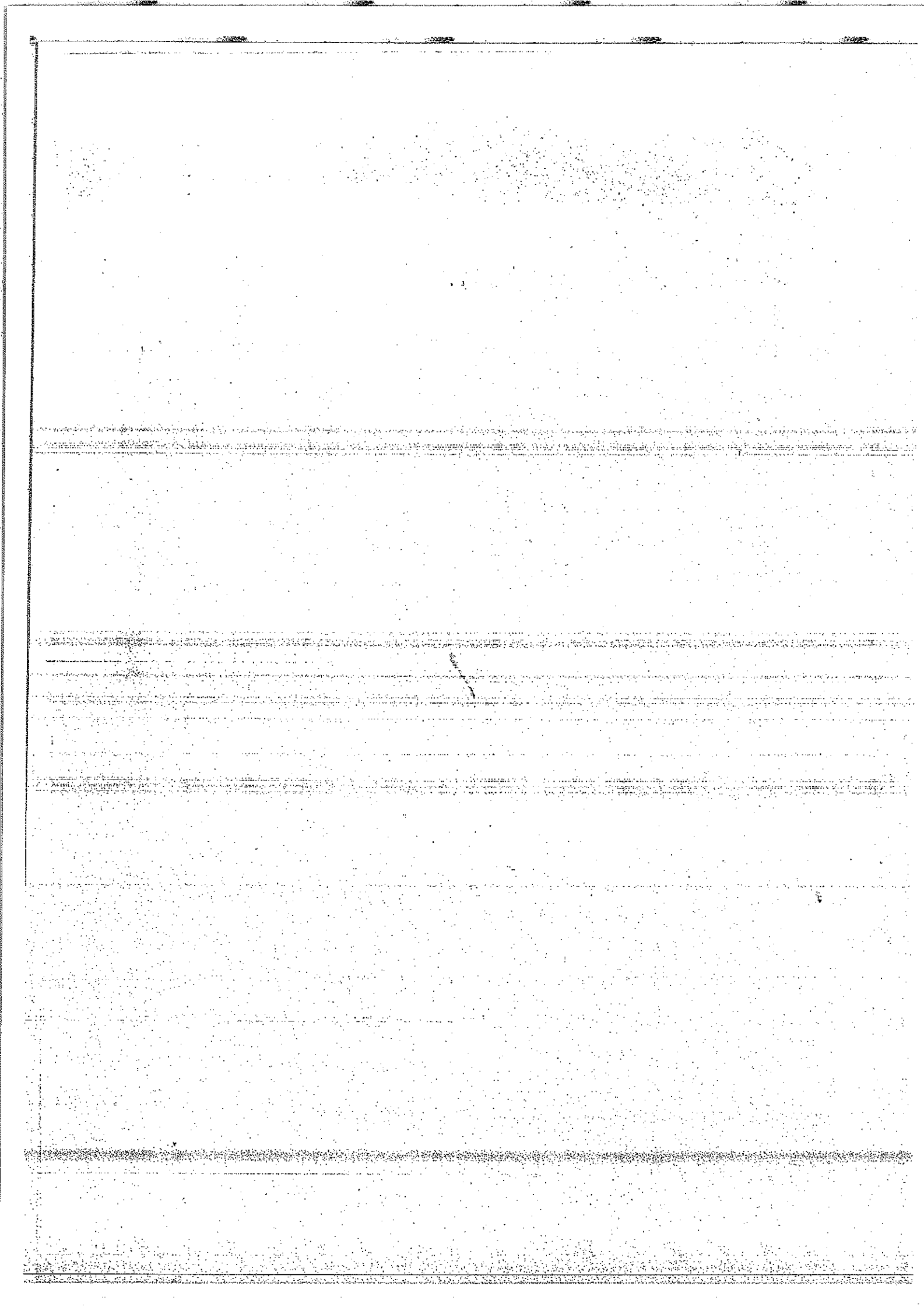
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Chapter 1

Pharmacopeia and Regulations

Pharmaceutical water generally refers to water of various quality specifications used during the pharmaceutical production process. Pharmaceutical water is an important raw material for pharmaceutical production. It is involved in the whole production process, including APIs preparation, separation and purification, preparation of finished drugs, washing process, cleaning process, and disinfection process. Therefore, the pharmaceutical water systems are of utmost importance to the pharmaceutical production process.

Pharmaceutical steam is a type of media for moist heat sterilization, mainly used for the sterilization of important equipment and systems, such as the WFI systems, moisture heat sterilizers, bioreactors, solution preparation tanks, pipeline systems, and filters. A common pharmaceutical steam system mainly refers to a pure steam system. The condensate of pure steam can be in direct contact with the surfaces of the equipment or articles or with the materials used for analyzing the properties of the articles. The quality of the condensate of pure steam should satisfy the quality standards for WFI. Therefore, the pharmaceutical steam systems are also very important component of sterile the production process in the pharmaceutical industry.

The quality of pharmaceutical water and steam is very important from the view point of the GMP and pharmacopeia as well as from the view point of the GEP and economy. Pharmaceutical enterprises must prove the used pharmaceutical water and steam systems can always produce pharmaceutical water and steam meeting quality standards.

Usually, a pharmaceutical water system and a pharmaceutical steam system are collectively called a pharmaceutical water system (or water system for short) in the pharmaceutical industry. The essence of producing pharmaceutical water is to reduce or eliminate the potential contaminants. EU and WHO have taken the foreign matter in pharmaceutical water as one of the potential sources of foreign matter. Due to this consideration, this book has put forward how to design the preparation, storage, and distribution systems of pharmaceutical water and ensure the control of contamination risks.

1.1 Classification of Pharmaceutical Water

The definition of pharmaceutical water and its usage are usually subject to the pharmacopeia. Each country's pharmacopeia usually has a different definition and stipulations in reference to the pharmaceutical water and its usage.

From the standpoint of water usage, pharmaceutical water can be mainly classified into bulk water and packaged water. Bulk water is also called raw water, particularly referring to the water used during the pharmaceutical production process; for example, bulk water accepted by the *Chinese Pharmacopeia* (ChP) includes purified water and WFI. Bulk water accepted by the *European Pharmacopeia* (EP) includes purified water, high purity water, and WFI; and that accepted by the *US Pharmacopeia* (USP) includes purified water, hemodialysis water, and WFI. Packaged water is also called product water, particularly referring to the packaged product water produced according to pharmaceutical process; for example, the ChP has incorporated sterile WFI; the EP has incorporated packaged purified water and sterile WFI; and the USP has incorporated bacteriostatic WFI, sterile water for inhalation, sterile WFI, sterile water for irrigation, and sterile purified water (see Table 1.1).

Table 1.1 Classification of pharmaceutical water

Pharmacopeia	Raw water	Product water
ChP	Purified water and Water for Injection(WFI)	Sterile water for injection
EP	Purified water in bulk, high-purity water, WFI	Purified water in container, sterile WFI
USP	Purified water, hemodialysis water, WFI	Bacteriostatic WFI, sterile water for inhalation, sterile WFI, sterile water for irrigation, and sterile purified water

Sterile WFI is produced from WFI according to the injections production process and mainly used as solvent for sterilized powder injections, diluent for injections, and testing solvent; for example, the water used for bacterial endotoxin testing should be sterile WFI with the endotoxin content of less than 0.015 EU/ml (for sol-gel process) or 0.005 EU/ml (for photometric method) and without interference to the endotoxin testing.

Actually, the water of various quality specifications used for pharmaceutical process is not only limited to complying with pharmacopeia standards; pharmaceutical water can also be classified into pharmacopeia water and non-pharmacopeia water.

Pharmacopoeia water particularly refers to pharmaceutical water incorporated in a country or organization's pharmacopoeia; for example, the *Chinese Pharmacopeia* has incorporated purified water, WFI, and sterile WFI; the *European Pharmacopeia* (EP) has incorporated bulk purified water, packaged purified water, high purity water, WFI, and sterile WFI; and the *US Pharmacopeia* (USP) has incorporated purified water, hemodialysis water, WFI, pure steam, bacteriostatic WFI, sterile water for inhalation, sterile WFI, sterile water for irrigation, and sterile purified water.

Non-pharmacopeia water particularly refers to pharmaceutical water that is not incorporated in the pharmacopeia but can be used for pharmaceutical production, e.g. drinking water, softened water, distilled water, and RO water. Non-pharmacopeia water should at least comply with the requirement for drinking water; it usually requires other processing to comply with process requirements; non-pharmacopeia water may contain some additives for controlling microorganisms, so it is not necessary to comply with all pharmacopeia requirements. Sometimes, non-pharmacopeia water will be named by the final operation unit or key purification process adopted, e.g. RO water; in other cases, non-pharmacopeia water can be named according to particular quality attributes of the water, e.g. water with low endotoxin content. It should be noted that the quality of non-pharmacopeia water is not necessarily worse than that of pharmacopeia water. In fact, if required in the application, the quality of non-pharmacopeia water may be superior to that of pharmacopeia water. Common non-pharmacopeia water includes:

• Drinking water. It refers to the purified natural water and its quality must comply with official standards. It is one type of non-pharmacopeia water of the lowest grade that can be used for pharmaceutical production. For example, according to the *Standards for Drinking Water Quality of the PRC* (GB 5749—2006), microbial indexes of drinking water must comply with the following standards: total coliforms (MPN/100 ml or CFU/100 ml) must not be detected; thermotolerant coliforms (MPN/100 ml or CFU/100 ml) must not be detected; *E. coli* (MPN/100 ml or CFU/100 ml) must not be detected; and total number of bacterial colonies (CFU/ml) should be no more than 100. Drinking water can also be used as rinse water for the purifying process of traditional Chinese medicine (TCM) and primary washing of pharmaceutical tools; unless otherwise specified, drinking water can also be used as the extraction solvent for TCM.

• Softened water. It refers to the product water of drinking water after hardness treatment. The softening treatment is taken as the final operation unit or the most important operation unit to reduce water hardness usually arising from magnesium and calcium ionic contaminants.

• RO water. It refers to the water produced by the RO unit, which is taken as the final operation unit or the most important operation unit.

• Ultrafiltration water. It refers to the water produced by ultrafiltration process, which is taken as the final operation unit or the most important operation unit.

• De-ionized water. It refers to the water produced by deionization or ion exchange process, which is taken as the final operation unit or the most important operation unit. When a specific electrodeionization (EDI) process is used, it is called EDI water.

• Distilled water. It refers to the water produced by a distillation process, which is taken as the final operation unit or the most important operation unit.

• Laboratory water. It refers to a type of water specially produced from drinking water, which complies with the laboratory requirement.

With a reasonable explanation, non-pharmacopeia water can also be used in the whole pharmaceutical operation, including washing of production equipment, laboratory application, and as raw material for APIs production or synthesis. But it should be noted that the pharmacopeia formulations must be prepared with pharmacopeia water. The user should establish appropriate microbial limit either for pharmacopeia water or for non-pharmacopeia water; the importance of microorganisms in non-sterile preparations must be assessed according to the product usage, nature of the product itself, and potential hazards to the user. It is expected that the manufacturer should establish an appropriate alert limit and action limit of microorganism quantity according to the types of pharmaceutical water; the establishment of these limits must be based on the process requirements and historical record of the system concerned.

1.2 Composition of Water System

Pharmaceutical water that the pharmaceutical enterprises are concerned with mainly refers to raw water, i.e. purified water, high-purity water, and WFI. From the viewpoint of functions, a pharmaceutical water systems mainly consist of the generation unit and storage & distribution unit (see Fig1.1); and a pharmaceutical steam systems mainly consist of the generation unit and distribution unit.

The generation unit mainly consists of the softener, purified water machine, high-purity water machine, water distiller, and pure steam generator, which are mainly used for continuously and stably purifying the raw water into pharmaceutical water in compliance with the enterprise internal standards or pharmacopeia requirements. The storage and distribution unit mainly consists of the storage unit, distribution unit, and user point pipework unit; and its main function is to deliver pharmaceutical water to the required workstation with a certain buffer capacity to satisfy corresponding requirements for flow rate, pressure, and temperature; and the quality of pharmaceutical water must be maintained to meet the pharmacopeia requirements at all times.

Microorganisms breed very easily in pharmaceutical water; the microbial index is one of the most important quality indexes. Various measures need to be taken to inhibit the breeding of microorganisms during the design, installation, validation, operation, and maintenance process. Considering that the pharmaceutical water can be used both as raw material and washing media in the pharmaceutical industry and is very easy for microorganisms to breed in it, each country's pharmacopeia has a very specific definition and requirement for the quality standard and usage of pharmaceutical water. Pharmaceutical water has direct contact with the product, so it has direct effect on drug quality; each country or organization's GMP has taken pharmaceutical water generation, storage, and distribution systems as the key factor for pharmaceutical production; specific requirements have been put

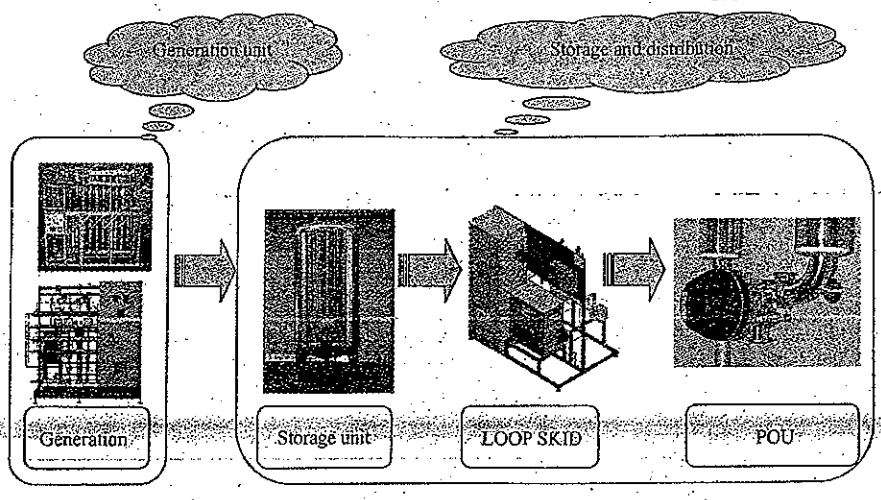


Fig 1.1 Composition of a pharmaceutical water systems

forward with respect to its installation, validation, operation, and maintenance.

1.3 Pharmacopeia Standards

Purified water and WFI are important raw materials for pharmaceutical production; the quality of purified water and WFI will directly influence the quality of the finished drug products. Therefore, each country or organization has specific stipulations about it. Table 1.2 and Table 1.3 give a list of different quality standards of the ChP, EP, and USP for purified water and WFI as raw materials.

Table 1.2 Comparison sheet for the quality of purified water as raw material

Items	*Chinese Pharmacopeia* 2015	*European Pharmacopoeia* 8.0	*US Pharmacopoeia* 38
Generation method	Purified water is a type of pharmaceutical water produced from drinking water① in compliance with official standards by use of distillation method, ion exchange process, RO method, or other appropriate methods	Purified water is a type of pharmaceutical water produced from drinking water in compliance with official standards by use of distillation method, ion exchange process, RO method, or other appropriate methods	The raw water of purified water must be drinking water free from any exogenous additives and must be produced by appropriate process
Description	Colorless and odorless clear liquid	—	—
pH/Acidity	Acidity in compliance with requirement	—	—
Ammonia	≤0.3 μg/ml	—	—
Nonvolatile matters	≤1 mg/100 ml	—	—
Nitrates	≤0.06 μg/ml	≤0.2 μg/ml	—
Nitrites	≤0.02 μg/ml	—	—
Heavy metals	≤0.1 μg/ml	≤0.1 μg/ml	—
Aluminum salt	—	No higher than 10 ppb This item needs to be controlled when dialysate is produced	—
Readily oxidizable substance	In compliance with stipulations②	In compliance with stipulations②	—
Total organic carbon	≤0.5 mg/L②	≤0.5 mg/L②	≤0.5 mg/L
Conductivity	In compliance with stipulations	In compliance with stipulations	In compliance with stipulations (Three-step method determination)
Bacterial endotoxins	—	<0.25 EU/ml This item needs to be controlled when dialysate is produced	—
Microbial limit	Total aerobic germ count ≤100 CFU/ml	Total aerobic germ count ≤100 CFU/ml	Total colony count ≤100 CFU/ml

① Please refer to Appendix Ⅰ *Standards for Drinking Water Quality* (GB 5749—2006) of this chapter.

② Either purified water TOC inspection method or readily oxidizable substance inspection method can be chosen for the testing.

Table 1.3 Comparison sheet for the quality of WFI as raw material

Items	*Chinese Pharmacopeia* 2015	*European Pharmacopoeia* 8.0	*US Pharmacopoeia* 38
Generation method	WFI is generated from purified water by distillation	WFI is generated from drinking water in compliance with official standards or generated from purified water by distillation	The raw water of WFI must be drinking water; there must be no exogenous additives; appropriate process equipment must be adopted (e.g. distillation method or purification method). The generation method must be validated

cont

Items	*Chinese Pharmacopeia* 2015	*European Pharmacopoeia* 8.0	*US Pharmacopoeia* 38
Description	Colorless and odorless clear liquid	Colorless clear liquid	—
pH	5.0～7.0	—	—
Ammonia	≤0.2 μg/ml	—	—
Nonvolatile matters	≤1 mg/100 ml	—	—
Nitrites	≤0.06 μg/ml	≤0.2 μg/ml	—
Nitrites	≤0.02 μg/ml	—	—
Heavy Metals	≤0.1 μg/ml	≤0.1 μg/ml	—
Aluminum salt	—	Maximum10 ppb This item needs to be controlled when dialysate is produced	—
Readily oxidizable substance	—	—	—
Total organic carbon	≤0.5 mg/L	≤0.5 mg/L	≤0.5 mg/L
Conductivity	In compliance with stipulations (Three-step method determination)	In compliance with stipulations (Three-step method determination)	In compliance with stipulations (Three-step method determination)
Bacterial endotoxins	<0.25 EU/ml	<0.25 EU/ml	0.25 EU/ml①
Microbial limit	Total aerobic germ count≤10 CFU/100 ml	Total aerobic germ count≤10 CFU/100 ml	Total colony count≤10 CFU/100 ml

① WFI as raw material for commercial purpose.

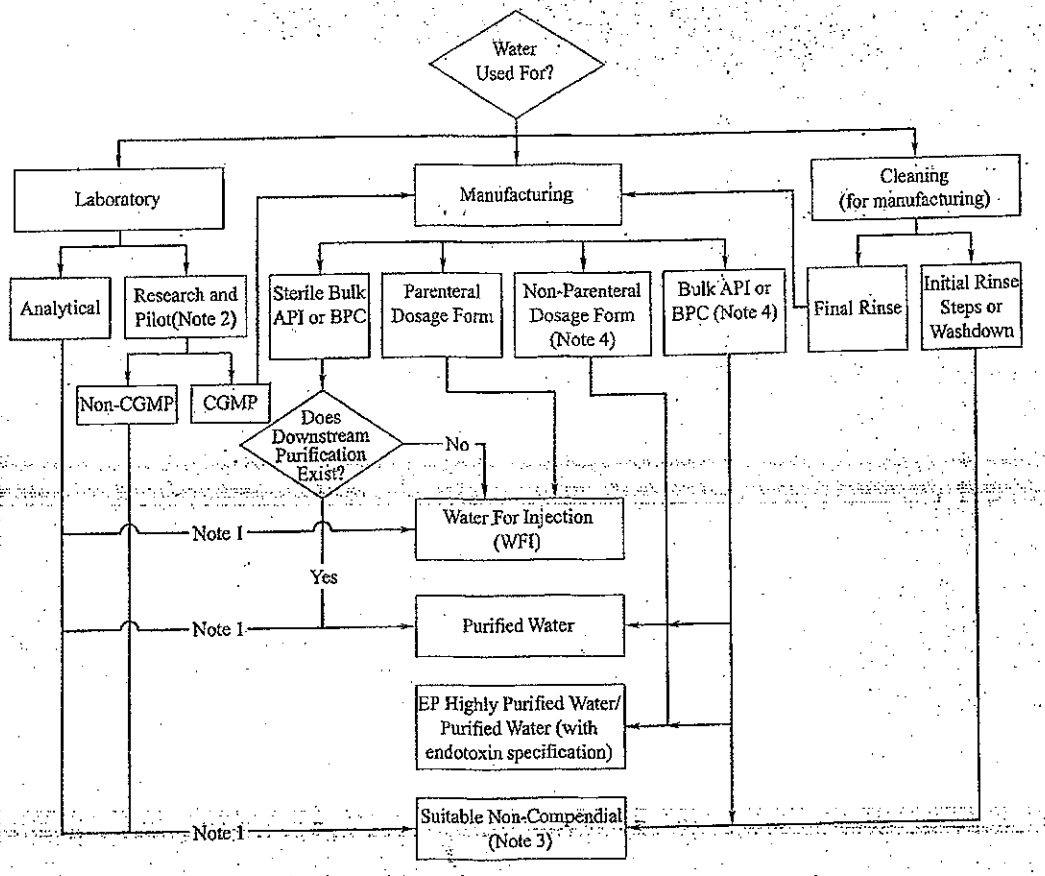
Fig 1.2 comes from the ISPE Volume 4 *Water and Steam Systems*; it shows a decision tree that can be used by manufacturer organizations to determine appropriate requirements for water used throughout their pharmaceutical manufacturing processes. The completed diagram should be accompanied by documentation supporting the options chosen with review and approval by the appropriate quality unit. Decisions should be based on product and process specific requirements as water supplied to any process must consistently meet or exceed the requirements, defined by the manufacturer, for safe and reliable manufacture of that product. Fig 1.2 includes the most common water types and selections; however, it is impractical to provide a single decision tree capable of covering the full breadth of diverse possible choices.

1.3.1 United States Pharmacopoeia

The *United States Pharmacopoeia* (USP) is a guideline for manufacturing drugs consumed inside the United States. The newest version USP is the 38th edition of the USP (USP 38), which was published in December, 2014 and came into force on May, 1, 2015. The USP gives a description of the detailed standards for the quality, purity, packaging, and labeling of pharmaceutical water, including raw water (purified water, hemodialysis water, and WFI) and product water (bacteriostatic WFI, sterile water for inhalation, sterile WFI, sterile water for irrigation, and sterile purified water).

In the USA, drinking water should comply with the basic national stipulation for drinking water promulgated by the U.S. Environmental Protection Agency. Relevant stipulations on drinking water by the EC or Japan are also applicable. The se stipulations can guarantee the absence of *Escherichia coli* in water. Drinking water may come from different sources, including public water production facilities, private water supply facilities, and mixed water supply sources. Drinking water is the specified water source for producing pharmaceutical water and can be used for preparing drug solutions or washing in the initial phase of the pharmaceutical production. The quality of drinking water varies with the change of seasons, which must be considered during the design of the production procedure of pharmaceutical water.

• The purified water specified in the USP is mainly used for the preparation of formulations except for those for parenteral use or for other applications in the pharmaceutical production, e.g. washing some



Notes:

1. By definition, some analytical methods require compendial waters. Quality should meet the needs of the analytical methods.
2. Laboratories performing both CGMP and non-CGMP operations should follow the CGMP path.
3. Non-compendial water may be of higher quality than compendial water.Endotoxin and microbial quality requirements are based on the process and quality needs of the product.Non-compendial water must meet applicable potable water requirements for microbiological quality as a minimun.
4. Water quality specifications which include endotoxin limits(e.g., WFI,USP PW with and endotoxin specification, or EP highly purified water) should be employed for waters used in the manufacturing of non-parenteral products where endotoxin control is required. This requirement is a function of the specific process and the nature of the downstream purification steps. "Purified water" could be an intermediate grade of water between "suitable non-compendial" and "EP highly purified/purified water (with endotoxin specification)" and is included as an option.

Fig 1.2 Pharmaceutical water quality decision tree

equipment or product ingredients except for those for parenteral use. The standards mainly include the following: the raw water of purified water must be drinking water at least; there must be no exogenous additives; appropriate process equipment must be used; it must comply with the USP requirements with respect to conductivity and TOC. It is strictly prohibited by the USP to use purified water as the solvent for parenteral formulations. A purified water system must be validated to verify that it can produce, store, and distribute pharmaceutical water in compliance with pharmacopeia requirements stably and reliably.

• The USP WFI is mainly used for producing formulations with strict endotoxin content requirements, e.g. parenteral formulations. Its standards mainly include the following: the raw water of WFI must be drinking water at least; there must be no exogenous additives; appropriate process equipment must be adopted (e.g. distillation method or purification method, which must be equivalent to or better than distillation method in removing microorganisms and compounds) to reduce microorganism growth; it must comply with the USP requirements with respect to WFI conductivity and TOC; raw material WFI for commercial use must satisfy the requirement for bacterial endotoxin, i.e. less than 0.25 EU/ml. USP stipulates that WFI can be used as the solvent for parenteral formulations. The WFI production, storage, and distribution systems must be designed to inhibit microbial contamination and formation of bacterial endotoxins; and the system must be validated.

Table 1.4 Development of USP pharmaceutical water testing

Item	USP 24 initial requirement for the variation	Item	USP 24 initial requirement for the variation
pH	Deleted	Easily oxidizable matter	Deleted, being replaced by TOC
Endotoxin	Reserved	Heavy metal	Deleted
Calcium salt	Deleted, being replaced by conductivity value	Total solids content	Deleted
Sulfate			
Chloride			
Ammonia		*E. Coli*	Deleted
Carbon dioxide		Microorganism content	Added

• The USP hemodialysis water is used for producing hemodialysis products, e.g. the dilution of hemodialysis concentrate. Hemodialysis water can be sealed and stored in inert containers for inhibiting the entry of bacteria; its standards mainly include the following: the raw water of hemodialysis water must be drinking water at least; there must be no preservatives in the water; an appropriate process must be adopted; it must comply with the USP requirements with respect to hemodialysis water conductivity as well as the requirement for the contents of TOC or easily oxidizable matters (either TOC or easily oxidizable matters can be chosen for testing); it must comply with the requirements for bacterial endotoxin and microorganism in hemodialysis water. It is strictly prohibited by the USP to use hemodialysis water as the solvent for injections.

• The USP standards for pure steam mainly include the following: heat raw water to over 100 ℃ and distill it to obtain pure steam; the distillation method should avoid raw water droplets being entrained into the pure steam product. The raw water of pure steam must be drinking water at least and there must be no exogenous additives; the saturation degree, dryness, and content of non-condensable gases should meet the requirements; the condensate of pure steam must meet the USP quality requirement for WFI; the collection of condensate should not affect the quality of pure steam; if pure steam is used for producing parenteral formulations, the condensate of pure steam must meet the requirement for bacterial endotoxin, i.e. less than 0.25 EU/ml.

• The USP sterile purified water refers to packaged sterile purified water, which is mainly used for the preparation of formulations except for those for parenteral use. Sterile purified water can also be used in the analytical application field; and sterile purified water can be used in the following conditions: the purified water systems cannot be validated; the consumption of purified water is very small; and when sterile purified water is required or the microbial limit of the packaged raw material purified water doesn't meet the requirement.

• The USP Sterile WFI refers to packaged sterile WFI, which is mainly used for the preparation of temporary prescriptions and the dilution of parenteral formulations. Sterile WFI is packaged in single-dose containers; and each piece must not exceed 1 L.

• The USP bacteriostatic WFI refers to a type of sterile WFI with at least one bacteriostatic agent added, being mainly used as a diluent for parenteral formulations. It is packaged in single dose or multiple-dose containers with a volume of no more than 30 ml.

• The USP sterile water for irrigation refers to a type of WFI packaged in a single-dose container with a volume of over 1 L, for the purpose of quick distributing and ensuring its sterility. Sterile water for irrigation doesn't necessarily comply with the requirement for particulate content in small volume injections.

• The USP sterile water for inhalation refers to a type of WFI packaged in a container to ensure its sterility and being used for inhalation therapy; it is used in inhalators for the preparation of inhalation solutions.

On November, 1996, the USP formally adopted the conductivity meter test method to replace the original micro-ion concentration test method. Table 1.4 shows the variation process of pharmaceutical water test indexes in the USP.

1.3.2 European Pharmacopoeia

The *European Pharmacopoeia* (EP) is the only literature for guiding drug quality testing in Europe. All manufacturers of drugs and drug substrates must

follow the EP quality standards during the process of promoting and using the products in the European region. The EP is published by the European Directorate for the Quality Control of Medicines (EDQCM), which was established in 1964 and published the first edition of the EP in 1977. In June 2013, the eighth edition (EP 8.0) was published and it is the newest version, which came into effect in January, 2014. The EP pharmaceutical water includes purified water, high-purity water, WFI, and sterile WFI. And the EP purified water includes purified water in bulk and purified water in containers.

• The EP standards for purified water as raw material mainly include the following: purified water as raw material is a type of pharmaceutical water produced from drinking water in compliance with official standards by use of the distillation method, ion exchange method, RO, or other appropriate method; it complies with the requirements for conductivity and the contents of TOC or easily oxidizable matters in purified water (a choice can be made in testing the content of TOC or easily oxidizable matters). Under normal conditions, the microbial limit is that the total aerobic bacteria count is not higher than 100 CFU/ml (it is incubated with agar culture medium S for 5 days under the environment of 30 to 35 ℃ and then treated by membrane filtration method); the nitrate content is not higher than 0.2 μg/ml; the heavy metals content is not higher than 0.1 μg/ml; the aluminum salts content is not higher than 10 ppb (only applicable to the production of dialysate); and the bacterial endotoxins content is lower than 0.25 EU/ml (only applicable to the production of dialysate).

• The EP Purified water in containers refers to the purified water that is filled into or stored in a specific container and it is guaranteed that microbial indexes are met; besides all indexes for purified water as raw material, the following standards should be met: colorless and clear liquid, no exogenous additives, in compliance with the requirements for pH/acidity and contents of easily oxidizable matters, chloride, and sulfate; ammonia content of no higher than 0.2 μg/ml; in compliance with the requirement for calcium and magnesium contents; content of nonvolatile matter of no higher than 1 mg/100 ml; in normal conditions, the microbial limit is that the total aerobic bacteria count is no higher than 100 CFU/ml (it is incubated with agar culture medium B and then treated by membrane filtration method).

• High-purity water is the only raw material type accepted by the EU and WHO and was incorporated into the EP 4.0 on January 1, 2002. It is stipulated by the EU and WHO that high-purity water can be used if WFI is not required for the preparation but the system has strict control of microbial indexes in the water. The applicable scope of high-purity water includes: eye drop solutions, ear and nose drug solutions, skin drugs, nebula, primary rinsing of sterile product containers, non-sterile APIs for injections, etc. The standards mainly include the following: high-purity water is generated from drinking water in compliance with official standards, it is a colorless and clear liquid, it is in compliance with the conductivity requirement for high-purity water; it complies with the requirement for TOC content in high-purity water and the TOC content is not higher than 500 ppb; under normal conditions, the microbial limit is that the total aerobic bacteria count is not higher than 10 CFU/ml (it is incubated with agar culture medium S for five days under the environment of 30 to 35 ℃ and then treated by membrane filtration method, the sampling volume is not less than 200 ml); the nitrate content is not higher than 0.2 μg/ml; the heavy metals content is not higher than 0.1 μg/ml; the aluminum salts content is not higher than 10 ppb (only applicable to the production of dialysate); and the bacterial endotoxins content is lower than 0.25 EU/ml. High-purity water can be prepared by a combination of RO technology, ultrafiltration, or deionization technology. Correct operation and maintenance management is of utmost importance for high-purity water systems.

• The EP WFI standards mainly include the following: WFI is generated from drinking water in compliance with official standards or produced from purified water by distillation; the components of the distillation equipment in contact with water should be made of neutral glass, quartz, or appropriate metals; the equipment is installed with some device that can prevent the entrainment of liquid droplets. The EP WFI standards mainly include the following: it is a colorless and clear liquid, it is in compliance with the conductivity requirement for WFI; it complies with the requirement for TOC content in WFI; under normal conditions, the microbial limit is that the total aerobic bacteria count is not higher than 10 CFU/100 ml (it is incubated with agar culture medium S for five days un-

der the environment of 30 to 35 ℃ and then treated by membrane filtration method, the sampling volume is not less than 200 ml); the nitrate content is not higher than 0.2 μg/ml; the heavy metals content is not higher than 0.1 μg/ml; the aluminum salts content is not higher than 10 ppb (only applicable to the production of dialysate); and the bacterial endotoxins content is lower than 0.25 EU/ml.

For a long term, the production of WFI has been restricted to the distillation method. During the 154th session convened in Strasbourg, France on March 15-16, 2016, the EP Commission adopted a revision of the WFI (0169) monograph. This revision permits to produce WFI by means of a purification process equivalent to the distillation method, i.e. RO +appropriate technology. This revised monograph also points out that the regulatory authority of the manufacturer must be informed before a non-distillation technology is used for producing WFI. This revised monograph is the result of a wide range of negotiations with relevant parties; it is based on the results of the European Directorate for the Quality Control of Medicines (EDQM) investigation, conducted in March, 2010, with respect to the data collected during WFI production by non-distillation method as well as the investigation results presented by a specialist team of EDQM in March, 2011 with respect to the Potential Production Usage of WFI-membrane system. It is allowed to use distillation or other purification technology that was proved to be equivalent to or superior to the distillation method as well as the technical innovation of producing WFI by ultrafiltration after the distillation unit or RO unit to shorten the gap between EP and USP as well as JP.

The quality of WFI produced by any non-distillation technology must be equivalent to that of the WFI produced by the distillation technology, which means that the same quality standard will apply and the stability of the production method should also be taken into consideration. Therefore, the EU GMP guideline Appendix I "*Sterile Drug Production*" which is being revised will cover new guidelines for WFI production methods. To guarantee that the necessary guidelines are available when the revised WFI monograph comes into effect, the Q&A documents prepared by a team of GMP/GMDP inspectors of the European Medicines Agency are near completion. The revised WFI monograph (0169) will be published in Supplement 9.1 of EP and will come into effect in April, 2017.

1.3.3 Chinese Pharmacopeia

The latest version of the *Chinese Pharmacopeia* (ChP) is the 2015 edition, which came into force on Dec. 1, 2015. The ChP 2015 is divided into four volumes. Volume Ⅰ covers TCM; Volume Ⅱ covers chemicals, Volume Ⅲ covers Biologicals; and Volume Ⅳ covers general notices and excipients standards, which is the most prominent feature of the ChP 2015 (the excipients standards), integrating and optimizing the appendices of the original Volume Ⅰ, Ⅱ, and Ⅲ of ChP 2010.

The ChP pharmaceutical water includes purified water, WFI, and sterile WFI. In comparison to the ChP 2010, the odorless requirement of purified water, WFI, and sterile WFI has been cancelled in the ChP 2015. Meanwhile, with reference to the microbial limit testing method of the EP and USP for pharmaceutical water, the ChP 2015 has made major revisions to the selected culture media and method for microbial limit testing of purified water and WFI; the reason for the revisions is that the nutrient agar culture medium possibly only detected a small portion of the total bacteria in the water sample; other non detectable bacteria possibly grow relatively slow or cannot grow in the test environment; therefore, undetected bacteria cannot form visible bacterial colonies in the set period; as the R2A agar culture medium can promote the restorative re-growth of damaged bacteria, the maximum bacteria colonies count obtained after an incubation period of seven days at 20 ℃ is always higher than that of the nutrient agar culture medium and m-SPC. In addition, the counting result is higher for the uniform coating of R2A agar culture medium; the growth speed of bacteria on R2A agar culture medium is relatively slow, so the count of formed colonies is relatively small and it is difficult to make an accurate count within 48 hours. Therefore, the incubation time should be prolonged to at least 5 days when R2A agar culture medium is adopted for the incubation.

The comparison analysis of test items stipulated in various countries' pharmacopeias has shown that the development process of the ChP 2015 with respect to the variation of testing indexes of raw material purified water and raw material WFI is very similar to that of the USP in comparison with ChP 2005, e.g. the introduction of the TOC test method. At present, the ChP requirement for the quality of raw material purified wa-

ter and raw material WFI is nearer to that of the EP. The change of the ChP has shown that the regulatory requirement of our country's latest version pharmacopeia for pharmaceutical water quality indexes is in the process of meeting international standards. With the development of the Chinese pharmaceutical industry, new technologies such as the production of WFI from drinking water by the purification method will surely be promoted and popularized in the Chinese pharmaceutical industry in the near future.

• The quality of the ChP 2015 purified water should comply with the relevant stipulations of Volume II regarding purified water. Purified water can be used as the solvent or laboratory water for the preparation of common drug formulations, used as the extraction solvent for the medicinal materials used for producing TCM injections, eye drops, and other sterile formulations, used as solvent or diluent for the preparation of oral and topical formulations, used as washing water for apparatus for non-sterile formulations, also used as extraction solvent for medicinal materials in non-sterile formulations. Purified water must not be used for the preparation and dilution of injections. There are many production methods for purified water; various production steps should be strictly monitored to prevent microbial contamination and ensure the water quality at each user point. The ChP 2015 quality standards for purified water are as follows:

Purified Water

H_2O 18.02

This product is a type of pharmaceutical water produced from drinking water by use of the distillation method, ion exchange method, RO process, or other appropriate methods and doesn't contain any additives.

Description: this product is a colorless, odorless, and transparent liquid.

Test items: acidity and alkalinity. Take 10 ml of this product and it must not turn red if two drops of Methyl Red Indicator are added; take another 10 ml of this product and it must not turn blue if five drops of Bromothymol blue indicator are added.

• Nitrates. Place 5 ml in a test-tube immersed in iced water, add 0.4 ml of a 10% solution of potassium chloride and 0.1 ml of 0.1% diphenylamine sulfate solution and, dropwise with shaking, 5 ml of sulfuric acid. Transfer the tube to a water-bath at 50 ℃. After 15min, any developed blue color in the solution should not be darker than that in a mixture treated in the same way with 0.3 ml standard prepared nitrate solution [take 0.163g potassium nitrate and add into water for dissolving and diluting to 100 ml, shake it and accurately take 1 ml of the solution, which will be diluted to 100 ml by adding water, then precisely take another 10 ml of the diluted solution and add water to dilute it until a volume of 100 ml; shake it to obtain the solution (every 1 ml equivalent to 1 μg NO_3)] and 4.7ml of nitrate-free water (0.000006%).

• Nitrite. Place 10 ml in a Nessler tube, add 1 ml of p-aminobenzenesulfonamide dilute hydrochloric acid solution (1→100) and 1 ml of hydrochloric acid naphthalene ethylenediamine solution (1→100), any developed pink color in the solution should not be darker than that in a mixture treated in the same way of 0.2 ml standard prepared nitrite solution [take 0.750g potassium nitrite (on dry basis) and add into water for dissolving and diluting to 100 ml, shake it and accurately take 1 ml of the solution, which will be diluted to 100 ml by adding water, then precisely take another 1 ml of the diluted solution and add water to dilute it until a volume of 50 ml; shake it to obtain the solution (every 1 ml equivalent to 1 μg NO_2)] and 9.8ml of nitrite-free water (0.000002%).

• Ammonia. Take 50 ml and add 2 ml of alkaline potassium tetraiodomercurate solution. After 15 minutes, any color developed in the solution must not be darker than the reference solution prepared by adding 48 ml non-ammonia water and 2 ml alkaline potassium mercury iodide solution into 1.5 ml ammonium chloride (take 31.5 mg ammonium chloride and add an appropriate amount of ammonia-free water to dissolve it and dilute until 1000 ml) (0.00003%).

• Conductivity. In compliance with relevant stipulations (General notice 0681).

• TOC. Not exceed 0.50 mg/L (General notice 0682).

• Easily oxidizable matter. Take 100 ml and add 10 ml of dilute sulphuric acid. After being boiled, add 0.10 ml potassium permanganate of 0.02 mol/L for boiling another 10 minutes. The solution remains faintly pink.

Either TOC or easily oxidizable matters can be chosen for testing.

• Non-volatile matter. Take 100 ml and place on an evaporation plate at 105 ℃, (the non volatile matter will maintain a constant weight when being boiled dry in a water bath); and then dry it to the constant weight at 105 ℃. The residue weighs no more than 1 mg.

• Heavy metals. Take 100 ml and add 19ml water and evaporate to 20 ml, after cooling, add 2 ml acetate buffer solution (pH 3.5) and an appropriate amount of water until 25 ml, then add 2 ml thioacetamide test solution and shake it. After 2 minutes, any developed color must not be darker than the solution treated in the same way and prepared by adding 19ml water into 1.0 ml lead standard solution (0.00001%).

• Microbial limit. Take no less than 1 ml and treat using the membrane filtration method; then incubate with a R2A agar culture medium for no less than 5 days at 30 to 35 ℃; when being tested according to the General notice 1105, the total aerobic bacteria count in 1 ml test solution must not exceed 100CFU.

Prescription and preparation of the R2A agar culture medium:

Yeast extract powder	0.5 g
Peptone	0.5 g
Casein hydrolysate	0.5 g
Glucose	0.5 g
Soluble starch	0.5 g
Dipotassium phosphate	0.3 g
Anhydrous magnesium sulfate	0.024 g
Sodium Pyruvate	0.3 g
Agar	15 g
Purified water	1000 ml

Take above mentioned ingredients except for the glucose and agar, mix and dissolve them at a not too high temperature; adjust the pH value to 7.2±0.2 at a temperature of 25 ℃; add some agar and heat for dissolving, then add some glucose, shake for filling and sterilization.

R2A agar culture medium applicability test. The test should be carried out according to the applicability test method of Tryptic (Trypticase) Soy Agar Medium in the "Counting Culture Medium Applicability Test" of microbial enumeration test (General notice 1105) in the Microbial limit test of nonsterile products. The test strains are Pseudomonas aeruginosa and Bacillus subtilis.

Category: Solvent, diluent.

Storage: it should be stored in tightly closed containers.

• The quality of the ChP 2015 WFI should comply with the relevant stipulations of Volume Ⅱ regarding WFI. WFI must be produced, stored, and distributed under conditions that can inhibit the growth of bacterial endotoxins. WFI can be used as the solvent or diluent for the preparation of injections, eye drops, and other sterile formulations, and also used for special washing of containers. In order to guarantee WFI quality, the bacterial endotoxins in raw water should be reduced and the various steps for producing WFI by distillation method should be monitored to prevent microbial contamination; the WFI systems should be regularly washed and disinfected. The storage method of WFI should be validated to ensure that water quality can meet quality standards, e.g. thermally-insulated recirculating at a temperature of over 70 ℃. See below for the quality standards of ChP 2015 for WFI:

Water for Injection

The product is the water being produced from purified water by the distillation method.

Description: this product is a colorless, odorless, and transparent liquid.

Test item: pH value. Take 100 ml of this product and add 0.3 ml of potassium chloride saturated solution; the pH value should be 5.0 to 7.0 when being determined according to General notice 0631.

• Ammonia. Take 50 ml for being tested according to the method for purified water, but the volume of the reference ammonia chloride solution is changed to 1.0 ml; the result should comply with relevant stipulations (0.00002%).

• Nitrate and Nitrite, conductivity, TOC, non-volatile matters, and heavy metals. The tests will be carried out according to the above mentioned methods for purified water; and the results should comply with relevant stipulations.

• Bacterial endotoxin. Take a certain quantity of this product and test it according to general notice 1143. The content of endotoxins should be less than 0.25 EU/ml.

• Microbial limit. Take no less than 100-ml for being treated by membrane filtration method; then incubate with R2A agar culture medium for no less than 5 days at 30 to 35 ℃; when being tested according to General Notice 1105, the total aerobic bacteria count in 100 ml test solution must not exceed 10cfu.

• The prescription, preparation, and applicability tests of the R2A agar culture medium will be carried out according to the above mentioned methods for purified water; and the results should comply with relevant stipulations.

Category: solvent.

Storage: it should be stored in tightly closed containers.

• The quality of the ChP 2015 sterile WFI should comply with the relevant stipulations of Volume Ⅱ regarding sterile WFI. The ChP sterile WFI doesn't contain any additive. It is mainly used as the solvent for sterile injection powders or the diluent for injections. Its quality complies with relevant stipulations of the ChP for sterile WFI. The filling specification of sterile WFI should adapt to clinical needs to avoid any contamination due to large volume and therefore multiple usage. The quality standards of the ChP 2015 for sterile WFI are as follows:

Sterile Water for Injection

This product is produced from WFI using the production process of injections.

Description: this product is a colorless, odorless, and transparent liquid.

Test item: pH value. Take 100 ml of this product and add 0.3 ml of saturated potassium chloride solution; the pH value should be 5.0 to 7.0 when being determined according to General notice 0631.

• Chloride, sulfate, and calcium salts. Take the product and place it into three test tubes respectively, each test tube containing 50 ml; add five drops of nitric acid and 1 ml silver nitrate solution into the first tube; add 5ml barium chloride test solution into the second tube and add 2 ml ammonium oxalate test solution into the third tube; there should be no turbidity in the three test tubes.

• Carbon Dioxide. Take 25ml of the product and put it into a 50 ml measuring cylinder with stopper, add 25 ml calcium hydroxide test solution into the cylinder, seal it with the stopper and shake it, then leave it to rest; there must be no turbidity within one hour.

• Easily oxidizable matters. Take 100 ml of the product and add 10 ml dilute sulfuric acid into it; after boiling, add 0.10 ml potassium permanganate standard solution (0.02mol/L) and boil it for another 10 minutes; the pink color must not disappear completely.

• Nitrate and nitrite, ammonia, conductivity, non-volatile matter, heavy metals, and bacterial endotoxins. The tests will be carried out according to the specified methods for WFI; the test results should comply with relevant stipulations.

Other test results should comply with various stipulations for WFI (General notice 0102).

Category: solvent, irrigating solution.

Specification: (1) 1 ml (2) 2 ml (3) 3 ml (4) 5 ml (5) 10 ml (6) 20 ml (7) 50 ml (8) 500 ml (9) 1000 ml (10) 3000 ml (for irrigating).

Storage: it should be stored in a tightly closed container.

1.4 GMP Standards

1.4.1 FDA cGMP

The US FDA cGMP doesn't include direct requirements for pharmaceutical water and it rarely involves design requirements for pharmaceutical water. It is requested in the US FDA cGMP that the surfaces in contact with pharmaceutical ingredients, process raw materials, or the finished drugs must not react with or adsorb the materials to avoid any change of drug safeness, uniformity, strength, quality, or purity. The following points are some default requirements of the US FDA cGMP for pharmaceutical water systems:

• The vent outlet can satisfy air-break requirements;

• Double tube sheet tubular heat exchanger should be adopted for avoiding cross contamination;

• Air aspirator should be installed on the tank;

• Routine maintenance schedule should be prepared;

• Written procedure for washing and disinfection should be provided and records should be kept;

• Standard operating procedure for pharmaceutical water systems should be prepared.

In addition to the US FDA cGMP requirements, pharmaceutical water systems should also meet other governmental laws and regulations in US. Pharmaceutical enterprises need to establish appropriate quality standards according to the *Guide to Inspections of High Purity Water Systems*, which has the following key requirements for pharmaceutical water systems:

• Fewest dead points;

• No filter is installed at the user point of the WFI circuit;

• Most pipes of the WFI distribution systems are made of 316L stainless steel;

• Heat exchanger should adopt double-end sheet design or differential pressure monitoring;

• The tank should be equipped with aspirator to prevent external pollution;

• Pipeline slope should comply with relevant requirement;

• Sanitary seal pump should be used;

• The water should be consumed within 24 hours under standstill state;

• When sterile drugs are produced, the final rinsing water should meet WFI standards;

• Pure steam doesn't contain any volatile matters.

1.4.2 EU GMP

According to the stipulations of the EU GMP, the design, installation, and maintenance of water treatment facilities and the distribution systems should ensure that the supply water can meet appropriate quality standards; the operation of a water system must not exceed its design capacity; the production, storage, and distribution of WFI should be able to avoid microbial growth; for example, WFI should be thermally insulated and recirculated at over 70 ℃.

• The EU GMP requirements for pharmaceutical water mainly consist of the following three aspects;

• EU GMP emphasizes that the quality of pharmaceutical water needs to satisfy relevant requirements of EU Pharmacopeia;

• EU GMP emphasizes the concept of *Quality by Design*; the design capacity of pharmaceutical water needs to match with the operation capability;

• EU GMP emphasizes the importance of *Process Control* and specifies that *Prevention of Microbial Growth* is the most important concern in the design, construction, operation, and management of pharmaceutical water systems.

1.4.3 WHO GMP

On Oct. 10-14, 2011, the 46th expert panel meeting of the WHO International Pharmacopeia and Drugs Expert Panel was convened in Geneva, Switzerland and "*Annex 2 WHO Good Manufacturing Practices: Water For Pharmaceutical Use*" was published as a result of the meeting; and it has very specific requirements for the water for pharmaceutical use; the main contents include: general requirements for water for pharmaceutical use, quality standards for water for pharmaceutical use, application of water for pharmaceutical use in the processes and dosage forms, purification method of water for pharmaceutical use, storage and distribution systems of water for pharmaceutical use, operational considerations of pharmaceutical water systems, other guidance and requirements for pharmaceutical water systems, etc. The details are as follows:

• General requirements for water for pharmaceutical use. The main concern of the WHO GMP is whether the systems can produce pharmaceutical water of expected quality stably and continuously; the usage procedures of the water systems (e.g. preventive maintenance schedule) should be approved by QA department; testing and recording should be carried out regularly with respect to the conductivity, TOC, microorganisms, endotoxins, and physical properties (e.g. temperature) of the water source and the produced purified water and WFI of the water system; in case of any usage of chemicals, it must be verified that the chemicals have been thoroughly removed.

• Quality standards for water for pharmaceutical use. The WHO GMP gives a specific description of the quality standards for drinking water, purified water, high-purity water, WFI and other grades of water for pharmaceutical use (e.g. analytical water).

• Application of water for pharmaceutical use in the processes and dosage forms. The WHO GMP specifies that drug regulatory agencies will establish the standards and principles for the usage of pharmaceutical water in various processes and dosage forms; the features of intermediates or final products need to

be considered for the quality requirements of pharmaceutical water. Some specific description should be made for high purity water; meanwhile, the quality index of the condensate of pure steam should correspond with the quality specifications of WFI.

• Purification, storage and distribution systems of water for pharmaceutical use. An introduction is specifically made in the WHO GMP with respect to the purification methods of drinking water, purified water, high-purity water, and WFI. The storage and distribution systems are important component of a pharmaceutical water systems. As the storage and distribution systems don't have any purification function, the prevention of secondary contamination of the pharmaceutical water in the storage and distribution systems are surely very critical. The manufacturing material of the storage and distribution systems should be applicable to pharmaceutical water of any quality and will not have any ill effect on water quality. The storage and distribution systems should be designed with proper disinfection or sterilization methods to effectively control bioburden. Water temperature is to be controlled in the range of 70 to 80 ℃; meanwhile, the temperature range of 15 to 20 ℃ is also accepted. Air aspirators, pressure monitors, and rupture discs need to be installed in the storage tanks for purified water and WFI; buffer ability should be available to satisfy continuous and intermittent operation requirements. The pipework should be kept in a turbulent state to avoid the presence of dead points ($L<3D$); thermal disinfection (>70 ℃) and chemical disinfection (ozone disinfection, ozone to be removed before the usage) are both good methods for controlling microbial indexes.

• Operational considerations of pharmaceutical water systems. Valid Factory Acceptance Test (FAT) and Site Acceptance Test (SAT) reports are required; a validation plan should be provided and it should follow the principle of Design Qualification (DQ), Installation Qualification (IQ), and Operational Qualification (OQ); Performance Qualification (PQ) will be carried out by a three-phase approach.

• Guide requirements for pharmaceutical water systems. On-line or off-line water quality monitoring will be carried out; systems maintenance will be carried out according to the established procedure at the specified intervals; and various components of the systems will be regularly inspected.

1.4.4 Chinese GMP

Specific stipulations have been made for water for preparation of pharmaceutical goods in Section 6 of Chapter 5 Equipment of the *Chinese GMP* (2010 *Revision*). The details are as follows:

Article 96 *Water used for preparation of pharmaceutical goods must be suitable for its purpose, and in accordance with the quality standard and related requirements of the Pharmacopoeia of the Peoples' Republic of China. Water used for preparation of pharmaceutical goods must be produced using drinking water at least.*

Article 97 *The design, installation, function and maintenance of water disposal equipment and its transportation system must ensure the water used for preparation of pharmaceutical goods achieve the set quality standard. The function of water disposal equipment must not exceed its designed ability.*

Article 98 *The material used for purified water, WFI storage tank and transportation pipe must be non-poisonous and corrosion resistant; the vent of the storage tank must be complete with hydrophobic aseptic filter without shedding fibers; the design and installation of the pipeline must avoid dead angle and blind pipe.*

Article 99 *The preparation, storage and distribution of purified water, water for injection must prevent the reproduction of microorganism. Purified water can be circulated, and water for injection can undergo heat preservation circulation above 70 ℃.*

Article 100 *The water quality of the preparation water and original water must be monitored regularly, and corresponding records kept.*

Article 101 *The pipe of purified water and water for injection must be cleaned and sterilized according to operation procedures, and corresponding records kept. If the microorganism pollution of the preparation water reaches the alarm limit, or deviation rectify limit, disposal must be done under operation procedures.*

According to Appendix I Sterile Medicinal Products of the *Chinese GMP* (2010 *Revision*), the requirements for monitoring bacterial endotoxins in pharmaceutical water are as follows:

Article 50 *Bacterial endotoxins for pharmaceutical water should be monitored regularly. Records of the monitoring results and of any corrective action taken should be maintained.*

In comparison with the *Chinese GMP* (1998 *Revision*), the requirements of the *Chinese GMP* (2010 *Revision*) for pharmaceutical water are nearer to those of the EU GMP. The new version pharmacopeia adopts

more scientific methods for testing water quality and introduces some test indexes prevalent in foreign countries such as conductivity and TOC. Meanwhile, the *Chinese GMP* (2010 *Revision*) adopts the analytical concept of *Process Control* and emphasizes that the production, storage, and distribution of purified water and WFI can prevent microbial growth; and it has cancelled the compulsory constraint for the operation temperature of pharmaceutical water systems; in addition; it is suggested in the *Chinese Pharmacopeia* (2010 *Revision*) that some method convenient for trend analysis should be adopted for storing data such as pharmaceutical water conductivity, TOC, temperature, and microorganism monitoring data. It emphasizes the importance of automation control and recording as well as the traceability of the documentation systems and the systems as a whole. At the same time, such industry standards as the *Code for Design of Pharmaceutical Process Water Systems* (GB 50913—2013) and the *GMP Implementation Guideline for Water Systems* (2010 *version*) have provided technical reference and regulatory suggestions for the design, construction, commissioning, validation, and maintenance of the Chinese pharmaceutical water systems.

1.5 Key Water Quality Indexes

Each country or region's pharmacopeia has different test indexes for purified water and WFI, but conductivity, TOC, microbial limit, and bacterial endotoxins are four key test indexes of all pharmacopeias. This book will put an emphasis on the introduction of these four key quality indexes.

1.5.1 Conductivity

Conductivity is a type of physical quantity representing the ability to conduct an electric current of an object; its value is the reciprocal of the electrical resistance of an object, expressed in S/cm (Siemens) or μS/cm. Water molecules in purified water will ionize to some extent to produce hydrogen ions and hydroxide ions; therefore, although purified water has weak conducting ability, it also has measurable conductivity. Water conductivity has very close relationship with water purity; the higher the water purity is, the smaller the conductivity is, and vice versa. When carbon dioxide and other gases in the air dissolve in and interact with the water, corresponding ions can be produced, so that the water conductivity will increase.

The conductivity determination method is a method for testing the conductivity of pharmaceutical water and for further controlling the total amount of electrolyte in water. For the detailed test method, please refer to the General notice 0681 Determination method for conductivity of pharmaceutical water of Volume Ⅳ of ChP 2015. A precise and calibrated conductivity meter must be used for measuring the conductivity of the water; the conductivity cell consists of two parallel electrodes, which are usually protected by a glass tube; or other types of conductivity cells can also be used. The conductivity meter should be regularly calibrated according to the design function and usage degree; the conductivity cell constant can be directly calibrated by using a conductance standard solution or be indirectly compared to instruments; and the cell constant must be in the range of ±2% of the specified value of the instruments. When the instruments are being calibrated, each measuring range of conductivity meter should be separately calibrated. The minimum resolution of the instrument should be 0.1 μS/cm; and the instruments' accuracy should achieve ±0.1 μS/cm.

The temperature has a relatively large influence on the conductivity measuring value of the sample (see Fig 1.3); the conductivity meter can automatically compensate the measuring value according to the temperature of the tested sample and can display the compensated readings. The obtained value of water conductivity according to the temperature correction computation method has a relatively large error; therefore, a non-temperature compensation mode should be used for the measurement of conductivity; the accuracy of the temperature measurement should be within ±2 ℃. At present, the on-line conductivity testing technology has been popularized and promoted in pharmaceutical water systems. The correct installation position of the on-line conductivity meter should reflect the real quality of the water; the optimum position for on-line testing is generally located after the valve in the last user point of the pipeline and also in the main pipework before returning to the main tank.

For the ChP /EP purified water, an on-line or off-line conductivity meter can be used for the testing and the measurement temperature will be recorded. In Fig 1.3 of the temperature and conductivity limits, the conductivity value corresponding to the measurement

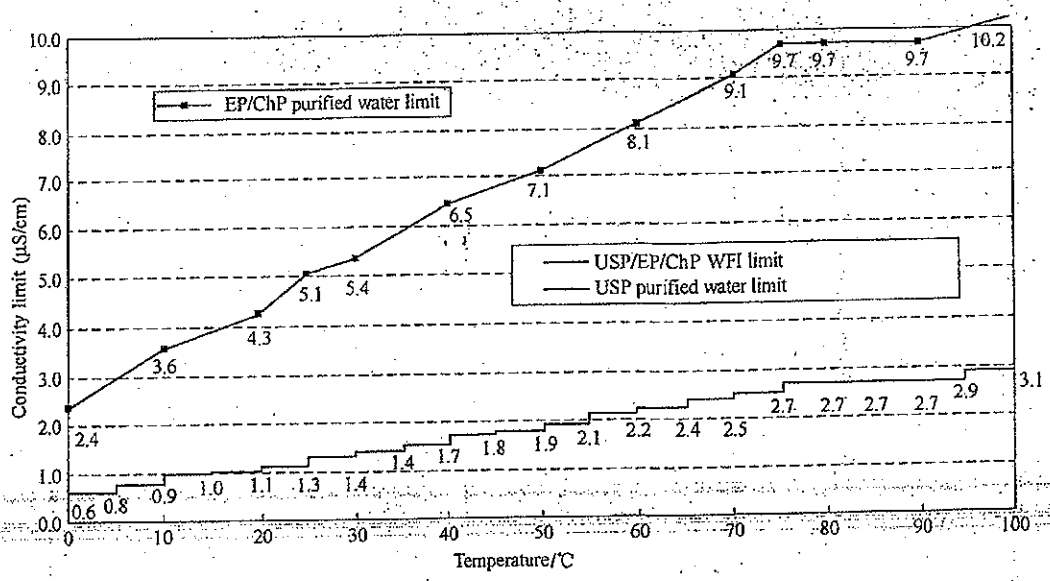


Fig 1.3 Relationship of temperature and conductivity limit

temperature is the limit value; if the measurement temperature is not indicated in the fig, the linear interpolation method will be used for computing the limit value; if the measured conductivity value is no more than the limit value, it will be considered as qualified; if the measured conductivity value is more than the limit value, it will be considered as unqualified.

Computation formula of the interpolation method:

$$\kappa=(T-T_0)\times(\kappa_1-\kappa_0)/(T_1-T_0)+\kappa_0 \quad (1.1)$$

In which, κ represents the conductivity limit value at the measurement temperature;

κ_1 represents the corresponding conductivity limit value at the closest temperature higher than the measurement temperature;

κ_0 represents the corresponding conductivity limit value at the closest temperature lower than the measurement temperature;

T represents the measurement temperature;

T_1 represents the closest temperature higher than the measurement temperature;

T_0 represents closest temperature lower than the measurement temperature.

The three-step method needs to be adopted for measuring the conductivity of the USP purified water and WFI, EP WFI, and ChP WFI; an on-line or off-line conductivity meter can be used for the testing.

Step 1: Firstly, find the closest temperature that is lower than the measurement temperature in the above table of temperature and conductivity limits, then the corresponding conductivity is the limit value; if the measured conductivity is no more than the corresponding limit value, it can be considered as qualified; if the measured conductivity is more than the corresponding limit value, continue with the next step.

Step 2: Take a sufficient amount of water sample (no less than 100 ml) and put into an appropriate container, stir it and adjust the temperature to 25 ℃; then stir it violently and measure the conductivity every five minutes; when the variation of conductivity is less than 0.1 μS/cm, record the conductivity value; if the measured conductivity is no more than 2.1 μS/cm, the result will be considered as qualified; if the measured conductivity is more than 2.1 μS/cm, continue with the next step.

Step 3: The measurement should be carried out within five minutes after the last step. Adjust the temperature to 25 ℃ and add saturated potassium chloride solution into the same water sample (0.3 ml for each 100 ml water sample), and measure the pH value accurately to 0.1pH, then find the corresponding conductivity limit in Table 1.5 Relationship of pH value and conductivity limit; and compare the limit with the measured conductivity in step 2; if the measured conductivity in step 2 is no more than the limit, the result will be considered as qualified; if the measured conductivity in step 2 exceeds the limit or pH value is not in the range of 5.0 to 7.0, the result will be judged as unqualified.

Table 1.5 Relationship of pH value and conductivity limit

pH	Conductivity/(μS/cm)	pH	Conductivity/(μS/cm)
5.0	4.7	6.1	2.4
5.1	4.1	6.2	2.5

cont.

pH	Conductivity/(μS/cm)	pH	Conductivity/(μS/cm)
5.2	3.6	6.3	2.4
5.3	3.3	6.4	2.3
5.4	3.0	6.5	2.2
5.5	2.8	6.6	2.1
5.6	2.6	6.7	2.6
5.7	2.5	6.8	3.1
5.8	2.4	6.9	3.8
5.9	2.4	7.0	4.6
6.0	2.4		

The conductivity of ChP sterile WFI is measured according to the following method: adjust the temperature to 25 ℃ and measure the conductivity with the off-line conductivity meter. When the indicated filling volume is no more than 10 ml, the conductivity limit is 25 μS/cm; when the indicated filling volume is more than 10 ml, the conductivity limit is 5 μS/cm. If the measured conductivity is no more than the limit, the result will be considered as qualified; if the measured conductivity is more than the limit, the result will be considered as unqualified.

1.5.2 TOC

TOC refers to the total content of carbons in dissolved and suspended organic substances in the water body. There are a variety of organic substances in water, which cannot be totally separated and identified at present and are commonly represented by TOC. The USP, EP, JP, and ChP all have some stipulations on the TOC content in pharmaceutical water; all major pharmacopeias accept the same TOC limit value (500 ppb or 0.5 mg/L).

TOC testing started from 1998; TOC is one of the test indexes of the USP with respect to WFI and PW for pharmaceutical use. Before 1998, organic substance testing in the USP was "Hard oxidizable matters testing", which was carried out using a chemical reaction method with color change in a $KMnO_4$ solution. The development of measuring instruments has promoted a change in using the solution testing method; the improvement in testing speed and sensitivity has made TOC measurement by analytical instrument become a quicker and better method. In <643> of the USP 1996, TOC measurement was an alternative to hard oxidizable matter testing; afterwards, TOC measurement has become a specified method in Appendix 5 of USP 23, which stipulates that the TOC of all the USP water must be less than 500 ppb or 0.5 mg/L.

There are many routes for organic carbon to enter the pharmaceutical water systems. The common one is that organic carbon is brought in the systems along with the raw water; TOC mainly comes from biological matters, e.g. rotting of animals and plants, bacterial activities, and animal excrements. The se biological matters will enter the well by penetration or overflow into lakes and rivers before being introduced in the city water. The molecular weight of the synthetic substances containing carbon is in a wide range from low to high, such as methanol with low molecular weight and multi-ring substances with high molecular weight; other sources of organic matters include industrial waste water, pesticides, herbicides, and chemicals; these chemicals are very powerful and can cause severe health problems. Under the guidance of the local environmental protection bureau and health bureau, most of the organic carbon can be removed from raw water through purification. All pharmacopeias require that pharmaceutical enterprises should take the standards for drinking water as the starting point. Generally speaking, the TOC limit of drinking water is 10-20 times higher than that of pharmaceutical water. Other contributions to the TOC are from the pharmaceutical factory itself. The accidental entry of organic carbon is caused by operator error or degrading of the water systems. Operator error is considered an unforeseen accident; e.g. wrong opening of valves, etc. The entry of organic carbon may be due to design or operation process defects, e.g. residue of disinfectants after being used for wiping an area with leaking points; in addition, TOC can be increased due to system fault, e.g. RO and EDI membrane pore problem. Bacterial contamination and breeding may cause the rise of TOC value. Whatever the source of TOC, appropriate testing, monitoring, and controlling should be made for TOC content in pharmaceutical water systems.

TOC is a comprehensive index that can be quickly identified; the total amount of organic matters in water represents the carbon amount. TOC cannot reflect the variety and composition of organic matters in water, so it cannot reflect different contamination consequence arising from the same TOC. The TOC determination method is used for testing the total amount of organic carbon in pharmaceutical water and subsequently indirect control of the content of organic

matters in water. TOC is generally used as an important basis for evaluating the contamination degree of the water body by organic matters. At present, online TOC testing technology has been popularized and promoted in pharmaceutical water systems. TOC testing has been widely used for the process flow control of water production systems, e. g. monitoring the efficiency of purification units and water delivery units. For details, refer to the General notice 0682 *Determination method of TOC in Pharmaceutical water* of Volume Ⅳ of ChP 2015.

Main principle for TOC determination: firstly, the samples are oxidized to decompose organic matters into carbon dioxide; then the TOC value can be indirectly obtained by testing carbon dioxide. Oxidization technologies mainly include: high temperature oxidization, supercritical oxidization, oxidization of heated persulfate oxidation, ultraviolet plus persulfate oxidation, ultraviolet oxidation, and ultraviolet plus titanium dioxide oxidation. Carbon dioxide testing technologies mainly include: Nondispersive Infrared (NDIR) sensing, direct conductivity sensing, and selective membrane conductivity detecting. On the basis of the research results and wide investigation of pharmaceutical water systems in the industry, the USP has determined the limit value of 0. 5 mg/L or 500 ppb. On May 15, 1998, the USP officially adopted the TOC testing method and deleted the easily oxidizable matters method from the eighth supplementary edition of USP 23.

Organic matters in pharmaceutical water generally come from raw water and the growth of bacteria in the pharmaceutical water production, storage, and distribution systems. Generally, sucrose is used as an easily oxidizable organic matter and 1,4-benzoquinone is used as a hard oxidizable organic matter; and the standard solutions of these two organic matters will be prepared as stipulated; corresponding response values will be measured respectively by a TOC meter to investigate the oxidization ability of the adopted technology and applicability of the instrument in the systems.

a. General requirements for the instrument. Multiple methods can be used for TOC determination. The se technologies can be used for TOC determination only if the following conditions are met:

• TOC determination technology can differentiate inorganic carbon (carbon dioxide dissolved in water and carbon dioxide produced by the decomposition of bicarbonate) from organic carbon (carbon dioxide produced by the oxidization of organic matters); and it can eliminate the interference of inorganic carbon for the determination of organic carbon.

• It should satisfy the requirements of system applicability testing.

• It should have enough test sensitivity (the minimum detection limit for carbon content is no more than 0. 05 mg/L).

A water system should be on-line monitored or off-line tested in laboratory with calibrated instruments. Online monitoring can achieve real-time testing and real-time process flow control of water systems conveniently; off-line testing may bring about many problems, e. g. contamination by the sample, sampling container, and uncontrolled environmental factors (e. g. vapors of organic matters). Water is produced batchwise or continuously, so the choice of off-line testing or on-line testing should depend on the water production conditions and the specific situation.

b. Water for TOC testing. High purity water should be used, with TOC less than 0. 10 mg/L and a conductivity of less than 1. 0 μS/cm (25 ℃). The water for TOC testing, water for preparing reference solution, and the water for system applicability test solution should come from the same container.

c. Preparation of reference solution.

• Sucrose reference solution. Unless otherwise specified, take an appropriate amount of sucrose reference substance which has been dried to a constant weight under 105 ℃ to precisely weight it; add some water for TOC testing to dissolve it and then dilute to a solution with a concentration of 1. 20 mg/L (carbon content of 0. 50 mg/L).

• 1, 4-benzoquinone reference solution. Unless otherwise specified, take an appropriate amount of 1,4-benzoquinone reference substance to precisely weight it; add some water for TOC testing to dissolve it and then dilute to a solution with a concentration of 0. 75 mg/L (carbon content of 0. 50 mg/L).

d. Test solution.

• Off-line testing. The water sample may be contaminated during the process of sampling and transferring to the test apparatus; meanwhile, contamination of organic matters and absorption of carbon dioxide will influence the truthfulness of test results; therefore, one should be very cautious at the various steps of the testing. Sealed containers should be used for sampling.

After sampling, the headspace of the container should be as small as possible and the testing should be performed timely. The glassware to be used should be carefully washed to remove organic residues; and water for TOC testing should be used for the final rinsing.

d. On-line testing. Connect the on-line TOC testing device with the water production systems properly. The water sampling and testing systems must be thoroughly washed.

e. System applicability testing. Take some water for TOC testing, sucrose reference solution and 1,4-benzoquinone reference solution and sample respectively; record TOC response values of the instrument successively. According to the following formula, the calculated response efficiency should be 85% to 115%.

$$[(r_{ss}-r_w)/(r_s-r_w)]\times 100\% \qquad (1.2)$$

In which, r_w represents blank response value of the water for TOC testing; r_s represents the response value of sucrose reference solution; r_{ss} represents the response value of 1,4-Benzoquinone reference solution.

f. Determination method. Take an appropriate amount of pharmaceutical water for testing; test it according to the specified method of the instrument; record the response value of the instrument r_u. Unless otherwise specified, the response value of pharmaceutical water for testing should not be more than r_s-r_w (0.50 mg/L).

This method can be applied to on-line testers or offline testers which have been pre-calibrated and passed the system applicability test. The water quality result tested by the on-line or off-line tester is closely related to the water sampling position in the water system. It should be noted that the water sampling position must truly reflect the quality of the pharmaceutical water.

1.5.3 Microbial Limit

There isa very strict requirement for the cleanliness of the pharmaceutical water used in pharmaceutical production, but the pharmaceutical water is not sterile; and it is widely used in solution preparation, online washing, apparatus washing, etc. The quality of pharmaceutical water has direct effect on product quality. In order to reduce bioburden during sterile production process, the microbial count in pharmaceutical water must be controlled. At present, the R&D activities have completed for on-line microbial limit testing technology for pharmaceutical water systems and this technology is now in the popularizing and promoting phase. For the detailed testing method, please refer to the General notice 1105 Microbial Limit Test for Non-sterile Product: Microbial Count Method of Volume Ⅳ of ChP 2015.

Gram-negative bacteria are the most harmful to pharmaceutical water systems, because they can very easily form biofilms, which will become endotoxin contaminants. According to the guideline of the Food and Drug Administration (FDA), the microbial indexes of WFI and purified water should not be higher than 10 CFU/100 ml and 100 CFU/ml respectively, which are only the alert limits but not the standard for determining whether or not the water is qualified; if the alert limit is exceeded, the enterprise must investigate to find the reason and take corrective measures; analysis should be done with respect to the influence of the water exceeding the limit on microbial contamination; and the investigation results must be recorded.

The purpose of specifying an alert limit is to guarantee that the water systems can operate in controlled conditions. The specification of water systems alert limit depends on the water production situation of the systems, finished preparations production process, and product usage; if the formula of antacid doesn't contain effective preservatives, the water is prone to be contaminated; therefore, the alert microbial limit of the water systems should not be less than 100 CFU/ml. Each pharmaceutical enterprise must assess its own products and production methods and formulate internal control microbial limits acceptable to the water systems based on the most dangerous case; at the same time, the internal control microbial limit of the enterprise must not exceed the maximum alert limit specified in pharmacopeia.

Microorganisms in the water systems generally float in the water or adhere to the tank wall or pipe wall to form a layer of biofilm, which can continuously release microbial cells. Therefore, when there is biofilm in the system, the contamination will not be uniform, so the water sample cannot represent the type or quantity of the contaminating bacteria; for example, the bacteria count of a water sample is 10 CFU/ml, but that of the other sample may be 1000 CFU/ml; such a testing result will be meaningless; therefore, it is pointed out in the *Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories*

of the FDA that microbial testing should include the identification of colonies found during the testing of the total bacteria count.

Off-line sampling is generally used for microbial indexes testing of the pharmaceutical water systems. As water sampling is often carried out in a non-sterile area, a sterile operation cannot be guaranteed; a small quantity of bacteria may be introduced due to sampling error; meanwhile, the WFI is one of major raw materials for sterile production process; it is required that the bioburden of the drug solution should not be higher than 10 CFU/100 ml before the filtration for bacteria removal by filtration.; therefore, a WFI microbial limit of ≤10 CFU/100 ml is specified on the basis of a comprehensive consideration of economic factors, quality control, and safe operation.

1.5.4 Bacterial Endotoxin

The issue of most concern for injections is the bacterial endotoxin index; if the index exceeds the limit, a severe pyrogen reaction may be caused; it is stipulated in pharmacopeia that the endotoxin index in WFI should be less than 0.25 EU/ml. Off line sampling is generally used for analyzing bacterial endotoxin indexes in the water systems; for the detailed test method, refer to the General notice 1143 *Test Method for Bacterial Endotoxin* of ChP 2015 Volume Ⅳ.

There are two bacterial endotoxin testing methods, i.e. the sol-gel process and the photometric method; either method can be used with the test solution; in case of any conflict, the results obtained by the sol-gel process will prevail unless otherwise specified.

The sol-gel process is a method using the agglutination reaction between Tachypleus Amebocyte Lysate (TAL) and endotoxin to inspect or semi-quantify the endotoxin content. The TAL is made by extracting amebocyte lysate from the blue blood of limulus which is a marine arthropod and then freeze-drying it at low temperature; TAL is a biological reagent specific for bacterial endotoxins testing. Until now, the limulus test has been the best method for testing endotoxins and has been accepted as the statutory endotoxin testing method by the EP, USP, and ChP due to its simplicity, quickness, sensitivity, and accuracy. At present, it has been adopted in various countries.

The photometric methods include the turbidimetry and chromogenic technique; turbidimetry refers to a method of determining the endotoxin content by inspecting the turbidity change during the reaction process of TAL and endotoxins; chromogenic technique refers to a determination method that uses the coagulase produced during the reaction process of TAL and endotoxin, as the coagulase can release chromogen to enable a specific substrate to develop color.

During the bacterial endotoxin testing process, microorganism and endotoxin contamination should be avoided. The water used for bacterial endotoxin testing is sterile WFI with endotoxin content of less than 0.015 EU/ml (for sol-gel process) or 0.005 EU/ml (for photometric method) and without interference to endotoxin testing; the utensils to be used should be treated to remove any potential exogenous endotoxins; dry-heat sterilization is normally used for heat resistant utensils for a period of over 30 minutes under 250 ℃; other appropriate method without inference to bacterial endotoxin testing can also be used. If plastic instruments (e.g. micro-hole plate and nipples for microloader) are used, they must be indicated to be free from endotoxins and have no interference to the testing.

Chapter 2

Design Concept

As the most widely used process raw material in the pharmaceutical industry, the pharmaceutical water participates in the whole pharmaceutical production process, including raw material production, separation and purification, finished product preparation, etc. It can be the main compound, solvent, diluent, etc. of the drug products. Meanwhile, pharmaceutical water has very strong solubility and few impurities; this is widely applied in the cleaning of pharmaceutical equipment and systems, as a direct impact system during the drug production process, and an important part of the GMP quality management and validation of pharmaceutical enterprises. Therefore, the essence of maintaining the quality of pharmaceutical water systems is to control bioburden and particle burden in the pharmaceutical production process with the concept of quality by design (Fig 2.1).

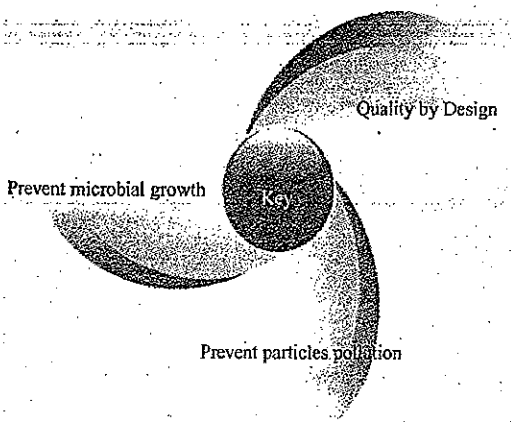


Fig 2.1 Core concept of pharmaceutical water systems

2.1 Prevention of Microbial Contamination

Form the hygiene of drug production standpoint, the microorganisms' contamination of the raw materials, production environment and finished products is the important factor causing production failure and finished products rejection. The Annex 1 *Sterile Drugs* of the *Chinese Good Manufacturing Practice* (2010 *Revision*) stipulates that "*the production of sterile drugs must meet the requirements of quality and intended use, reduce the contamination of microorganism, various particles and pyrogens to the maximum. The skills, received training and work attitude of the production personnel are critical factors to reach the above objectives. The production of sterile drugs must be in strict accordance with well-designed and validated methods and procedures. The sterility and other quality attributes of the product never only depend on any form of terminal treatment or finished product inspection*".

To ensure the medication safety, the final quality of sterile drugs should comply with relevant requirements of pharmacopoeia, and injections must adopt an aseptic production process and ensure the finished products is sterile and free of pyrogen. An aseptic production process is a method of producing sterile preparations under the conditions of aseptic control. Aseptic filling and lyophilization are the most common aseptic production process, and the latter must adopt filtration sterilization during the production process. Aseptic production process should have the cleanliness of the production environment strictly monitored, and filtration conducted under conditions of aseptic control. Relevant equipment, packaging containers, stoppers and other articles should be sterilized with appropriate methods, and secondary contamination prevented. The sterility assurance in the aseptic production process should be validated by media fill validation. During the production process, the sterile air quality in the production environment, the proficiency of operators and sterility of each article should be strictly monitored. An aseptic production process should be validated periodically, including the validation of the effectiveness of air filtration systems and media fill validation test.

Table 2.1 The oretical value of bacterial reproduction

Time/h	Bacterial population	Time/h	Bacterial population
0	1	3.33	1,024
0.33	2	3.67	2,048
0.67	4	4	4,096
1	8	5	32,768
1.33	16	6	262,144
1.67	32	7	2,097,152
2	64	8(batch 1)	16,777,216
2.33	128	16(batch 2)	281,470,000,000,000
2.67	256	24(batch 3)	4,720,400,000,000,000,000,000
3	512		

An aseptic production process has strict requirements on the environment of drug liquid preparation. For example, the preparation of a basic medium solution can be divided into terminal sterilization and non-terminal sterilization (filtration sterilization); a solution requiring sterilizing filtration or sterilization during the production process should be prepared in a grade C area at least, and a product requiring no sterilizing filtration or sterilization after preparation must be prepared in local grade A area with the background of grade B. The cleaned utensils should be stored in a grade D area at least. The solutions used during the production process include diluent and buffer solutions, etc. For the preparation of such solutions, sterilizing filtration is usually used, and preparation is done in grade C area at least.

2.1.1 Introduction of Microorganisms

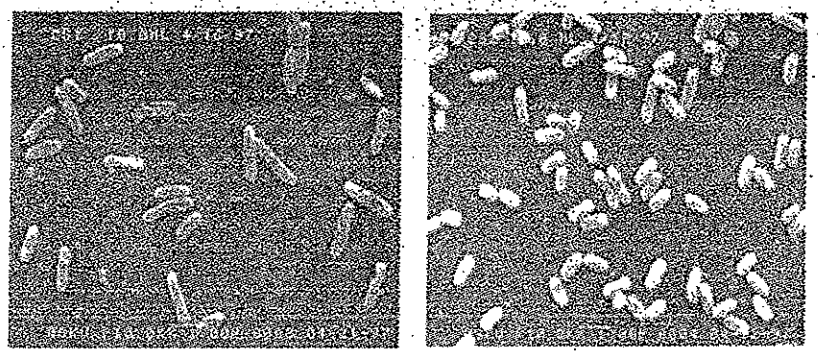
Microorganism is the general term for very small organisms which cannot be seen with the naked eye, but can be observed under magnification of hundreds of times, thousands of times and even tens of thousands of times when using an optical microscope or electron microscope. All raw water contains microorganisms, i.e. bacteria, fungi, algae and viruses. The general size of bacteria is 1-3 μm, microorganisms can be regarded as colloidal substance, which is removed according to the pretreatment method of preventing colloid contamination, but the difference from lifeless particles is the reproductive capacity, it can form biological films in appropriate survival conditions.

Microorganisms have characteristics such as small size, simple structure, rapid reproduction, easy variation, great variety, wide distribution, etc. Theoretically, if only one bacterium survives in the system and calculation is done on the basis of fissiparity once per 20 min, it will cause serious microbial contamination within 24 hours (Table 2.1).

Certainly, it is impossible for microorganisms to reproduce constantly at a geometric logarithmic rate due to the impact of the reproduction environment, nutrient substances and physiological properties of the microorganism itself, etc. However, if *R. pickettii* bacteria are taken as an example, the bacterial population will be increased in multiples within 24h (Fig 2.2). The risk of microbial contamination in pharmaceutical water will be increased due to the rapid increase of microbial reproduction as time goes by.

Microorganisms can be classified into three types according to features such as the existence of basic cell structure, differentiation degree, chemical composition, etc. The first type is noncellular microorganisms, which has no cellular structure, no enzyme system for generating energy, and is composed of single nucleic acid (DNA/RNA) and protein capsid. It must proliferate in viable cells; viruses belong to this type of microorganisms. The second type is the prokaryotic cell microorganisms, which have low cell nucleus differentiation, only have nucleoids containing DNA. It has no nucleolus and nuclear membrane. This kind of microorganisms includes bacteria, chlamydia, mycoplasma, spiochete and actinomycete. The third type is an enkaryocyte microorganism, which has a high cell nucleus differentiation, nuclear membrane, nucleolus and chromosome, and can perform karyokinesis, such as fungi, algae, etc.

Most microorganisms are beneficial to humans and



(a) 0 hour (b) 24 hour

Fig 2.2 Rapid reproduction of microorganism

animals. Microorganisms are widely used in agriculture, food, pharmaceutical, brewing, leather, petroleum and other industry, and play a more and more important role. For example, yogurt, liquor, antibiotics, vaccines, etc. which are closely associated with our daily life. Some microorganisms may cause disease to humans, animals and plants, these microorganisms with pathogenicity are called pathogenic microorganism, many infectious diseases (influenza, typhoid fever, dysentery, tuberculosis, poliomyelitis, virus hepatitis, etc.) in humans are caused by pathogenic microorganisms.

a. Bacteria. Bacteria are widely distributed; they are a type of prokaryotic microorganism with a thin and short cell, simple structure, tenacious cell wall and vegetative propagation by means of binary fission. Although bacteria are small, they have a cellular structure and functions. Cell wall, cell membrane, cytoplasm and nucleoplasm are present in various bacteria as basic structure.

The most commonly used instrument for observing bacteria is the optical microscope, bacteria size can be measured with a micrometer under the microscope, usually the micrometer can be taken as the unit. Bacteria are mainly divided into coccus, bacillus and spiral bacteria based on the bacterial morphology. The diameter of most coccus is about 1 μm, and they have spherical or near-spherical shapes. Different arrangements can be formed due to the differences in the division surface when propagating. They can be further divided into *diplococcus*, *streptococcus*, *staphylococcus*, etc. The morphology of the bacillus mostly appeares as a straight rod shape, some thallus are slightly bent and exist dispersedly or arranged in catenation. They are divided into *corynebacterium*, *bacillus catenulus*, *coccobacillus* etc. The shape of spiral bacteria is bent, appears as an arc or spiral, e. g. *helicobacter*.

Binary fission (fissiparity) is the most common and primary mode of reproduction. The cell lengthens and the chromosome is duplicated before fission, and is perpendicular to the macroaxis for fission, the plasma membrane near the cellular equator constricts and forms a diaphragm and diaphragmatic wall, so that two sub-cells are generated. The bacteria grow very fast and divide once about 20min. At this division rate, the bacterial colony will grow to an inconceivable extent, but actually, due to the gradual consumption of nutrient substances and gradual accumulation of harmful metabolites during bacterial reproduction, it is impossible for bacteria to reproduce infinitely at such high rate. After a period of time, the rate of bacterial reproduction will be gradually slowed, and the number of dead bacteria is increased, the growth rate of viable bacteria will be decreased accordingly and trend to stagnation.

A single or a few bacterial cells will form many visible daughter cell groups with a certain structure by the taking parent cell as a center. It is a bacterial colony. A bacterial colony often appears wet, viscous, smooth, transparent, and easy to remove from surface, the texture is uniform, the positive and negative surfaces or edges have the same color as the central part, etc.

b. Fungi. Fungi are eukaryocyte microorganisms, and have a cell wall but no chlorophyll, survive through parasitism or pythogenesis and conduct asexual or sexual propagation. Fungi are divided into single cell and multiple cell. Single cell fungi are round or oval, these are called yeasts. Multiple cell fungi are composed of hypha and spores, and interweave into clusters, which are called filamentous bacteria or mol-

ds. The most suitable temperature for fungi growth is 22-28℃, and the most suitable pH is 4-6. Its reproductive capacity is strong, but growth speed is lower than that of bacteria, it usually requires 1-4 weeks to form a bacterial colony. The thermal resistance of fungi is not strong; they are usually killed at 60-70 ℃ for 1h. Fungi are sensitive to 2.5% iodine and 10% formaldehyde, but resistant to dryness, sunlight, ultraviolet rays and some chemical sanitizers.

Yeasts are widely distributed in nature; they grow best in a slightly acidic environment where sugar is available, e.g., a very common growing environment is on the surface of fruits, vegetables and nectars. Yeast is a single cell eucaryotic microbe; its cell usually has the shape of a sphere, oval, sausage, ellipse, lemon or lotus rhizome knot, etc. It is much larger than an individual bacterial single cell, usually between (1-5) μm×(5-30) μm. Yeast has the typical structure of eukaryocyte with cell wall, cell membrane, cell nucleus, cytoplasm, vacuole, mitochondria, etc. Yeast has various modes of propagation, including asexual propagation and sexual propagation. The scientific community calls the yeast with only asexual propagation "false yeast", while the yeast with sexual propagation is known as "real yeast". The characteristics of the colony of most yeasts are similar to that of bacteria, but it is larger and thicker than the bacterial colony, the surface of a colony is smooth, wet, viscous, easily removed from the substrate; the texture of a colony is uniform, the positive and negative surfaces and edge have the same color as the central part. The colony is creamy white; some are red, even black.

Molds are commonly known as filamentous fungi, also known as "mold fungi". They usually form a mycelium with flourishing branches, but do not generate large-scale sporocarps like mushrooms. The mold trophozoite grows in the form of a hypha, which is a tubular filament, and looks like a transparent sebific duct when observed under a microscope. Its diameter is usually 3-10 μm, which is several to dozens of times thicker than a bacterial cell. The hypha can extend and generate branches, and if many branches of hypha are interwoven they form a mycelium. Molds have very strong reproductive capacity, and the modes of reproduction are various. In nature, molds are reproduced by means of generating all forms of spores. Spores are something like vegetal seeds, but very small and in large numbers. The spores of molds are small, light, dry, in very large numbers, with different forms and colors, long period of dormancy and strong stress resistance, etc. The number of spores generated by each hypha is hundreds of thousands, and sometimes tens or even hundreds of billions, or much more. These characteristics help mold spread and propagate anywhere in nature. For human activities, these features of spores are helpful for inoculation, enlarged cultivation, strain screening, preservation and identification, etc. and the disadvantages are that they easily cause contamination and mildew, and spread mold diseases of animals and plants. The mold hypha of is thicker and longer, therefore, it bacterial colony is larger, and some mold hyphe can extend with no limitation. The texture of the (mold) bacterial colony is usually relatively loose, with a dry and nontransparent appearance. It appears as a tight or loose spider web, a villiform or flocculent texture. The bacterial colony is tightly connected to the attachment and difficult to pick. The color of positive and negative surfaces and edges of the bacterial colony can be different from the color of the center.

c. Virus. Virus is a non-cellular microorganism, which is widely distributed in nature, lives in humans, animals, plants, fungi and bacteria and causes infection. A virus is a microorganism with the smallest volume and simplest structure. It only has one kind of nucleic acid (DNA or RNA) as its genetic material. A virus must live in a viable host cell to complete its reproduction depending on the energy, nutrient substance and biomacromolecule synthesis mechanism provided by the cell. Viruses have s close relationship with human beings, and about 75% of infectious diseases are caused by viruses. Some viruses have very strong infectivity, which can cause pandemics (e.g. influenza, HIV, etc.). The volume of a virus is very small, and most viruses can only be seen under magnification of thousands of times or tens of thousands of times using an electron microscope. The morphology of viruses can vary; it can be divided into three types: baculoviruses, spherical viruses and combinations of these two morphologies

A virus has no cell structure, the main ingredients of a virion are nucleic acid and protein, which are proliferated by replication of the nucleic acid and assembly of nucleic acid protein with the help of the host cell. The structure of a virus usually includes helical symmetry, icosahedral symmetry and complex symmetry. A virus

can propagate only in a viable host cell, and the proliferation of a virus is not done by binary fission, but takes the genome as a template, and combines DNA polymerase or RNA polymerase and other necessary factors to replicate the genome of the virus by a complex biochemical synthesis process. At that moment, the biochemical synthesis of the host cell is inhibited, and the virogene generates a large amount of virus protein through the process of transcription and interpretation, etc. and finally releases the progeny virus through assembly. The proliferation of a virus using the nucleic acid as a template is known as self-replication.

Most viruses can resist cold but not heat, the infectivity of a virus can be maintained for several months or even several years at dry-ice temperature (−70 ℃) and liquid nitrogen temperature (−196 ℃), while it can be inactivated at 50-60 ℃ for 30 min, or at 100 ℃ for several seconds. Most viruses are stable at pH 5-9; they can be inactivated in strong acidic or alkaline conditions. Additionally, X rays, γ rays and ultraviolet rays can inactivate viruses. The chemical agents for inactivating viruses are mainly chemical disinfectants antibiotics, Chinese herbal medicines, etc. Except for strong acid and alkaline sanitizers, phenols, oxidants, halogens, alcohols have inactivation effect to viruses.

2.1.2 Sterility Test

A sterility test is a method of detecting whether the drug products, medical devices, raw materials, excipients and other items required to be sterile by pharmacopoeia are sterile. If the test sample complies with the stipulations of the sterility test method, it only indicates that microbial contamination is not detected in the test sample under the test conditions. In pharmaceutical water systems, some of the product water, as stipulated by the pharmacopoeia, must meet the requirements of the sterility test. For example, sterile purified water, sterile water for injection, etc. The raw material water, such as purified water, high purity water and water for injection itself is not required to meet the requirements of the sterility test, for example, the microbial limit of purified water is 100 CFU/ml, the microbial limit of water for injection is 10 CFU/100 ml. The GMP has strict requirements on microbial control of raw material water; pharmaceutical water systems must undergo periodic sanitation or sterilization procedures, especially for water for injection that has direct contact with products. How to prevent microbial contamination has become the most critical issue for pharmaceutical water systems, therefore, this book presents detailed explanations to the relevant requirements of the sterility test.

A sterility test should be performed in a unidirectional air flow area with grade A cleanliness or an isolation system; the whole process should be in strict accordance with aseptic operation requirements to prevent microbial contamination. The measures for preventing contamination should not affect the detection of microorganism in the test samples. The unidirectional air flow area, work bench and environment should undergo cleanliness validation according to the current national standards of *Test Method of Airborne Particle, Airborne Microbe and Settling Microbe in Cleanrooms (Areas) of Pharmaceutical Industry* (GB 16294—2010). An isolation system should be validated as per relevant requirements; the cleanliness of the internal environment should comply with the requirements of the sterility test. Routine tests should include the monitoring of the test environment. The personnel involved in sterility test must have specialized knowledge of microorganisms and receive training on aseptic techniques.

The main purpose of implementing a sterilization method is to kill or remove all microbial vegetative forms and spores, improve the safety of pharmaceutical preparations to the maximum, protect the stability of preparations, and ensure the clinical effects of preparations. Therefore, the research and selection of effective sterilization methods has significant importance on the product quality assurance. In pharmaceutical industry, the common sterilization methods can be divided into physical sterilization methods and chemical sterilization methods. The techniques used to kill or remove microorganisms by means of heating, radiation and filtration methods using the characteristics of proteins and nucleic acids which are unstable when exposed to heat and radiation are physical sterilization methods, also known as physical sterilization techniques, which include dry heat sterilization methods, moist heat sterilization methods, sterilizing filtration methods and radiation sterilization methods, etc. A chemical sterilization method means killing microorganisms by direct chemical action. The chemicals used can be divided into gaseous sterilants and liquid steri-

lants, for example, ethylene oxide is one type of gaseous sterilant.

The *General notice* 1421 *Sterilization Method* in Volume Ⅳ of the *Chinese Pharmacopoeia* (2015) stipulates that sterile articles means that the articles contain no viable microorganisms. The commonly used sterilization methods include moist heat sterilization, dry heat sterilization, radiation sterilization, gas sterilization and filtration sterilization. One or more combinations of multiple methods can be adopted for sterilization according to the characteristics of the articles to be sterilized. If it is acceptable for the articles, terminal sterilization should be adopted for sterilization as far as possible. If the articles are not suitable for using the terminal sterilization method, filtration sterilization or aseptic production processes can be selected to meet the requirements of sterility assurance. If possible, the non-terminal sterilization articles should be treated with supplementary sterilization, e. g. circulated steam sanitation can be adopted.

2.2 Prevention of Particles Contamination

In recent years, the hazards caused by foreign matters and particlescontamination in injections have been subject to public scrutiny. Larger particles may cause local circulatory disturbances, and induce vascular thrombosis. Too many particles may cause local blood flow blocking and insufficient blood supply, histanoxia and induce edema and phlebitis. The foreign matters will invade the tissue and cause the proliferation of macrophage, inducing granuloma. Additionally, particles may cause anaphylaxis and pyrogen reactions. Therefore, if the injections contain a large amount of foreign matter which is invisible to the naked eye, there's a potential for danger even in the long-term. The identified particles in injections include carbon black, calcium carbonate, zinc oxide, cellulose, scraps of paper, clay, chips of glass, bacteria, fungi, fungal spores, crystals, etc. In order to ensure the product quality, the *Chinese Pharmacopoeia* (2015) specifies the particle size and allowable limit.

There are many reasons for the generation of particles.

a. Problems in the process operation, e. g., air cleanliness in the workshop is inadequate, infusion bottles, rubber stoppers and membranes are not clean, the selection of the filter is inappropriate, and the filtration method is not good, the filling operation does not comply with requirements, process design is inadequate, etc. In recent years, measures such as isolators or RABS air purification and isolation systems, deep bed filters, linkage production lines, etc. have been taken taken to solve the problems besides, strengthening the process management to greatly improve the clarity of injections.

b. Packaging materials contaminate the drug liquid. After analyzing "small particles" in the infusion solution it is found that they contain calcium, zinc, silicate, iron, and other substances. In a sodium chloride solution stored for 11 years calcium and magnesium were detected, these substances were mainly from the rubber stopper and glass container. A contrast test was conducted on an infusion solution packed in a polyvinyl chloride bag and one packed in a glass bottle by shaking the test samples for 2 hours continuously; it is found that the number of particles (2. 3-5 mm) produced in the former is 5 times the number in the latter. The first sample was analyzed by thin layer chromatography and infrared broad spectrum and it was found the particles are made of plasticizer di-(2-ethylhexyl) phthalate (DEHP), which is a substance hazardous to the human body.

c. Impact of raw and auxiliary materials, e. g. glucosefor injection may contain a small amount of protein, incompletely hydrolyzed dextrin and calcium and sometimes other impurities. Sodium chloride and sodium bicarbonate (raw materials) contain calcium salts, magnesium salts and sulfates. Calcium chloride raw materials contain more alkaline substances [e. g., $Ca(OH)_2$, $CaCl_2$, CaO, $CaCl_2$]. The presence of these impurities may make infusion solution exhibit opalescence, small particles and turbidity. Active carbon is the most commonly used auxiliary material for clarity and adsorption, it contains many impurities, which not only affects the clarity of the infusion solution, but also affects the stability of the drug liquid, therefore, the quality of raw and auxiliary materials must be in strict accordance with the established specifications in China.

Pharmaceutical water is the most used process raw material and cleaning reagent in the pharmaceutical production, the content of particles in the purified water, water for injection and pure steam must be strictly controlled. During the generation of pharmaceutical water, the main function of the pharmaceutical

water generation unit (e. g. purified water generator, water distillator, and pure steam generator) is to stably provide pharmaceutical water complying with specifications stipulated in the pharmacopoeia for the storage and distribution systems. The unit operation steps such as mechanical filtration, softening and distillation, all contribute to the removal of a large number of particles in the raw water. The stipulations on the items such as clarity and nonvolatile matters in pharmacopoeia are also to control the particles contamination in pharmaceutical water effectively. Under normal conditions, the generation equipment for pharmaceutical water can control the content of particles in generated water perfectly. During the pharmaceutical water storage and distribution process, the system itself has no purification function. It has been proved by practice that the risk of particle contamination in pharmaceutical water systems mostly occurs in the storage and distribution process. During the design, selection, installation and operation phase of the whole pharmaceutical water storage and distribution systems, the following are main causes of particle contamination:

• The quality of the systems components does not comply with the design requirements. For example, the material of pipeline does not comply with the 316L standard; the material of the EPDM/PTFE diaphragm does not comply with FDA requirements; the spray ball sheds off scraps of iron; the particle contamination caused by the air source or oxygen source ozone generator (including the release of cancerogens), etc;

• The design of the pipeline system does not comply with actual operation requirements, which results in "suck-back of dirty air" in the point of use pipeline;

• External contamination caused by damage of the vent filter element;

• Inadequate cleaning caused by dead leg exceeding $3D$, which results in out of specification of residues;

• Cleaning residue out of specification caused by insufficient polishing of system components;

• Rouge caused by inadequate pickling and passivation of the system;

• Corrosion of welded junctions caused by excessive oxidation of weldings, resulting in rouge;

• Rouge caused by too high temperature of circulating water;

• Personnel contamination risk caused by manual operation;

• Secondary contamination caused by suck-back of dirty air in the drainage pipeline after the "complete drain" following the system disinfection;

• Inadequate self-draining of the system caused by insufficient slope;

• Inadequate self-draining of the system caused by inappropriate equipment selection, e. g. vertical transfer pumps and double-tube plate heat exchangers are adopted in the storage and distribution systems;

• The water quality index of the water generation equipment is too low, which causes exogenous particle contamination of the storage and distribution system;

• Exogenous contamination caused by use of single plate heat exchangers;

• Ozone water contamination caused by insufficient degradation by ultraviolet lamp after ozone disinfection;

• Chemical sanitizer residual risk present after the chemical sanitation of RO/EDI;

During the actual operation of pharmaceutical water systems, the particle contamination caused by rouge happens frequently due to the extensive use of stainless steel construction materials, the impact of the high temperature operating environment and welding, passivation and other factors. Fig 2. 3 shows class I rouging after the centrifugal pump of a water for injection system was run for about 6 months. At present, rouge is the leading particle contamination source in pharmaceutical water systems. How to avoid rouge contamination caused by the operation of the system has been a major concern for most pharmaceutical enterprises.

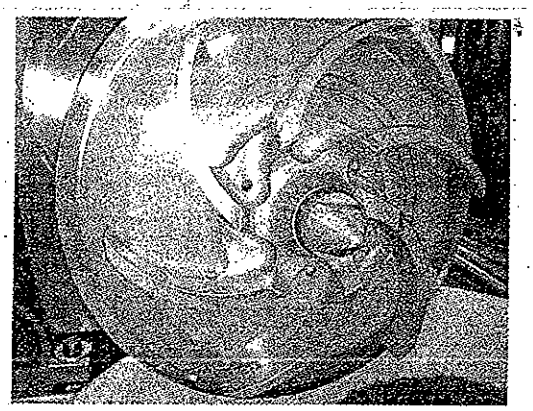


Fig 2. 3 Class I rouge in the centrifugal pump chamber

In order to reduce the risk of rouging in pharmaceutical water systems, it is recommended to adopt the concept of "*Quality by Design*" for adequate design

and strict control of welding and passivation quality, and avoidance of the risk of rapidly generating rouge. For example, lower the circulating temperature of water for injection system appropriately and maintain it at 70-85 ℃; strictly adhere to the 3*D* dead leg principle in the system to prevent crystal corrosion caused by residues; select fixed or rotary spray balls with reliable quality to prevent the introduction of exogenous iron ions caused by shedding of iron scraps; ensure good pickling and passivation and generate passive film effectively; conduct periodic maintenance and passivation for the system to regenerate the passive film; select raw materials with quality assurance for system installation, conduct system traceability to the material certificate of stainless steel pipe fittings to ensure the quality and polish of 316L stainless steel; weld in strict accordance with standard operating procedures for welding, etc. For this purpose, the writer addresses the hazards, mechanism of production and prevention of rouge and relevant contents in Chapter 9 and Chapter 10 of this book.

2.3 Quality Influencing Factors

Quality is the source of enterprise development, and the quality reliability of the pharmaceutical water systems is the cornerstone of the product quality assurance of a pharmaceutical enterprise. Along with the implementation of international strategies by more and more Chinese pharmaceutical enterprises, the design and validation of the pharmaceutical water systems, which is as one of the critical systems in the construction of the whole facility, have become the emphasis for renovated and new projects in domestic pharmaceutical enterprises.

Innovation in the pharmaceutical industry is constantly introduced on a global scale, and the scientific technology related to the pharmaceutical industry is also developing rapidly, especially the filtration technology having direct relation to drug production and safety. The root causes of all these are originated from the assiduous seek to natural science and unremitting efforts by human beings. The more the humans know, the more motive the humans decrypt the unknowns and update the backwards.

In pharmaceutical industry, product safety is the most important factor from the perspective of a country or a region of the world, or the drug manufacturer and supervising agencies. Any processing or treatment can only be accepted by the industry and the public if through scientific evidence is provided. Therefore, safer and more effective technologies, with an emphasis on energy conservation and emissions reduction, innovative process methods and equipment will be used in the future, fostering a fresh and vibrant growth of the pharmaceutical industry.

For a better understanding of the importance of quality to pharmaceutical water systems, it is critical to analyze in detail various designs affecting the water quality of the pharmaceutical water systems and the design attributes during operation. Factors such as calculation, dead leg, polish, slope and modularized design are critical design attributes affecting the pharmaceutical water systems.

2.3.1 Dead Leg

The dead leg inspection is an important item during the installation qualification (IQ) of the system. The existence of any dead leg may cause contamination of the whole system in pharmaceutical water systems. The risk brought by an oversized dead leg is mainly includes:

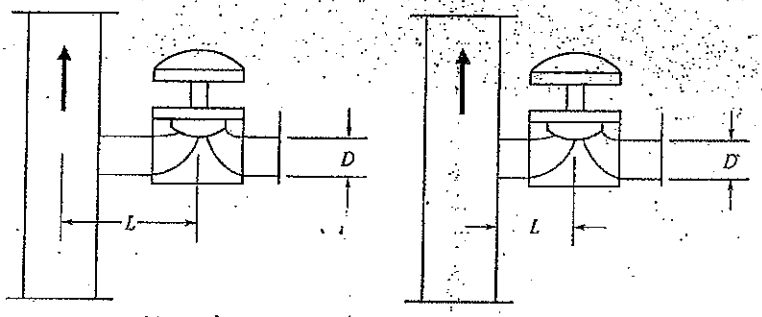
a. Provide a "hotbed" for microbial propagation and result in the formation of "biological films" causing out of specification microorganism, TOC or endotoxin, and cause the specification of water to not be in compliance with pharmacopoeia requirements.

b. Secondary contamination caused by inadequate system sanitation or sterilization.

c. Secondary particle contamination or product cross contamination caused by inadequate system cleaning. Therefore, the *Chinese GMP* (2010 *Revision*) requires "*the design and installation of the pipeline should avoid dead leg and blind pipe*".

The American Society of Mechanical Engineers Bioprocessing Equipment Standard (ASME BPE) (2014) has the exact definition on dead leg as an area of entrapment in a vessel or piping run that could lead to contamination of the product.

In 1976, the US FDA has performed quality management on dead leg with a quantitative method for the first time in the CFR 212; it is commonly known as "6*D*" principle in engineering, which is defined as follows: "when $L/D<6$, it is demonstrated that there is no dead leg", in which, L refers to the distance from the center of the main pipeline at the flow side to



(a) 6D rule (b) 3D rule

Fig 2.4 Development of dead leg

the blind plate in the branch (or the center of the point of use valve), D is the diameter of branch. Subsequent research indicates that $3D$ principle is better from the point of view of compliance with the requirement of microbial control in clean fluid process systems, and the definition of L is changed to the distance from the wall of the main pipeline at flow side to the blind plate in the branch (or the center of the point of use valve) (Fig 2.4).

A more accurate dead leg quantitative definition is from the ASME BPE standard (Fig 2.5). The definition explicitly stipulates that L is the distance from the internal wall of the main pipeline at flow side to the blind plate in the branch (or the center of the point of use valve). D refers to the inner diameter of the branch pipeline at non-flow side.

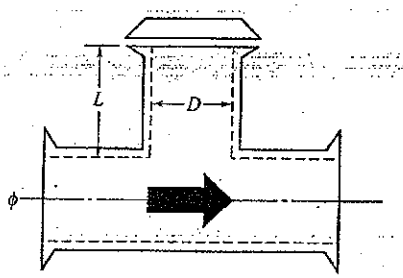


Fig 2.5 Exact quantitative definition of dead leg

Sanitation validation of dead leg: The branch with the dead leg of less than $3D$ (L/D equals to 0, 1.5 in the figure) can reach the predetermined sanitation temperature quickly. The branch cannot always reach the predetermined sanitation temperature, when the flow rate of the dead leg that is more than $3D$ (L/D equals to 4.0, 5.6, 9.4) vertically downward or upward at the branch is 0.4 m/s to 1.2 m/s; if the flow rate is increased to 2.0 m/s, except for the $4D$ branch vertically downward which can reach the sanitation temperature (Fig 2.6), other branches cannot constantly reach the predetermined sanitation temperature (Fig 2.7). The above experiment indicates that the dead leg is a critical factor, while the flow rate is a subcritical factor affecting branch cleaning.

Cleaning validation of dead leg: Fig 2.8(a) shows a simulation of a dead leg (as per the "ASME BPE definition"), the L/D of the dead leg is 6, the preset number of detectable particles at the dead leg is 10^5, and the acceptable criteria of cleaning is the final number of residual particles $<10^2$. It can be seen from the figure that when the cleaning flow rate is 0.5 m/s, the number of residual particles at the dead leg will be obviously decreased at the beginning of cleaning, but when the cleaning time exceeds 10 min, the number of residual particles will be maintained at a level higher than 10^4, and the number of particles is not reduced any more. When the cleaning flow rate is increased to 1.0 m/s, the number of residual particles at the dead leg can be reduced from 10^5 to 10^3 within 20min of cleaning time. When the cleaning flow rate is increased to 2.0 m/s and 2.5 m/s, the data curve of the cleaning validation is basically consistent, i.e., the number of residual particles at the dead leg can be reduced from 10^5 to 10^2 within a very short cleaning time (about 1-2 min), but it cannot reach the acceptable criteria for cleaning.

The dead leg L/D in Fig 2.8(b) is 2.8, it assumes the same work conditions and acceptable criteria for cleaning. It can be seen from the figure that when the cleaning flow rate is 0.5 m/s, the number of residual particles at the dead leg will be obviously decreased at the beginning of cleaning, but when the cleaning time exceeds 1min, the descending range of the number of residual particles is not large. When the cleaning time exceeds 10 min, the number of residual particles will be maintained at 10^2, and will not reach the acceptable criteria for cleaning. When the cleaning flow rate is increased to 1.0 m/s, the number of resid-

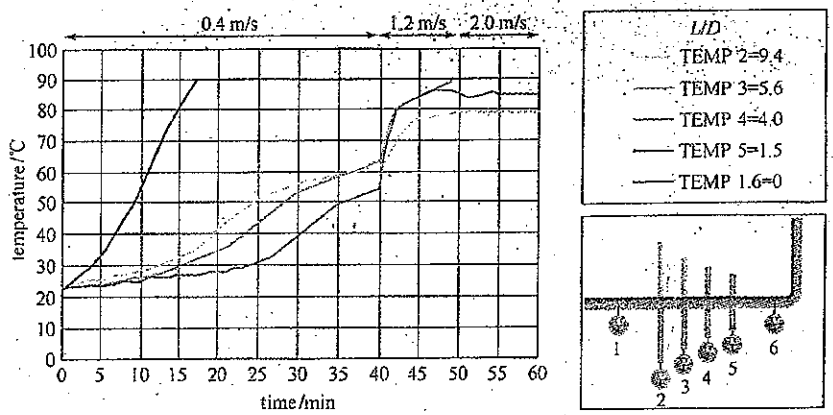


Fig 2.6 Sanitation validation of dead leg when the branch is vertically downward

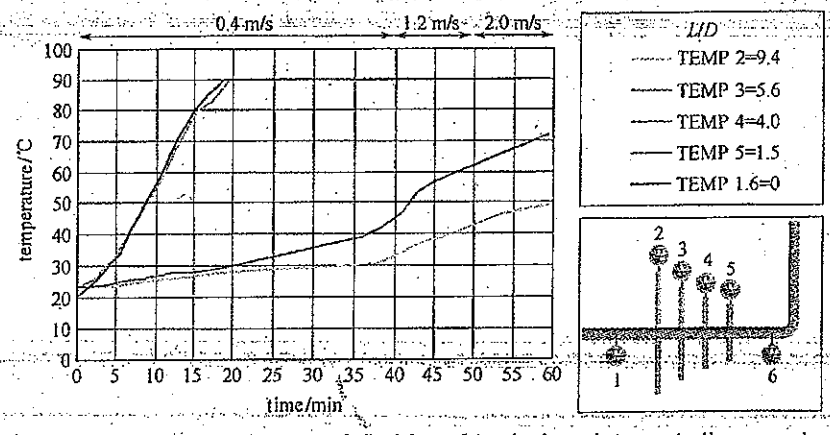


Fig 2.7 Sanitation validation of dead leg when the branch is vertically upward

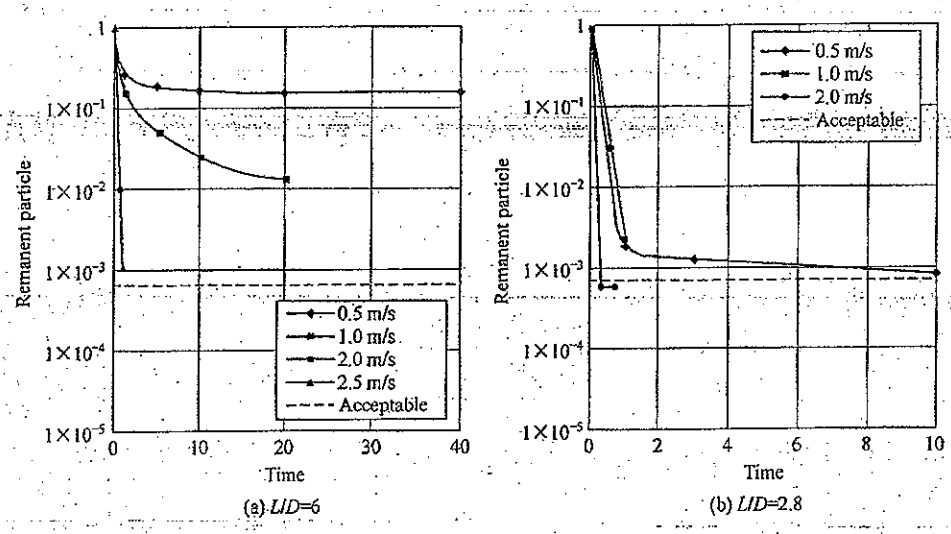
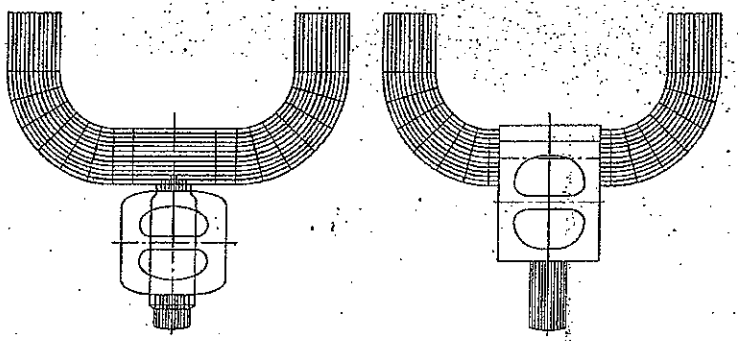


Fig 2.8 Cleaning validation of dead leg

ual particles at dead leg will be obviously decreased within a very short cleaning time. When the cleaning flow rate is increased to 2.0 m/s, the number of residual particles at the dead leg can be decreased from 10^5 to an acceptable number for cleaning within an extremely short cleaning time (about 10-20 s), and then it is maintained at this low level.

The above model further indicates that the dead leg is a critical factor, while the flow rate is a subcritical factor affecting branch cleaning.

In fact, from the point of view of the abovementioned sanitation validation and cleaning validation, it is obvious that the 3*D* dead leg principle in the design and processing of pharmaceutical water systems is ac-



(a) Design of U bend (b) Design of valve with no dead leg

Fig 2.9 Control of dead leg of the water point of use valve

ceptable. Most of the GMP regulations have no specific stipulations for the maximum value of dead leg standard (except the WHO GMP), and some GMPs only give suggestions for controlling the 3*D* dead leg in the inspection guides. The "3*D* principle" for the dead leg has been widely accepted and promoted by the pharmaceutical industry.

Most enterprises following the Chinese GMP, EU GMP, WHO GMP and the US FDA cGMP use the 3*D* principle ($L<3D$) as the inspection standard for dead leg during installation qualification. Because the risk of cross contamination in pharmaceutical processes such as biological fermentation is relatively large, the ASME BPE standard requires the biopharmaceutical enterprises to utilize the much stricter "2*D* principle" ($L<2D$) as the inspection standard for dead leg during installation qualification.

There are many design concepts for controlling dead leg in the design of pharmaceutical water systems. For example, the installation of point of use valves of pharmaceutical water can be done using two methods. The first method is to connect a U bend with a two-way valve, and the second method is to install a T type valve with no dead leg. Both of above methods can meet the requirements of 3*D* dead leg (Fig 2.9). The first installation method is less costly than the installation method using the valve with no dead leg, but its risk of microbial contamination is increased, therefore, it is recommended by the ISPE that consideration should be given to compensating for the risk of microbial contamination by increasing the lowest speed if a two-way diaphragm valve with larger pipe diameter is used instead of the T type valve with no dead leg.

Automatic argon arc welding is the safest connection method for stainless steel components. The automatic welding of the U bend and two-way diaphragm valve will not affect the replacement and maintenance of the diaphragm of diaphragm valve. This valve is a diaphragm valve and known as "welding at one end and clamp at the other end" specially developed by the supplier according to the actual requirements of the engineering company or customer (Fig 2.10). It can be identified by comparing to the standard sizes of diaphragm valves used in the pharmaceutical industry; the combination of the two-way diaphragm valve and U bend with specifications according to DN25 for automatic argon arc welding should meet the requirements of 3*D* dead leg for water point of use. The clamp connection of the DN25 valve and U bend would cause the dead leg to exceed 3*D*. Theoretically, manual welding of DN20 or DN15 valve and U bend can also comply with the 3*D* standard, but the quality of the junction welded by manual welding is very uneven, and the quality of the endoscope image is usually not ideal, so it is not recommended from an engineering perspective.

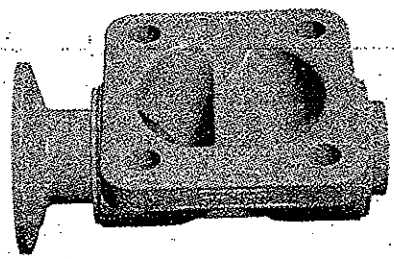
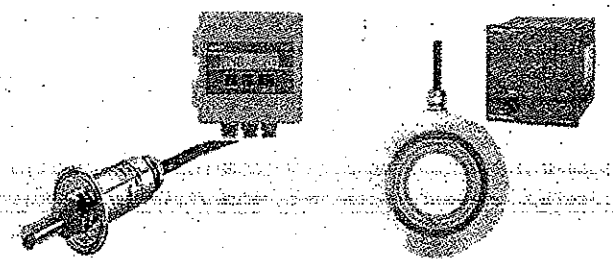


Fig 2.10 Diaphragm valve with welding at one end and clamp at the other end

Another typical design for controlling the dead leg is based on using various sensors. The commonly used sensors in the pharmaceutical water systems are divided into two types as per the design structure. The first type is plug-in sensors, and the second type is flow through sensors. The product-contact part of the flow through sensor is a straight pipe with no dead leg;

it is very convenient for cleaning and sterilization. Temperature sensors, pressure sensors, conductivity sensors and flow sensors can be designed as flow through type. Fig 2.11 shows structure diagrams of a typical plug-in sensor and a flow through sensor. Another example is a surface acoustic wave flow sensor (refer to Chapter 12 in this book for details), this is also a typical flow through sensor.



(a) Plug-in sensor (b) Flow through sensor

Fig 2.11 The structure of conductivity sensor

The 3*D* principle of dead leg is mainly applicable to the pharmaceutical water systems requiring bioburden control behind the section of RO, including purified water systems, high purity water systems and water for injection systems. For new pharmaceutical water systems, efforts should be made to make the whole system comply with the design principle of 3*D* dead leg, which is very effective in controlling the risk of microbial contamination in the whole system. It is recommended to strictly implement it during installation qualification. For gas systems, such as pure steam systems, clean nitrogen systems and clean compressed air systems, the "3*D* dead leg" principle is not necessary because of the systems' lack of water for microbial propagation or the systems go through moist heat sterilization for a long term. The GEP suggests the dead leg of above mentioned systems should be as short as possible. Additionally, the NA clamp (Fig 2.12) is also an effective method for controlling the dead leg in adapting pieces of tanks. It can realize no dead leg for installation of tank attachments, and resolve well the risk of possible microbial breeding at the connections of tank attachments.

It should be noted that "dead leg" refers to the area where product contamination is caused when pipelines or containers are used; an installation point exceeding 3*D* does not mean an actual "dead leg" exists at that point. For example, the return water pipe of water for injection at the sampling valve of the TOC detector usually has a small pipe diameter such as DN8

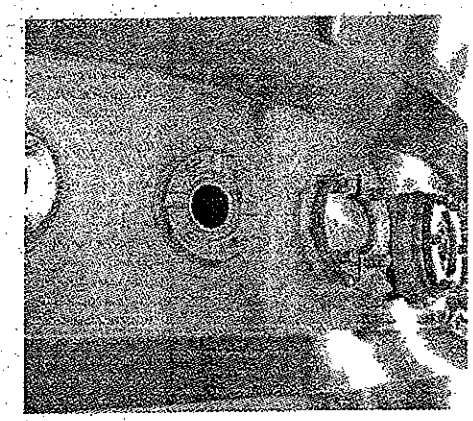


Fig 2.12 NA clamp

or DN15. Although the point cannot meet the 3*D* requirements, it stays in frequent self-rinsing state for a long term, the risk of microbial contamination can be controlled, and dead leg does not exist.

Compared with increasing the flow rate or polish degree of the pipe, implementing the 3*D* principle of dead leg has a relative small impact on the project investment of pharmaceutical enterprises, but it has significant importance on the quality assurance of fluid process systems, therefore, enterprises should make the dead leg control an important inspection item during the installation qualification of pharmaceutical water systems. Meanwhile, when the control of dead leg is not very good (e.g., exceeding 3*D*), the pipeline flow rate or sanitation frequency can be increased appropriately for compensation.

2.3.2 Polish Degree

The polish degree is also called surface roughness, which refers to microscopic geometrical shape characteristics composed of smaller space and peak valley on the processing surface (Fig 2.13). It is an important part of the material certificate of stainless steel raw materials, and an important inspection item when warehousing raw materials. The surface roughness of pharmaceutical water systems components should comply with the actual requirements of production, cleaning and sterilization of the pharmaceutical water. The treatment of internal surface roughness of stainless steel pipelines, pipe fittings and other raw materials has an important impact on pharmaceutical water systems.

The polishing treatment can significantly reduce the contact area of the system internal surface, which is helpful in reducing the residual amount transferred

by the pharmaceutical water systems and the risk of attached impurities, make the internal surfaces of pharmaceutical water systems smoother, and easy to clean, contribute to preventing microbial settling and propagation, and provide reliable assurance for the compliance with the microbial limit.

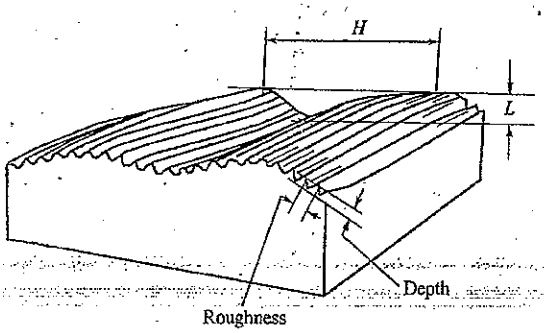


Fig 2.13 Surface roughness

In the pharmaceutical and biological industries, the treatment of internal surfaces is mainly realized by mechanical polishing and electropolishing. Mechanical polishing refers to polishing with special polishing machines to eliminate polishing scratches by means of very fine polishing powders and relative grinding and rolling actions generated between grinding surfaces. It can be divided into rough polishing and fine polishing. Electropolishing is based on the mechanical polishing, making the workpiece to be polished as the anode and an insoluble metal as the cathode, both of which are immersed into an electrolytic bath and imposed a voltage of 2-25 V causing a strong chemical reaction and the occurrence of selective anode dissolution doe to the effect of the current (Fig 2.14). Usually, the highest point of the metal surface is removed first by electropolishing achieving the effect of increased brightness of the surface of the workpiece.

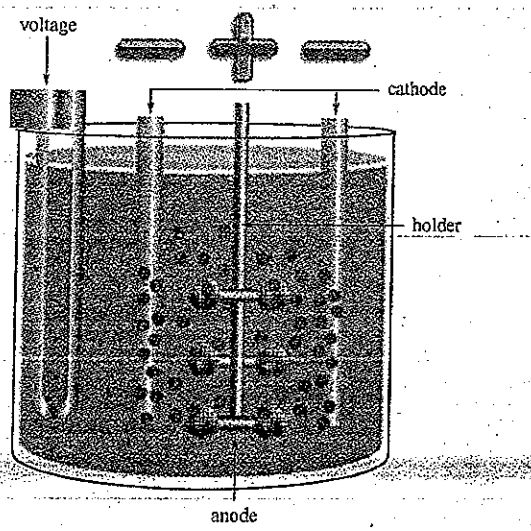


Fig 2.14 Schematic diagram of electropolishing

The critical factors of electropolishing include the electrolyte solution temperature, cathode amplitude (the distance from the cathode to the workpiece to be polished), acid solution mixing concentration and electrolysis time. Under normal conditions, the immersion time in the electrolytic bath is determined by the features of the workpiece to be polished. The ASME BPE prohibits strike plating electropolishing, i.e. the workpiece to be polished is taken out from the electrolytic bath for a very short time.

Compared with mechanical polishing, electropolishing can increase the corrosion resistance of the surface of the stainless steel pipeline, ensure the luster of the internal and external surface is consistent. Electropolishing can reveal surface defects after visual inspection, it can effectively reduce the internal surface area of the stainless steel, improve surface finish, help achieve rapid and efficient cleaning of the equipment, and remove surface inrush which can cause iron oxidization and discoloration resulted from mechanical polishing (Fig 2.15).

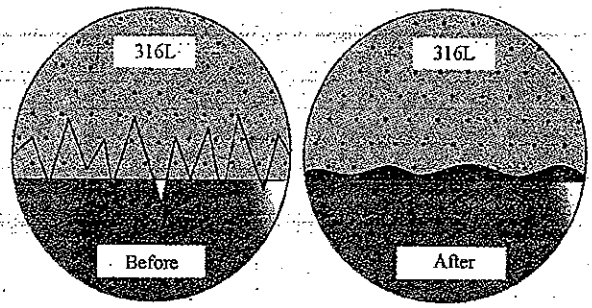


Fig 2.15 Effects of electropolishing

Electropolishing will remove the free iron on the surface, which is helpful to increase Cr/Fe ratio of the surface, enhance the passivation protective layer, and reduce the risk of rouge generation. Fig 2.16 shows mechanical polishing and electropolishing under a scanning electron microscope. It can be observed that the surface after electropolishing is smoother and flatter than after mechanical polishing. Therefore, the ASME BPE requires that the thickness of the passive layer after electropolishing should be not be less than 15Å.

The distance between two peaks or two troughs of the surface roughness is very short, usually it is below 1mm, and difficult to distinguish with the naked eye, and needs special instruments to be measured. The smaller surface roughness, the smoother surface of materials. The parameters used to evaluate the surface

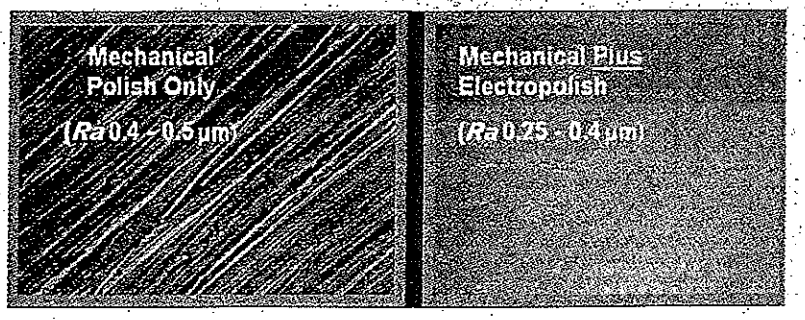


Fig 2.16 Mechanical polishing and electropolishing

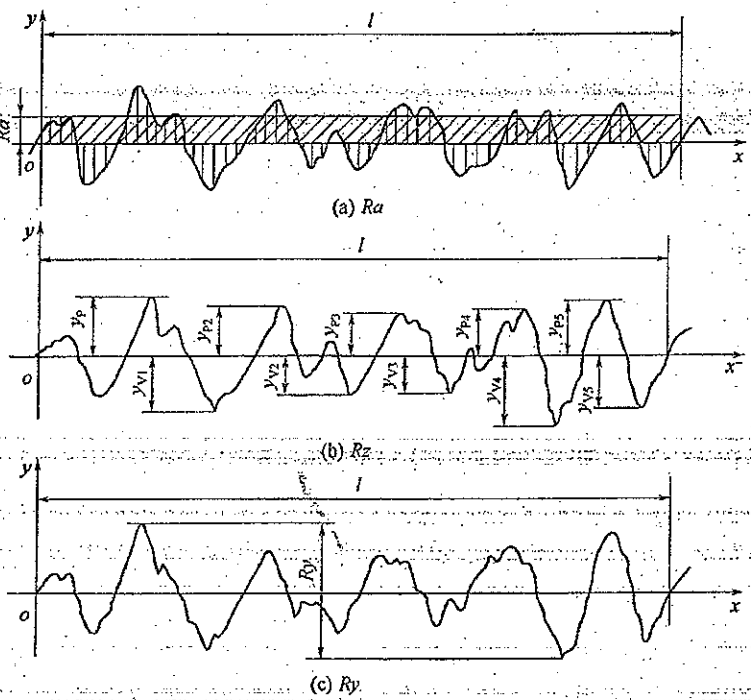


Fig 2.17 Parameters for evaluating surface roughness

roughness mainly include the arithmetic average deviation of the profile Ra, ten point height of microcosmic irregularities Rz and maximum height of the profile Ry, etc. Fig 2.17 shows the details.

a. The arithmetic average deviation of the profile Ra is the arithmetic average of profile offset distance absolute value within sampling length L, $Ra = \frac{1}{l}\int_0^l |y(x)|dx$ or appropriate as $Ra = \frac{1}{n}\sum_{i=1}^{n} |y_i|$, in which, profile offset distance y refers to the distance between a profile point and datum line in the measuring direction. The datum line is the least square center line 0, this line passes through the profiles and the square sum of the profile deviations from the line is the smallest. The Ra value can objectively reflect the microcosmic geometrical characeristics of the surface to be measured, the smaller Ra indicates the smaller peak valley distances on the surface to be measured i. e. a smoother surface, a larger Ra indicates a rougher surface. The Ra value can be measured by a contact pin type inductive profilometer; it is limited by the radius of the contact pin and the instrument working principle, it is mainly applicable to material surfaces with Ra between 0.025-6.3 μm, It is also the routine measuring method for the polish degree of stainless steel components in pharmaceutical solution preparation systems.

It should be noted that the smaller surface roughness Ra value (arithmetic average deviation of the profile) indicates the smoother surface, but Ra only represents the arithmetic average of profile offset distance within the sampling length. The rougher internal surface of the stainless steel pipe fitting, the easier to generate frictional wear, the non-uniform surface easily forms cracks and is subject to corrosion,

but it is also easier for contaminants to accumulate. In order to get an ideal *Ra* value, mechanical polishing of pipe fittings to be processed needs to be conducted, but during mechanical processing, it is inevitable to produce metal particles and other contaminants (Fig 2.18), additionally, various external mixing contaminants are all easy to remain on the surface of the pipe fittings. Therefore, the sanitary industry usually adopts the electropolishing process to enhance the smoothness of the surface of pipe fittings subjected to mechanical polishing, and remove contaminant residues effectively.

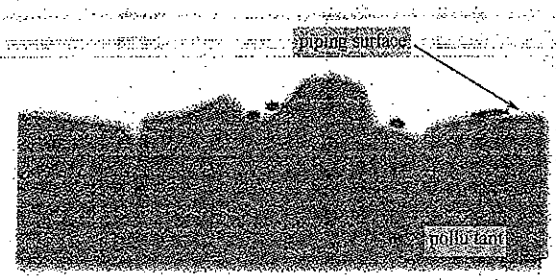


Fig 2.18 Contaminants on the internal surface caused by mechanical polishing

b. Ten point height of microscopic irregularities *Rz* is the sum of the average of 5 maximum profile peak heights and the average of 5 maximum profile valley depths, $Rz=\frac{\sum_{i=1}^{5} y_{pi}+\sum_{i=1}^{5} y_{vi}}{5}$, in which, y_{pi} is the i maximum profile peak height; y_{vi} is the i maximum profile valley depth.

c. Profile maximum height *Ry* is the distance between the profile peak top line and profile valley bottom line within the sampling length *L*.

Different standards correspond to different surface roughness, Table 2.2 shows the comparison results of particle size and surface roughness in different standards.

Table 2.2 Surface roughness comparison table

American standard	British standard	ISO1302 standard *Ra*	
Particle size	Particle size	μm	μin
—	120	3.2	125
—	180	2.0	85
80	—	1.65	70
—	240	1.5	50
—	320	0.75	30
180	—	0.62	25
240	—	0.45	18
—	500	0.4	16
320	—	0.25	10

The ASME BPE standard divides the polish degree into seven grades: SF0, SF1, SF2, SF3, SF4, SF5 and SF6 (Table 2.3). At present, the common ASME BPE standard pipe fittings used on the market are SF1 (mechanical polishing, $Ra<0.51$ μm) and SF4 (electropolishing, $Ra<0.38$ μm). The common pipe fittings of the ISO 2037 standard (some specifications are the same as SMS 3008) are mainly four grades: *Ra* not higher than 0.8 μm, 0.6 μm, 0.5 μm and 0.4 μm. The ISPE recommends that the polish degree of pharmaceutical water systems should be $Ra<0.76$ μm, while the ASME BPE standard recommends that the polish degree of pharmaceutical water systems should be $Ra<0.6$ μm and electropolishing should be applied as far as possible. Water for injection systems and pure steam systems have direct contact with the final products, their production processes and cleaning requirements are relatively high, therefore, it is usually suggested that the internal surface finish of pipelines and tanks in water for injection systems and pure steam systems should have a $Ra<0.4$ μm, and electropolishing should be applied as far as possible. Based on the risk considerations and economic analysis of the whole system, an appropriate surface roughness can completely meet the requirements of production, cleaning and sterilization of the pharmaceutical water systems. Electropolishing has the advantage of better cleaning and microbial control than mechanical polishing, but its cost is relatively high, the enterprise can select it for use considering its particular conditions.

Table 2.3 Grades of polish degree

Grade of polish degree	Mechanically polished	
	Ra Max	
	μin.	μm
SF0	No polish requirement	No polish requirement
SF1	20	0.51
SF2	25	0.64
SF3	30	0.76
	Electropolished	
	Ra Max	
	μin.	μm
SF4	15	0.38
SF5	20	0.51
SF6	25	0.64

Surface roughness has direct impact on the system cleaning. In the cleaning validation model of the surface roughness, the stainless steel surfaces of dif-

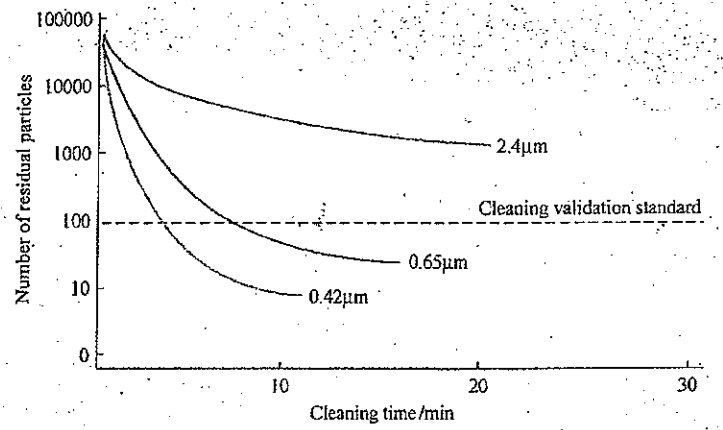


Fig 2.19 Surface roughness and cleaning validation

ferent surface roughness are required to put 10^5 detectable particles respectively, and the acceptable standard of cleaning is the number of final residual particles to be $<10^2$. It can be seen from Fig 2.19, that when the surface roughness after mechanical polishing is 2.4 μm, the number of residual particles on the surface of stainless steel will be decreased in the preliminary cleaning stage; after cleaning for about 20 min, the number of residual particles will be always maintained at a level higher than 10^3, the cleaning result cannot meet the acceptance criteria. When the surface roughness after mechanical polishing is 0.65 μm, the number of residual particles on the surface of stainless steel will be decreased rapidly in the preliminary cleaning stage, after cleaning for about 15 min, the number of residual particles will be finally maintained at an ideal level of $<10^2$; the cleaning result can be accepted. When the surface roughness after electropolishing is 0.42 μm, the number of residual particles on the surface of stainless steel will be decreased rapidly in the preliminary cleaning stage, after cleaning for about 10min, the number of residual particles will be finally maintained at an ideal level of $<10^1$, the cleaning result completely meets the acceptance criteria. The above experiments demonstrate that the higher the surface finish, the shorter the cleaning time required by the system, and the better cleaning effect under the same conditions.

The surface roughness report is an important part of the material traceability evidence in the clean fluid process system. For example, the material certificates of main materials of pipelines, pipe fittings, diaphragm valves, heat exchangers, centrifugal pumps, etc. provided by the supplier will be included in the printing records for measurement of the material surface roughness.

2.3.3 Slope

The action of gravity is an effective way to facilitate system drainage; slope inspection is another important item in the installation qualification of the system. The slope of pharmaceutical water systems should comply with the requirements of relevant regulations. If the slope is insufficient or there is no slope, the quality risks present in the pharmaceutical water systems mainly include:

a. Iron slags remaining in the system, which affects passivation effect.

b. Pharmaceutical water cannot drain out by itself, which affects the system cleaning effect.

c. Condensate water remains after pure steam sterilization, the system sterilization is not thorough, so as to cause serious microbial contamination such as generation of biological films in the pharmaceutical water systems.

d. Residual water stains cause serious particle contamination such as generation of rouge in the pharmaceutical water systems.

For pharmaceutical water systems sterilized by pure steam, the ISPE recommends the whole system should follow the principle of "*complete drainage by gravity*" to ensure the condensate water can be drained out completely by gravity. Most of purified water systems are sanitized by ozone or superheated water, but the design and installation of the whole system is also suggested to follow the principle of "*complete drainage by gravity*" considering the risks of system maintenance and the principle of low point drainage.

The ASME BPE standard divides the pipeline slope of fluid process systems into four grades: GSD0,

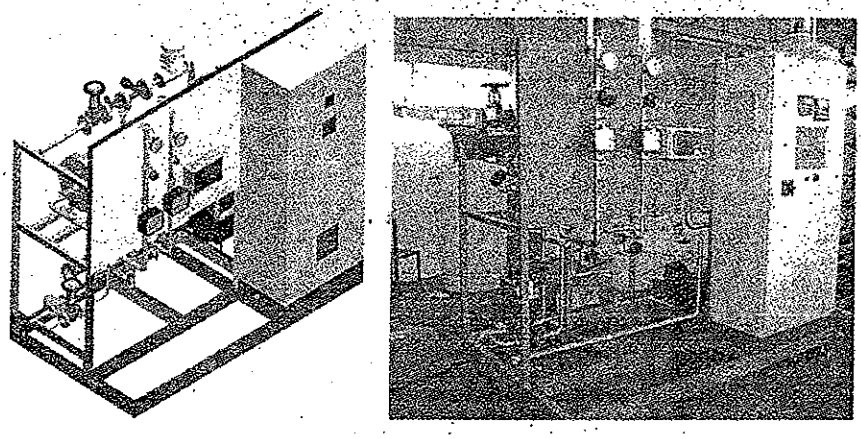


Fig 2.20 Modular design

GSD1, GSD2 and GSD3 (Table 2.4). The requirements for the pipeline slope in the standard mainly include the following contents: For the drug liquid process systems in pharmaceutical liquid preparation system, the slope of the transfer pipe should be not lower than GSD2 (equivalent to 1%); for CIP supply and return systems, the slope of the transfer pipe should be not lower than GSD2 (equivalent to 1%); for clean gas systems involved in aseptic processes, the slope of the transfer pipe should be not lower than GSD3 (equivalent to 2%); for waste gas exhaust systems not involved in aseptic processes, the slope of the transfer pipe should be not lower than GSD3 (equivalent to 2%).

Table 2.4 Comparison table of slope grades

Grade of slope	Minimum slope /(In/ft)	Minimum slope /(mm/m)	Minimum slope /%	Minimum slope /°
GSD1	1/16	5	0.5	0.29
GSD2	1/8	10	1.0	0.57
GSD3	1/4	20	2.0	1.15
GSD0	No slope requiremet			

At present, some enterprises or engineering companies in China adopt "the slope of purified wate system and water for injection system not lower than 0.5%, and slope of pure steam and sterile gas system not lower than 1%" to perform the IQ inspection based on routine engineering experience. However, it is recommended to adopt "the slope of purified water system and water for injection system not lower than 1%, and slope of pure steam and sterile gas system not lower than 2%" to control the slope of the system based on the consideration of risks and suggestions of the ASME BPE standard. It is a more reasonable choice.

2.3.4 Modular Design

During the construction of pharmaceutical water systems, the SKID modular design has been widely used, for example, the purified water unit, water distillator, pure steam generator, water distribution systems and other modules are all recommended to adopt professional three-dimensional design software to perform SKID modular design and guide the assembly. Modular assembly is part of the GEP, the purified water distribution module is taken as an example (Fig 2.20), the application of modular assembly helps implement factory performance tests, save floor area, reduce production costs, stabilize product quality and is convenient for operation. It is in full compliance with the production management concept of modern pharmaceutical enterprises.

During the production preparation phase, the equipment assembly personnel should conduct SKID modular assembly in accordance with process documents, operating procedures, raw material BOM list, P&ID drawing, three-dimensional design drawing, SKID square steel support drawing and electrical control cabinet drawing. It is required to conduct materials receiving management, and check material specifications, quantity and appearance against the BOM list before assembly. Components such as the water pump, heat exchanger, SS316L pipe and fitting, diaphragm valve and sampling valve should be provided with a 3.1 material certificate. All instruments should be provided with a 3.1 material certificate and C calibration certificate. The components and valves used in the cold and hot sources of the heat exchanger should be provided with a 2.2 certificate of qualification. The touch screen, paper recorder, TOC instrument,

water pump, UV lamp, etc. should be provided with operation manuals (Table 2.5). Meanwhile, raw materials and spare parts coming in direct contact with pharmaceutical water should be provided with documentary evidences such as polish degree.

Table 2.5 Required material certificate for raw materials

No.	Component Name	Required Certificate
1	Centrifugal pump	3.1 material certificate
2	Heat exchanger	3.1 material certificate
3	UV lamp	3.1 material certificate
4	TOC sensor	2.2 certificate of qualification;C calibration certificate
5	pH probe	3.1 material certificate;C calibration certificate
6	Ozone sensor	2.2 certificate of qualification;C calibration certificate
7	Conductivity probe	3.1 material certificate;C calibration certificate
8	Recorder	2.2 certificate of qualification;C calibration certificate
9	Flow sensor	3.1 material certificate;C calibration certificate
10	Pressure gauge	3.1 material certificate;C calibration certificate
11	Temperature sensor	3.1 material certificate;C calibration certificate
12	Sampling valve	3.1 material certificate
13	Diaphragm valve	3.1 material certificate
14	Steam trap/ temperature control valve	2.2 certificate of qualification
15	Plant steam valve	2.2 certificate of qualification
16	SS316L clean pipes and fittings	3.1 material certificate

The SKID support is made of SUS304 stainless steel square tubes, and the base frame is usually made of stainless steel square tubes with specifications of 100 mm×50 mm×2.5 mm, the stereoscopic frame and landing leg are usually made of stainless steel square tubes with specifications of 50 mm×50 mm×2.5 mm, and the decoration panel can use SUS304 stainless steel plate with thickness of not less than 2.0 mm, the square tube support is connected by full weld of argon arc welding. The footing selects M16 or M20 based on the size of the support. The surface treatment of the support can adopt multiple methods such as sand blasting or wiredrawing as required by the customer.

The blanking of the clean pipe should be processed with a special pipe cutter to ensure the pipe end is parallel and level, the end face can be processed with a special stainless steel mouth machine when necessary, and then the inside of the pipe end should be wiped with a lint-free cloth dipped in anhydrous alcohol after filing with dedicated file. Spot welding in the docking point should be uniform, and the diameter of the weld spot should be not more than 2 mm. It is suggested that the pipeline support uses a stainless steel pipe carrier, the connection between the pipe carrier and support must be a full weld.

The inside of pipe should be blanketed with enough inert gas for protection during the spot welding in the docking point, and to ensure each open port of the welded pipeline system is effectively plugged, and the gas supply and exhaust is reasonable and effective. All spot ports and open ports should be effectively protected after the completion of the spot welding. The $3D$ dead leg principle must be used during the blowdown and spot welding to ensure the source of danger produced in the circulatory system is reduced to the maximum. The pipeline system should be drained at the lowest point. It is recommended that the pipeline system should have the system slope of not less than 1% to ensure the system can be self-drained by the action of gravity.

The electrical control cabinet should be inspected before assembly to check whether the oil paint is damaged or bumped, whether the attachments are complete, etc. During the assembly, the operator should arrange, index, match drills, cut and install trunking in strict accordance with the process documents and electric installation drawings, meanwhile, the installation of a guide rail, electrical elements such as the PLC module, breakers, wiring module, terminal blocks, touch screen, paper recorder, conductivity meter, frequency converter and transformer, internal cables and wires, etc. should be considered.

After the completion of the assembly, the equipment should be subjected to inspection and qualification activities, which mainly include design documents verification, P&ID verification, component inspection, dead leg inspection, low point drainage inspection, welding documents inspection, circuit diagram inspection, equipment power-up state and operation inspection, equipment appearance and safety inspection, etc. All activities should be implemented in strict accordance with relevant contents of installation qualification and operational qualification, and factory test reports should be provided.

After the inspection of the equipment, a final packaging check will be conducted and it will be assessed whether it is ready to be delivered to the use site. Wooden packaging materials are usually used (the timber used for packing equipment delivered to foreign countries should be inspected and sealed by the local inspection department). The bottom of the equipment should be stacked on wood bricks during packaging to elevate the equipment, and the foundation bolt of the equipment should be screwed short to prevent it from damage during transportation. After the equipment is well fixed, it should be wrapped with packaging film or packed in plastic housing, the packing crate should be nailed with pilot nails, the lifting position and matters needing attention labeled, shipping mark sprayed and equipment listed to complete all packing and inspection activities before delivery.

The water treatment room is the generation and storage distribution station for purified water, water for injection and pure steam. The equipment in the water treatment room mainly include the purified water generation system, purified water storage tank, purified water distribution module, water for injection generation system, water for injection storage tank, water for injection distribution module, and pure steam generator (Fig 2. 21). Some enterprises may install a small-scale electrically heated boiler in the water treatment room, for energy conservation, which is used for the temperature constancy of water for injection distribution system. An excellent equipment layout plan of the water treatment room is not only saves costs, is convenient for operation and maintenance, but also presents the image of a modern pharmaceutical factory.

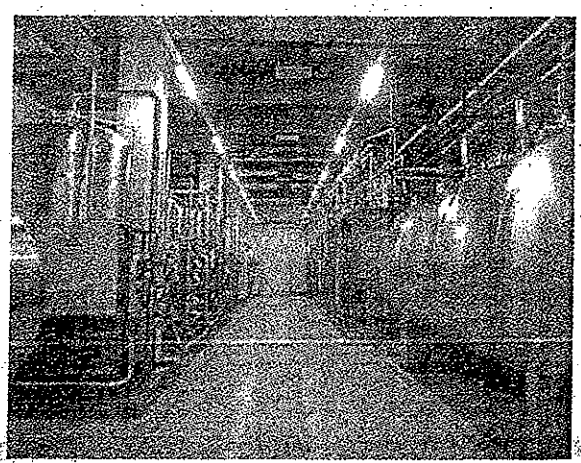


Fig 2. 21 Typical layout of water treatment room

The location of the water treatment room should be close to the load center of the process water, the water supply and drainage should be reasonable. It should facilitate the transportation and installation of equipment, and avoid being near the sites which generate toxic or harmful gases, corrosive media and dusts. The area of the water treatment room should not be too small, and should have enough operation and maintenance space. The expansion and renovation of water treatment rooms is rather common. Due to the development of production and promotion of new processes and new technologies of pharmaceutical water generation, the layout of the water treatment room may undergo significant changes. Therefore, the scale of the water treatment room should be determined according to the task regulated in the production planning, by taking the short-term target as the principal concern and also making a comprehensive analysis of the future development requirements.

It is preferred to use a brick and concrete or reinforced concrete structure for the water treatment room, a non-independent water treatment room should be considered as part of the main building. The fire risk of the water treatment room is classified a group e production site according to the relevant stipulations in the current national standard GB 50016—2014 *Code for Fire Protection Design of Buildings*, combined with the specific circumstances of water treatment rooms. Considering the permanence and importance of the building of the water treatment room, the fire resistance rating should be not lower than grade two. The combustion performance and fire endurance of the building components should comply with the stipulations in relevant current national standards. For a non-independent water treatment room, its classification of fire hazard and fire resistance rating should be not lower than that of main building to prevent the water treatment room from being burnt down due to fire in the main building.

A water treatment room is a place where pharmaceutical water is generated, it has higher requirements for waterproofing, damp proofing and mould proofing and should be easy to clean, due to the large water demand. If the materials used for the water treatment room have no such characteristics, mildew, peeling, shedding to the floor, wall and ceiling, and deformation of doors and windows may occur, which will result in a negative impact on the production of process water, and even affect the quality of process water. Open ditch

drainage is prone to bacterial growth, a cofferdam can be used to conduct treatment for the equipment in the water treatment room, and water is drained to the flow drain by using an exposed pipe. It is helpful in controlling the bioburden in the water treatment room. An air gap can be used for the equipment drainage to prevent the backflow of drained water, which can contaminate the whole water generation system.

The immediate consequence of a power failure in water treatment room is to interrupt the supply of pharmaceutical water. The loss resulted from that is relatively small, therefore, the electric equipment in the water treatment room can be powered as a third class load, unless the production process definitely requires that the process water cannot be interrupted.

Cost saving and effective natural ventilation should be given priority to the water treatment room to ensure heat dissipated by the equipment is exhausted effectively and the temperature in work area is reduced. When the natural ventilation cannot meet the requirements due to the restrictions of the process layout and building style, mechanical ventilation should be used. For the control room of the water treatment room, it is better to have air conditioning and heating facilities to improve the working conditions. The noise in the water treatment room should comply with the stipulations in the current national standard GB/T 50087—2013 *Industrial Enterprise Noise Control Design Specification*.

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Chapter 3

Unit Operation and Components

For the manufacturing of drugs, the pharmaceutical water systems and steam systems are all clean fluid process systems. They are critical components for the entire drug manufacturing process. The unit operations are the important elements of a system. In a pharmaceutical water and steam system, the core unit operations include storage, cleaning, heating, cooling, transfer, filtration, etc. In this book we are going to introduce the critical unit operations and core equipment in combination with the process characteristics of the pharmaceutical water generation systems and storage and distribution systems.

3.1 Pressure Vessels

Vessels (Fig 3.1) are a type of process equipment and are widely used in various areas of pharmaceutical production technologies. The relevant knowledge in all such areas as the process, machinery, control, mechanical, material, aesthetic and economic areas should be used for the design of vessels. At the same time, the functions of the product during its entire life cycle and such factors as the marketing competition requirements, the environmental requirements and the resource utilization requirements should be considered in combination. Vessels are commonly used in pharmaceutical water systems. They are mainly used for the storage of soft water, purified water (PW) or water for injection (WFI). The vessels used in pharmaceutical water systems are divided into atmospheric vessels and pressure vessels. For example, all such vessels as the raw water tanks, the soft water tanks and the PW tank that are sanitized at atmospheric pressure with hot water are all atmospheric vessels. And all such vessels that are sterilized by high pressure steam or over heated water; such as highly pure water tanks and WFI tanks are all pressure vessels. Pressure vessels can be divided into many types. They can be divided into simple pressure vessels, fixed pressure vessels and movable pressure vessels by the application scope. They can be divided into pressure vessels designed following regulations and pressure vessels designed through analysis. Pressure vessels are subject to the *Safety and Technical Supervision Regulations on Fixed Pressure Vessels* (TSG R0004—2009), so pressure vessels are introduced in this chapter as critical vessels.

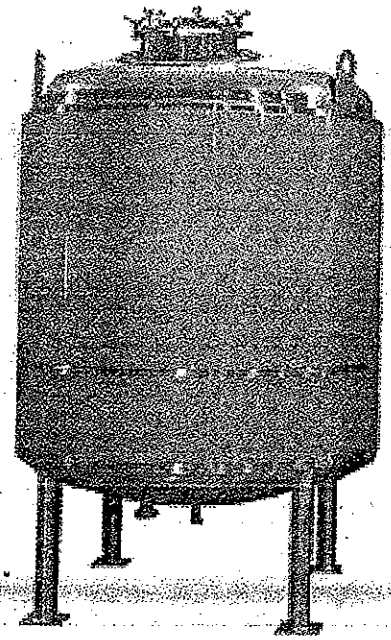


Fig 3.1 Vessels

3.1.1 Brief Introduction to Pressure Vessels

Pressure vessels are defined in several ways. In the GB/T 26929—2011 *Terminology for Pressure Vessels*, pressure vessels are defined as closed containers used for containing liquid media under certain pressures. In the Safety Laws on Special Equipment of the People's Republic of China, pressure vessels are defined as closed containers bearing certain pressures that are

used for containing gases or liquids. In the ASME standard pressure vessels are defined as containers bearing internal and external pressures.

The law and regulation system for pressure vessels in China is composed of laws, administrative regulations, department rules, safety and technical regulations and reference standards. Laws are social regulations that are generally binding, established and reinforced by government authorities to specify the rights and obligations of a litigant, which include the *Special Equipment Safety Law*, *Safe Production Law*, *Product Quality Law*, *Commodity Inspection Law*, etc. The *Special Equipment Safety Law* is a law issued by the State Council. It is the supreme law for pressure vessels. Its chapters include the *Special Equipment Quality Supervision and Safety Supervision Regulations* (State Bureau of Quality Technical Supervision), *Boiler Pressure Vessel Manufacturing Supervision* and *Administration Measures*, etc. The safety technology regulations and the compulsive national standards include the *Fixed Pressure Vessel Safety Technology Supervision Regulations* (FPVSTSR), *Pressure Vessel Periodic Inspection Rules*, *Pressure Vessel Pressure Pipeline Design Rules*, *Pressure Vessel Installation, Renovation and Maintenance Rules*, etc.

Once a national standard or an industry standard is referenced by a safety technology regulation, they will be equally effective and compulsory as the safety technology regulations and will become an integral part of the safety technology regulations. The commonly used pressure vessel regulations and standards include the *Special Equipment Safety Supervision Regulations* (implemented on May 1, 2009), the TSG R0004—2009 *Fixed Pressure Vessel Safety Technology Supervision Regulations* (implemented on December 1, 2009), the TSG R1001-2008 *Pressure Vessel, Pressure Pipeline Designer Qualification Licensing and Administration Rules* (implemented on January 1, 2003), the *Boiler Pressure Vessel Manufacturing Supervision and Administration Measures* (implemented on January 1, 2003), the GB 150.1～4—2011 *Pressure Vessels*, the JB4732—2005*Steel Pressure Vessels—Analysis Design Standards*, the GB/T 151—2014 *Heat Exchangers*, etc.

a. FPVSTSR vessels and GB 150 vessels. When designing a pressure vessel, it should be verified first based on the operation conditions to determine whether it is a pressure vessel. If it is a pressure vessel, it should be verified to determine whether it should follow the *Fixed Pressure Vessel Safety Technology Supervision Regulations* (FPVSTSR) and which method should be used for its design.

The criteria for a FPVSTSR vessel are that the working pressure should be no less than 0.1MPa (gauge pressure) and the product of the working pressure and the volume is no less than 2.5 MPa·L, the contained medium is a type of gas or liquefied gas, or a type of liquid whose maximum working temperature is no less than its standing boiling point. It should be noted that compulsory supervision and inspection are required for pressure vessels subject to the *Fixed Pressure Vessel Safety Technology Supervision Regulations* (FPVSTSR) and relevant qualifications are required for their design and manufacturing. Besides conforming to the FPVSTSR requirements, the design and manufacturing of FPVSTSR vessels should also conform to the requirements in GB 150.1～4—2011 *Pressure Vessels* or JB 4732—2005 *Steel Pressure Vessels—Analysis Design Standards*. The application scope of the *Fixed Pressure Vessel Safety Technology Supervision Regulations* (FPVSTSR) is determined based on the working parameters (i.e. the working pressure and the working temperature). And the classification is based on the design parameters (design pressure and volume).

The criteria for a GB 150 vessel are that the range of the design pressure (gauge pressure) of the steel pressure vessel should be 0.1 MPa≤ design pressure ≤35 MPa or the design pressure ≤−0.02 MPa, and the referenced standards should be followed for the pressure vessels made of other metal materials. The design temperature range should be−269 ℃ to 900 ℃, and the allowable use temperature specified for the materials listed in GB 150.2 should not be exceeded. The temperature should be determined based on the allowable use temperature listed in the reference standards for the pressure vessels made of other metal materials.

A FPVSTSR vessel includes the pressure vessel itself and the safety auxiliaries. The scope of the pressure vessel itself is defined from the groove face of the first circle joint of the welded connection between the pressure vessel and its external pipe or device, the end face of the first screwed joint of the screwed connection, the first flange end face of a flange connection, and the first sealing face of a dedicated connector or pipe con-

nector; the load bearing cover and its fasteners at a hole of the pressure vessel; the connection welding seam between a non-pressure part and the pressure vessel. The major pressure parts of a pressure vessel include the shell, the end covers (end plates), the expansion joints, the equipment flanges, the shell plates, the heat exchanger tube sheets and the heat exchangers, main equipment bolts M36 and above, and connecting pipes and flanges with a nominal diameter of 250mm or above. The installation auxiliaries of a pressure vessel include the safety valves, the rupture disks, the emergency cut-off devices, the safety interlocking devices, the pressure gauges, the level meters and the thermometers directly connected to the pressure vessel.

The scope of a GB150 vessel is defined starting from the connection section or sealing face between the vessel and any external pipes, the load bearing end plates, covers and fasteners of any connecting pipes, manholes and hand holes, the connection welding seam between a non-pressure part and a pressure part, any non-pressure parts, such as supports and skirts, directly connected onto the vessel, and the overpressure discharge devices of the vessel.

b. Classes of pressure vessels. Pressure vessels can be classified in many ways. The major classification methods are as listed below.

• Classification by pressure, product, medium toxicity and inflammability. They are classified as low pressure, medium pressure, high pressure and ultra-high pressure vessels by pressure. The first three classes have basically similar requirements on the material, the failure criteria (standards), the calculation method, and the manufacturing. However, ultra high pressure vessels have distinctly different requirements in these areas. The classification by the toxicity and the inflammability of the medium mainly considers the safety, i. e. the degree of hazards once there is an explosion or leakage event.

• Classification by manufacturing licensing level, safety and manufacturing difficulty: In this case P, P·V, medium properties and material strength are involved. The vessels are divided into fixed ones and movable ones by the installation position. Movable ones have higher safety requirements than fixed ones. And there should be special requirements on weight reduction, impact prevention, and installation of various instruments. Considering from the material point of view, there are significant differences in the manufacturing methods and the testing methods for metal vessels and non-metal vessels. Considering from the manufacturing point of view, different resources and safety quality requirements should be proposed for enterprises with different manufacturing licensing levels to facilitate the specialized production.

• Classification by actions and principles during production process. There are four types, reaction vessels, heat exchange vessels, separation vessels, and storage vessels. The reaction vessels have the highest requirements on safety. Changes in the pressure or the temperature may be caused during the physical and chemical reactions.

• Other common classification methods. They are classified as cylinder, spherical, combined and rectangular by the shape. They are classified as separated and combined by the chamber structure. They are classified as welded, forged or cased by the manufacturing method. They are classified as metal ones and non-metal ones by the materials. Metal ones include steel vessels, cast iron vessels, non-ferrous metal ones and alloy ones. And the steel ones are further divided into carbon steel ones, low alloy steel ones and high alloy steel ones.

c. Major characteristics of pressure vessel design and manufacturing. The design of a pressure vessel includes the structural design, the design calculations and the material selection. The structural design is the base for design calculation. The design calculation should be performed separately based on the structure and the shape. Three major factors, the strength, the rigidity and the stability, should be considered for the design calculation for pressure vessels. For the strength, there should be no plastic (permanent) deformations under the internal pressure. This is a major factor for safety, for such components as the shell and the end plates. For the rigidity, there should be no plastic deformations under the external forces during the manufacturing, transportation, installation and use, for such components as the flanges and the tube sheets. For the stability, the stability of the original shape should not be lost suddenly under an external force, for such vessels as a vacuum vessel. Different processing methods should be used to manufacture the different pressure parts based on their different structure and shape. The n the various parts are connected together through multiple connection methods

such as welding, flanges and bolts, and threaded connections to form an integral vessel. Welding is the major connection method to be used.

d. Major failure modes of pressure vessels. Pressure vessels have eight major types of failure modes, which are over elastic deformation (including instable elasticity), over plastic deformation, brittle fracture, damages caused by stresses/creep deformation, instable plasticity-increasing collapse, high stress and low circulation fatigue, stress corrosion and corrosion fatigue.

The routine design method for pressure vessels needs to be based on the elastic failure criteria. There are four strength theories for the elastic failure criteria. The first strength theory (the maximum principal stress theory) believes that, among the three major stresses of a material, once the maximum tensile stress σ_1 reaches the limit stress, the material will be damaged. The strength condition is $\sigma_1 \leqslant [\sigma]_t$. The second strength theory (the maximum deformation theory) believes that the material will be damaged when the maximum strain of the material reaches the limit statues. The strength condition is $\varepsilon_{max} \leqslant [\varepsilon]$. The third strength theory (the maximum shear stress theory) believes that the material will be damaged when the maximum shear stress τ_{max} reaches the limit stress. The strength condition is $\tau_{max} = (\sigma_1 - \sigma_3) \leqslant [\sigma]_t$. The fourth strength theory (the shearing deformation energy theory) believes that deformation and damage of the material will result when the internal deformation energy of the material reaches the limit.

3.1.2 Pressure Vessel Design

a. Types of pressure vessel designs. As specified in article 3 of TSG R1001—2008 *Pressure Vessel Pressure Pipeline Design Rules*, the pressure vessel designs are divided into types A, C, D and SAD.

The type A designs are further divided into types A1, A2, A3 and A4. Type A1 covers ultrahigh pressure vessels and high pressure vessels (the structures mainly include single layer, seamless, fore welding, multilayer wrapping, strip winding, hot jacket, coil wound, etc). A2 covers class Ⅲ low and medium pressure vessels. A3 covers spherical storage tanks. A4 covers non-metal pressure vessels. Type C is further divided into types C1, C2 and C3. C1 covers railway tanks. C2 covers truck tanks or long tube trailers. C3 covers tank containers. Type D is further divided into D1 and D2. D1 covers class Ⅰ pressure vessels. D2 covers class Ⅱ low and medium pressure vessels. Type SAD covers the analysis design of pressure vessels.

b. Common terms. The commonly used pressure terms include design pressure, calculated pressure, test pressure, maximum allowable working pressure, etc. The design pressure means the maximum pressure at the top of the vessel. It and the design temperature are used together as the design load conditions. Its value should be no less than the working pressure. The calculated pressure is the pressure used to determine the thickness of a component under the corresponding design temperature, which includes the hydrostatic fluid column pressure. The test pressure means the pressure at the top of the container when performing the pressure test or the leak test. The maximum allowable working pressure means the maximum pressure allowed at the top of the vessel at the corresponding specified temperature. It is different from the maximum working pressure.

The commonly used temperature terms include the design temperature, the test temperature, etc. The design temperature means the temperature set for the component metal (the average temperature along the section of the component metal) under the normal working conditions. The design temperature and the design pressure are used together as the design load conditions. The test temperature means the temperature of the vessel shell metal when performing the pressure test or the leak test.

The commonly used thickness terms include the calculated thickness, the design thickness, the nominal thickness, the effective thickness, the thickness addition, the negative deviation of material thickness, the corrosion allowance and the minimum forming thickness. The calculated thickness is the thickness calculated based on the thickness calculation formula. The design thickness is the sum of the calculated thickness and the corrosion allowance. The nominal thickness is the sum of the design thickness and the negative deviation of the material thickness rounded to the standard specifications of the material, i. e. the thickness noted on the drawings. The effective thickness is the result obtained using the nominal thickness minus the corrosion allowance and the negative deviation of the material thickness. The thickness addition is composed of two parts, the negative deviation of the material thickness C_1 and the corrosion

allowance C_2. The negative deviation of the material thickness should follow the specifications in the material standards. In order to prevent the reduction of the thickness of a vessel component caused by corrosion or mechanical abrasion, a corrosion allowance should be considered. For a component with homogeneous corrosion or abrasion, the expected vessel service life and the corrosion speed of the medium on the metal should be the determining factors. The corrosion allowance equals to the product of the corrosion speed and the design service life. In some cases the thickness calculated following the thickness calculation method is very small when the vessel is under a low internal pressure. However, the rigidity is insufficient. In order to solve the low rigidity problem, the minimum thickness of the shell after processing not including the corrosion allowance and the processing thickness reduction has been specified. For carbon steel and low alloy steel vessels, the thickness should be no less than 3 mm. For a high alloy steel vessel, the thickness should be no less than 2 mm. Fig 3. 2 is an example of PW tank with 6mm thickness.

The commonly used terms for corrosion include homogeneous corrosion, non-homogeneous corrosion, local corrosion, stress corrosion, intercrystalline corrosion, etc. Homogeneous corrosion is a type of continuous corrosion where the corrosion speed is approximately the same at the various parts of a metal surface. Non-homogeneous corrosion is a type of continuous corrosion where the corrosion speed is different at the various parts of a metal surface. Local corrosion is a type of corrosion that occurs at a local area, such as pitting corrosion (corroded pits) and spot corrosion (corroded spots). Stress corrosion is a type of corrosion caused by the combination of the eroding medium and stress. Stress corrosion cracking is a type of brittle cracking of metal under the combined actions of a persistent tensile strength and certain corrosion media. The entire stress corrosion process is the process in which cracking is resulted by the acceleration of the electrochemical corrosion of a metal due to the metal material, the corrosive medium and the tensile strength (the typical stress corrosion events includes the stress corrosion cracking of liquid ammonia vessels, the stress corrosion cracking of H_2S containing vessels, the stress corrosion cracking of caustic alkali containing vessels, the stress corrosion cracking of low carbon and low alloy steel vessels caused by NO_3^-, the stress corrosion cracking of stainless steel vessels caused by chlorine ion, etc. When performing the pressure test for an austenitic stainless steel vessel with water, the chlorine ion content in the water should be strictly controlled to be no more than 25 ppm. Any water should be removed completely once the test is completed.) Under the action of a corrosive medium, the intercrystalline binding force is damaged starting from the metal surface and deep into the metal along the crystal boundary. The material strength is almost lost completely in severe cases. This type of phenomenon is called intercrystalline corrosion [The intercrystalline corrosion of stainless steel can generally be explained by the "chromium depletion" theory. At present the measures used for improving the intercrystalline corrosion resistance of austenitic stainless steel include: ①solution treatment: heating at 1010 ℃ to 1120 ℃ followed by fast cooling, which makes chromium carbide (C_2Cr_3) dissolve in the austenite; ②reducing the carbon content in the steel: using ultra low carbon content ($C \leqslant 0.03\%$ or lower); ③adding stabilizing carbide elements: adding such stabilizing elements as Ti or Nb, and stabilizing at 850 ℃ to 900 ℃, to form fixed carbons TiC or NbC].

c. Pressure vessel materials. The use of the vessel (such as the design temperature, the design pressure, the media properties and the operation features), the welding properties of the material, the vessel manufacturing process and the economic rationality should be considered when selecting the steel for pressure vessels.

The upper limit temperatures listed corresponding to the allowable stresses of the various materials as specified in GB150 should be followed for the upper limit of the operating temperatures for the steel materials. The graphitization trend of the carbides in the steel materials should be considered when carbon steel materials and carbon manganese steel materials are used at a temperature higher than 425 ℃ for a long period of time. When the operating temperature of austenitic steel is higher than 525 ℃, the carbon content of the steel should be no less than 0.04%, and the lower limit of the operating temperature should be as specified in the relevant articles in Chapter 4-7 of GB 150. 2. The shock test can be avoided if the operating temperature of austenitic steel is no lower than −196 ℃.

d. Material allowable stress. generally, the lower of the tensile strength R_m at room temperature and the yield point R_{eL}^t ($R_{p0.2}^t$) at the design temperature di-

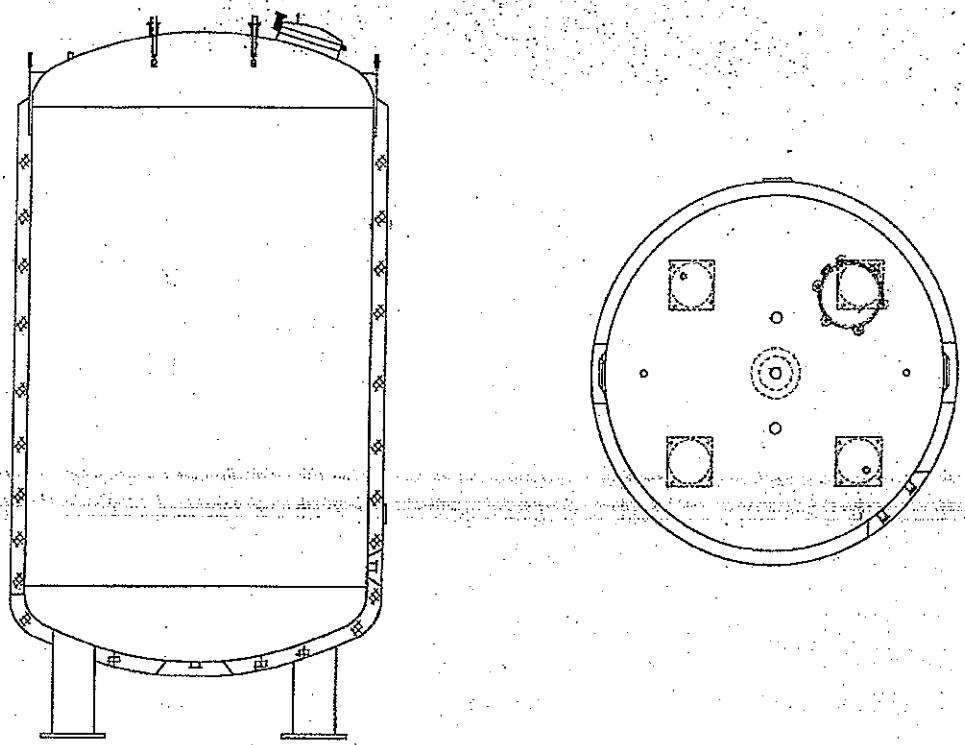


Fig 3.2 PW tank drawing

vided by their respective design safety coefficient. The mechanical properties are the commonly used parameters of the steel used for vessels. In class D vessels, the major parameters of the material are the tensile strength R_m and the yield point R_{EL}^t ($R_{p0.2}^t$). The vessel will be damaged once the tensile or yield point is reached. In the actual applications the stress of the vessel material must be controlled within the safe range, i. e. divide it by a coefficient n. And n is the allowable stress coefficient of the material (the design safety coefficient). Considering the ambient temperature tensile strength of steel, the design safety coefficient is taken as 3 (now it is 2.7). Considering the tensile strength of steel under the design temperature, the design safety coefficient for carbon steel and low alloy steel should be 1.6 (now it is 1.5). For high allow steel it should be 1.5.

The safety coefficient should be determined based on the following factors: ①deviations in the material performance stability; ② deviations in the estimated load statuses and values; ③the precision of the calculation method; ④the manufacturing process and the allowable deviations; ⑤the testing measures and the degree of strictness; ⑥ and the operation experience. The quality factors of the materials should also be considered when determining the allowable stress of the material.

e. Form and classification of welding joints. The classification of welding joints can help determining the welding seam structure, the inspection level and such data as the welding connection coefficient. The welding joints of the major pressure parts of a vessel are classified into classes A, B, C and D. Class A welding joints are longitudinal joints at cylinder parts, girth joints at hemispherical heads, all the butt joints of the various types of convex heads, and the joints between any embedded tubes and the shell. Class B welding joints are girth joints at the shell, and the joints between such components as the small ends of conical heads and long neck flanges, and the connection tubes. Class C welding joints are non-butt joints of flat covers, tube sheets and cylinders, joints between flanges and shells or connection tubes, and overlap joints between inner heads and cylinders. Class D welding joints are joints between the shell and such components as connection tubes, manholes, collars and stiffening rings. The welding joints between non-pressure parts and pressure parts are Class E welding joints.

f. Welding joint coefficient and non-destructive testing level. The welding joint coefficient (ϕ) is the welding seam reduction coefficient. It should be determined based on the ratio of the welding joint class and the duration of the non-destructive test, i. e. the ratio

of the weld strength and the base material strength. For double-welded butt joints and full penetration butt joints equivalent to double-welded butt joints, when $\phi = 1.00$, 100% non-destructive testing should be performed, the X-ray inspection technology level should be no lower than levels AB and the acceptance level should be no less than level Ⅱ. When $\phi = 0.85$, non-destructive testing should be performed at some locations, the X-ray inspection technology level should be no lower than levels AB and the acceptance level should be no less than level Ⅲ. It should be noted that when the Class A welding joints at the shell are double-welded butt joints, 20% X-ray inspection is required. In this case although the overlap joints at the convex head are inspected 100%, the joint coefficient used in the head thickness calculation formula should be 0.85. This is because the non-destructive testing acceptance level for the joints is the same as that for the shell, which is level Ⅲ. So the value cannot be taken as 1.0.

For single-welded butt joints (with a base plate closely attached to the base metal at the full length of the welding seam), when $\phi = 0.9$, 100% non-destructive testing should be performed, the X-ray inspection technology level should be no lower than levels AB and the acceptance level should be no less than level Ⅱ. When $\phi = 0.8$, non-destructive testing should be performed at some locations, the X-ray inspection technology level should be no lower than levels AB and the acceptance level should be no less than level Ⅲ.

g. Ratio of non-destructive testing. In the following cases, 100% non-destructive testing should be performed for the Classes A and B welding joints of pressure vessels (X-ray inspection should be performed if material thickness ≤38mm).

- Class Ⅲ pressure vessels with a design pressure of no less than 1.6 MPa;
- Pressure vessels manufactured following the analysis design standards;
- Pressure vessels using gas pressure tests or gas and liquid pressure tests;
- Pressure vessels whose welding joint coefficient is taken as 1.0 and pressure vessels for which the internal test cannot be performed after they are put into use;
- Pressure vessels in low alloy steel with a standard tensile strength lower limit of no less than 540Pa, some of the butt joints should also be tested with a testing method different from the originally used non-destructive testing method. And this test should cover all the overlapping welds;
- When required by the design drawing and the reference standards of this document.

h. Pressure test. A pressure test is a must for the inspection of the vessel quality during the vessel manufacturing process. It is mainly used to test the vessel strength and rigidity and the sealing quality at the welding joints and the seal connections that can be disassembled. The pressure test methods include hydraulic test, pneumatic test and mixed test.

i. Internal pressure cylinder calculation. The following formula should be used for the calculation under the design temperature.

$$\delta = \frac{p_c D_i}{2[\sigma]\phi - p_c} \qquad (3.1)$$

The application scope of this formula is $p_c \leqslant 0.4\phi[\sigma]_t$ or $D_o/D_i \leqslant 1.5$. The deduction of the stress in the formula is based on the film stress theory. Using the first strength theory, the circumferential stress should be calculated based on the average cylinder diameter, it should be corrected based on the difference between the maximum main stress on the cylinder wall and the average tensile stress, and the reduction in the strength of the longitudinal weld (Class A welding joints) relative to the parent material should be considered (Fig 3.3).

The stress should be calculated using the non-moment theory for thin wall cylinder vessels during a project. Under the internal pressure P, the cylinder wall

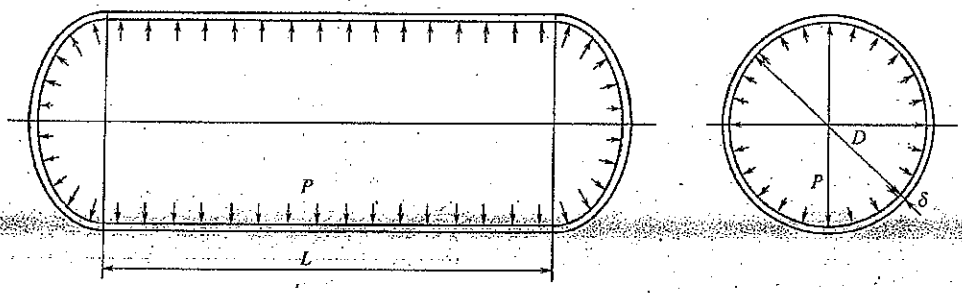


Fig 3.3 Calculation for internal pressure cylinder

is under axial stress and tangential stress (membrane stress). Because the shell wall is rather thin, the local stress at the shell and other connections are not considered, and the bending stress is neglected, this type of stress is called membrane stress.

j. Edge stress. When a component connected to a cylinder shell or a spherical shell or an oval shell is under pressure, the resulted deformations are different and are restrictive to each other; they are called discontinuous deformations. In this case, besides the expansion caused by the internal pressure, additional bending deformations will also result. Corresponding to the bending deformations, bending moments and shearing forces, which are called edge stresses, will also result at the shell wall. For a thin wall shell, the bending stress thus resulted can be far larger than the membrane stress. The larger the difference between two connectors the higher the resulted stress.

In the actual structures, the edge stress at the connection between a cylinder and a flat cover should be the largest. This type of stress occurs only at the boundary of two connectors, so it is called edge stress or discontinuous stress. The edge stresses caused by edge forces and edge moments are restrictive and self-limiting. Because the edge stresses are restrictive, it is acceptable to have local treatments on the structure during design, such as changing the structure at the connection, ensuring the quality of the edge welds, reducing the residual stress at the edge areas, and avoiding the concentration of any additional local stresses at the edge areas (for example, avoiding opening any holes at the edge areas).

k. External pressure cylinders and external pressure spherical shell. Loss of stability means the phenomenon that a vessel suddenly loses its original shape when the external pressure reaches a certain limit, a type of regular wave occurs, and the original shape cannot be resumed when the external pressure is removed. The major reasons that can cause the loss of stability of an external pressure vessel are insufficient strength and stability. The external pressure part is under a type of pressure stress and the damage that can result is mainly the loss of stability. The loss of stability can be divided into circumferential loss of stability and axial loss of stability. Circumferential loss of stability means the section turns from round to a type of wave. Axial loss of stability means that the axis turns from a direct line to a wave line. In order to prevent the loss of stability, the allowable pressure ($[P]$) for the prevention of the loss of stability of the shell should be made no less than the pressure (P_c) when the vessel loses stability. The cylinder stability safety coefficient should be 3.0, and the spherical shell stability safety coefficient should be 14.52.

• Calculation of circumferential loss of stability. Nomography is generally used for the calculation of the external pressure vessel shell wall thickness. The length is calculated based on the shell diameter (or radius). The coefficient is obtained from the chart based on the assumed wall thickness (δ_e) and the trademark of the used material. The n input the coefficient into the formula to obtain the allowable external pressure $[P]$, and make the $[P] \geqslant P_c$. Otherwise, repeat the calculation until the result is acceptable.

• Calculation of axial loss of stability. Obtain the coefficient from the chart based on the cylinder or pipe diameter, the wall thickness δ_e and the trademark of the used material. Input the coefficient into the formula to obtain the value of B, make the pressure P_c no more than the allowable axial compression stress. The lesser of the allowable stress $[\sigma]$ at the design temperature and the B value should be taken as the allowable axial compression stress.

The measures for the prevention of the loss of stability of an external pressure cylinder include increasing the cylinder wall thickness, reducing the calculated length of the cylinder and using reinforcing rings. The reinforcing rings should be placed around the entire cylinder and sufficient section area and combinational moment of inertia are required. The reinforcing rings should be placed inside or outside the vessel. The connection between the reinforcing ring and the cylinder can be in continuous welding or intermittent welding. The intermittent welding should be no less than 1/2 of the perimeter outside the cylinder and no less than 1/3 inside the cylinder.

l. Opening Reinforcement: An opening can not only reduce the vessel strength, but also cause a local concentration of stress. It is one of the important factors that can cause damages to a vessel. So the opening reinforcement is one of the critical parts for the design of a pressure vessel. The calculation methods for the reinforcement of an opening on the pressure vessel chamber wall include the equal area method and the analysis method.

The equal area method is applicable to round open-

ings, oval openings or oblong openings on the cylinder or the head, and non-round openings with a long and short diameter ratio $a/b \leqslant 2$. When the internal diameter of the cylinder $D_i \leqslant 1500$ mm, the maximum opening diameter $d_{op} \leqslant 1/2D_i$, and $d_{op} \leqslant 520$mm. When the D_i of the cylinder >1500 or for openings on conical heads, $d_{op} \leqslant 1/3D_i$, and $d_{op} \leqslant 1000$ mm (for openings on conical heads, D_i is the internal diameter of conical shell at the center of the opening).

The analysis method is obtained based on the elastic thin shell theory. It is used for the design of the opening reinforcement for a cylinder with a radial branch pipe under an internal pressure. Its application scope is $d \leqslant 0.9D$ and $\max[0.5, d/D] \leqslant \delta_e/\delta_e \leqslant 2$. The conditions for no additional reinforcement (see the opening reinforcement chapter in GB 150—2011) include, ① The pressure is no more than 2.5 MPa. ②The distance from the centers of two adjacent openings (the distance between curved faces is calculated based on the arc length) should be no less than two times of the sum of the two diameters; ③The nominal external diameter of the branch pipe should be no more than 89 mm; ④The minimum wall thickness of the branch pipe should meet the requirements specified in the corresponding table of GB 150.

The opening reinforcements are divided into overall reinforcement and local reinforcement. The overall reinforcement includes increasing the shell wall thickness, the pipe wall thickness and the overall reinforcement of the welds between forged parts and the shell. The local reinforcement includes reinforcement rings. When a reinforcement ring is used for opening reinforcement, the following rules should be followed: ①The lower limit of the standard tensile strength of the steel materials should be $\leqslant 540$MPa. ②The reinforcement ring thickness should be no more than 1.5 δ_n. ③The nominal thickness of the shell $\delta_n \leqslant 38$mm.

m. Flange design. The items to be considered for flange design should include: ① gasket tightening force, The minimum gasket tightening force at the pre-tightening state and that at the operation state should be calculated; ②bolts, the bolt load, the bolt area, and the bolt design load at the pre-tightening state and that at the operation state should be calculated; ③ flanges, the flange moment at the pre-tightening state and that at the operation state should be calculated. The flange stress should be verified.

3.1.3 Pressure Vessel Heads

The commonly used vessel heads include hemispheric heads, dish heads, oval heads, non-fold spherical heads, conical heads and flat heads. Spherical heads are usually used for high pressure vessels. Oval heads and dish heads are usually used for medium and low pressure vessels. Flat heads are usually used for ambient pressure and small diameter vessels. From the manufacturing and load point of view, the manufacturing difficulty becomes lower and lower and the load becomes worse and worse in the sequence of spherical heads, oval heads, dish heads, conical heads and flat heads.

a. Oval heads. Standard oval heads with a long axis and short axis ratio of 2 are usually used. Please see Fig 3.4 for the stress distribution. From the figure we can see that the maximum stress of a standard oval head is at the top of the head. At this point the radial stress equals to the circumferential stress. That is to say, the maximum stress of the head is at the bottom line of the head, where the absolute value of the radial stress equals to that of the circumferential stress.

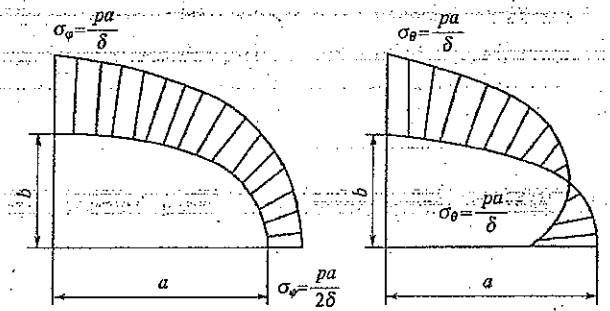


Fig 3.4 Oval head

For an oval head, a circumferential pressure stress will be generated at the bottom line under an internal pressure. Circumferential loss of stability can result at the head. So the problem of loss of stability must be considered at the pressure stress area for the head design. Under an external pressure, the short axis becomes shorter, a pressure stress is generated, and it becomes possible for the spherical part to lose its stability. Perform the verification calculation by the external pressure spherical shell design method, where R_0 is the equivalent spherical shell external radius of the oval head, and $R_0 = K_1 D_0$ (for standard oval heads, $K_1 = 0.9$). The formula for thickness calculation for standard oval head under internal pressure is as listed below.

$$\delta=\frac{KP_cD_i}{2[\sigma]_t\phi-0.5P_c} \qquad (3.2)$$

Where, δ is the calculated thickness of the oval head in mm. D_i is the internal diameter of the oval head in mm. K is the coefficient. And for a standard oval head, $K=1.0$. P_c is the design pressure in MPa. $[\sigma]$ is the allowable stress of the material in MPa.

b. Dish heads. A dish head is composed of a spherical face, a circular shell and a cylinder. The stress distribution is similar to that of an oval shell (Fig 3.5). The radial stress σ_r is the tensile stress. It is evenly distributed at the spherical surface area and is gradually reduced towards the circular shell and is reduced to a half of the original till the bottom line. The circumferential stress σ_θ is the tensile stress that is evenly distributed at the spherical surface part, and the compression stress at the spherical shell. It is reduced gradually from the connecting point to the bottom line and has its maximum at the connection between the spherical surface and the circular shell.

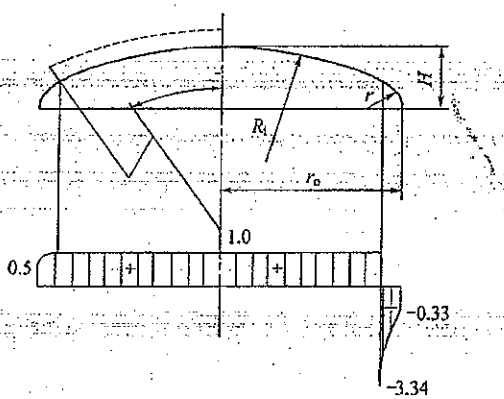


Fig 3.5 Dish heads

A dish head and an oval head are similar in shape. The difference is that the stress and the deformation are discontinuous and the additional moment (bending stress) of the two inflection points (the one between the spherical face and the circular shell, and the one between the circular shell and the cylinder) at the two boundaries are different. Under the internal pressure, the spherical face bulges outwards, the circular shell shrinks inwards, and the cylinder expands outwards. A circumferential loss of stability is possible. This can be prevented by controlling the minimum thickness. The smaller the r/R, the larger the stress between the spherical face and the circular shell will be. When $r/R\to1$ for the spherical shell, the bending moment $\to0$. So the maximum stress of a dish head is at the transition area from the spherical face to the circular shell. Under an external pressure, the short axis becomes shorter, a pressure stress is generated, and it becomes possible for the spherical part to lose its stability. The verification calculation is performed using the external pressure spherical shell design method, where R_0 is the external radius of the spherical face part of the dish head. The formula for thickness calculation for dish head under internal pressure is as listed below.

$$\delta=\frac{MP_cR_i}{2[\sigma]_t\phi-0.5P_c} \qquad (3.3)$$

Where, δ is the calculated thickness of the dish head in mm. R_i is the internal radius of the spherical face part of the dish head in mm. M is the shape coefficient, and for a standard dish head, $M=1.54$. P_c is the design pressure in MPa. $[\sigma]$ is the allowable stress of the material in MPa.

c. Conical head. The semi apex angle of a conical head $\alpha\leqslant60°$, and it is calculated taking the large end diameter as the equivalent cylinder diameter ($D_i/\cos\alpha$) (i.e. the calculation is performed based on the membrane stress of the equivalent cylinder). The circumferential stress at a dome diameter is twice that of the axis stress. The stress is different at different diameters. Full welding should be used for the connection between the conical shell and the cylinder. For the large end of an axial symmetric conical head, when the conical shell semi apex angle $\alpha\leqslant30$ ℃, a non-folded structure can be used. When $\alpha>30$ ℃, a folded structure with a transition section should be used. Otherwise it should be designed following the stress analysis method. When the semi apex angle $\alpha>60°$, the calculation should be based on a flat head. In this case the stress is mainly bending stress and the membrane theory is not applicable.

d. Spherical crown head. The calculated thickness of a spherical crown head under an internal pressure should be calculated based on the internal pressure spherical shell. The calculated thickness of a spherical crown head under an external pressure should be calculated based on the external pressure spherical shell. For an intermediate head, the worst case pressure combination at the two ends of the head should be considered.

e. Flat head. The thickness of a flat head is calculated based on the bending stress under a homogeneous load on the head.

$$\delta=D_c\cdot\sqrt{\frac{P_cK}{[\sigma]_t\phi}} \qquad (3.4)$$

Where K is the structural characteristic coefficient. It is divided into fixed support type (welding) and simple support type (bolt). By comparing the maximum deflection and the maximum stress under the two types of boundary conditions it is known that the deflection reflects the rigidity, and the stress reflects the strength. So the maximum deflection and the maximum bending stress of a fixed support flat head are smaller than those of a simple support flat head. From the rigidity and strength requirement point of view, fixed support is better than simple support.

3.1.4 Sanitary Pressure Vessels

In pharmaceutical water systems, sanitary pressure vessels are widely used, such as soft water storage tanks, PW storage tanks, and WFI storage tanks, which are all ambient pressure vessels or pressure vessels with different levels of sanitary requirements.

The purpose of designing and manufacturing a sanitary vessel is to maximally protect the product and the product contact surfaces during the process so that no contamination to the product will result, ensure that they are easy to clean, reduce the number of deadlegs that can cause any chemical or microbial contamination, and facilitate the cleaning, maintenance and testing activities. The sanitary vessel design is the supplementation and the embodiment of the design of steel pressure vessels with sanitary requirements. According to the GMP, any organizations engaged in drug manufacturing, and equipment design and manufacturing activities must follow the various requirements of the GMP. And the relevant requirements on the design of equipment with clean requirements are also specified in the *Codes for the Design of Clean Facilities of the pharmaceutical industry*. Because any designed or selected equipment will be eventually used in the drug manufacturing process, it is very important to verify whether the design or equipment selection is reasonable, whether the process requirements are met, whether it can facilitate operations and maintenance, and whether the GMP requirements are met. These can have significant influences on the GMP certification and the production activities of a pharmaceutical facility.

The available standards that can be referenced for the sanitary design of sanitary vessels include EN1672-2, EHEDG, ASME BPE, ISPE, 3-A, etc. The ASME BPE standards should be followed with priority for the design if the sanitary vessel has requirements on bio-burden control. So the general requirements for the design of a sanitary vessel in the pharmaceutical industry include: ① The design, selection and installation of the equipment should conform to the production requirements, the structure should be simple, any parts that need cleaning or sterilization should be easy to disassemble, any equipment that is difficult to be disassembled should be equipped with a cleaning port and manual or automatic cleaning devices should be installed. ② The equipment surfaces should be smooth and easy to clean. Any equipment internal walls in direct contact with the material should be smooth, even, easy to clean, corrosion resistant and free of deadleg. Mechanical polishing or electrochemical polishing can be used to meet the different surface finish requirements according to the clean classes of the fluids. ③ All the equipment internal surface in direct contact with the material should be made of materials that are not reactive to the medium and will not leach or absorb any substances. Austenitic stainless steel is often used. Glass lined equipment should be avoided as much as possible. No materials that can leach or absorb any substances such as rubber liners or glass fiber reinforced plastics should be used. The materials used should be non-toxic and corrosion resistant. And 316L ultra-low carbon stainless steel should be used for sanitary vessels for the formulation of injection solutions and the storage of WFI. ④ Equipment driving parts should be well sealed to prevent any contamination of the raw materials, the semi-finished products, the finished products, or materials by any leakage of lubricants or coolants. Packing seal is generally not recommended for the sealing of any driving parts. ⑤ For a piece of equipment with microbial requirements, the sanitization and sterilization requirements should also be met besides the above requirements. ⑥ Foundation bolts are not used for any equipment within a clean area, unless there is a special requirement. ⑦ The equipment insulation layer surface must be even, smooth and non-shedding. No asbestos or cements should be used. No joint or limb insulation layers should be used. The external surface should be completely covered by a metal shell. ⑧ Noise muffling and shock absorbing devices should be used for a piece of equipment that can generate noise or vibrations to improve the operation environment. The indoor noise level should be no more than 75dBA during an in operation test. ⑨ Sanitary flanges, NA connectors, Kest con-

nectors or clamps should be used for the connection of pipes and fittings. Polytetrafluoroethylene (PTFE) or sanitary rubber should be used as the sealing material. ⑩The auxiliaries of the equipment or machine, such as instruments, measurement devices and level meters, should be reasonably arranged. The measurement should be accurate and the regulations and controls should be stable and reliable. The material requirements should be the same as those for the equipment. The connections should meet the cleaning, sanitization or sterilization requirements. ⑪The equipment dimensions should be standard, universal, and conforming to mechanical requirements as much as possible. The consistent sealing and automatic testing during the production process are the basic assurance for meeting GMP requirements. ⑫Sanitary vessels are used for the drug solution preparation and storage for the manufacturing of sterile or non-sterile drugs, the drug solution preparation and storage for API refining, the storage of PW and WFI, and also the preparation and storage of materials in the food industry, the light industry and the cosmetic industry.

Generally, austenitic stainless steel is used for sanitary vessels. Ultra-low carbon stainless steel can be used if necessary. The commonly used materials include 06Cr19Ni10 (304), 022Cr19Ni10 (304L), 06Cr17Ni12Mo2 (316) and 022Cr17Ni12Mo2 (316L). The corrosion prevention requirements on the stainless steel materials for sanitary vessels are as specified below. ①The carbon content in the stainless steel should be reduced. Low carbon or ultra-low carbon stainless steel can be used if necessary to avoid or reduce the release of intercrystalline chromium carbide and reduce or avoid intercrystalline corrosion. ②The stainless steel should be treated with solid solution treatment so that all the carbides in the austenites can be dissolved to eliminate the tendency of intercrystalline corrosion. ③Molybdenum containing stainless steel should be used to form a protection layer that can effectively prevent pitting. ④When performing any welding operation, automatic argon arc welding should be preferred. The low current and fast cooling method should be used to reduce the heat affected area around the welding seam and reduce or avoid as much as possible any intercrystalline corrosion or pitting. ⑤The welding seams should be polished after welding. Pickling and passivation should be performed for the internal wall to form a dense passivation film at the surface to avoid any pitting caused by any chlorine ions penetrating through the passivation film.

Cold-rolled sheets should be used for the manufacturing of the vessels. And they should be solid solution treated, pickled and passivated. The surface quality level should be at least No. 2B and polished sheets should be used as much as possible. The steel pipes should conform to the relevant requirements specified in QB/T 2467 *Stainless Steel Pipes for Food Industry*. Thin wall pipes can be used and polished pipes should be used as much as possible. Fasteners should be made of 06Cr19Ni10 (304). Whole piece stainless steel materials must be used for such pressure parts as manholes, hand holes, sight glasses, vessel flanges and pipe flanges. Liners, bush rings, bead welding or coating should not be used. The material selected should be the same as that of the vessel itself. Such external parts as the jacket, the supports, the feet and the lugs of the vessels should be made of stainless steel. The insulation shell should be made of a whole polished piece of stainless steel material. The requirements on the welding materials for austenitic stainless steel sanitary vessels are as described below. ① The carbon content in the welding seam metal should be no more than 0.10. ②The GB/T 983 standard should be followed for welding rods for manual arc welding. The common models include E308, E308L, E316 and E316L. ③The YB/T 5091 standard should be followed for the welding wires for tungsten inert gas welding. The common welding wire models include HOCr21Ni10, HO0Cr21Ni10, H0Cr19Ni12Mo2 and HOOCr19Ni12Mo2. The sealing materials should be non-toxic expanded PTFE and sanitary rubbers, such as EPDM or silicone rubber. Gaskets containing asbestos should be strictly forbidden. The sanitary rubbers should meet the requirements specified in GB 4806.1.

Stainless steel liners are not allowed for sanitary vessels. This is because that it cannot be ensured that the stainless steel liners can be completely attached to the carbon steel vessel. There can be some residual gas within the gaps. So the material will be expanded because of the heat at the time of steam sterilization. Because the expansion coefficients of the stainless steel sheet, the carbon steel vessel and the residual gas are different, the plug welds can drop off and small cracks can result. The liquid within the vessel can enter into the gap between the stainless steel liner and the

carbon steel vessel, thus forming a deadleg. Deadleg should be avoided for the design of the internal wall and the internal structures of a sanitary vessel to avoid the ineffective or insufficient access of steam at the time of steam sterilization, which may cause insufficient sterilization.

Sanitary pressure vessels used for the storage of WFI have special requirements in the structural design for such vessel auxiliaries and connectors as shell accessories, flanges, branch pipes, manholes, hand holes, sight glasses, pressure gauges, thermometers, supports, and spraying devices. In pharmaceutical water systems, the pipe connectors for sanitary vessels are mainly divided into two types, thin wall pipe sterile pipe flanges and clamps.

Thin wall pipe sterile flanges are as shown in Fig 3.6. This type of design follows the DIN 11864—2 standard. It is proposed by the European Hygienic Engineering and Design Group (EHEDG) and is applicable to the food, chemical and pharmaceutical industries. The characteristic of this type of design is that there is no deadleg at the sealing face eliminating any contamination. The pipe flange sealing face has a complicated structure, a high machining precision and a very high requirement on the surface finish. The sterile pipe flanges have a rather good sterility assurance level and are also used in the vessels for pharmaceutical water systems.

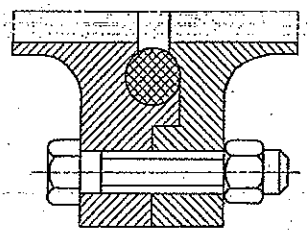


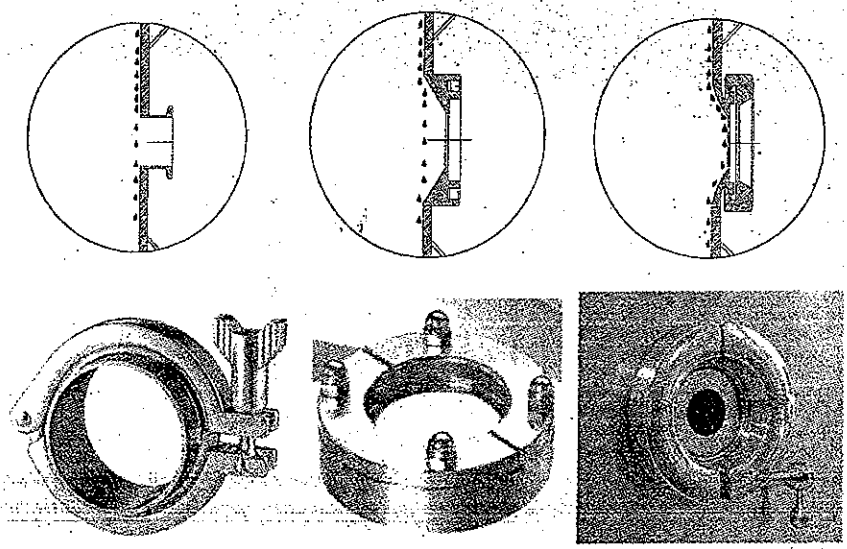
Fig 3.6 Sterile pipe flanges

Clamp connections are the most commonly used pipe connections in pharmaceutical water systems. The sizes are from DN15 to DN125 and the structure is as shown in Fig 3.7(a). Seal rings are installed at the sealing part of the welding pipe connections and they are fastened with clamps. The NA sterile connection [Fig 3.7(b)] and Kest sterile connections [Fig 3.7(c)] are two new types of sanitary connections. The ir design can effectively avoid the contamination risks caused at the deadleg of the pipe connection. The ir main advantage is the sterility assurance at the auxiliaries installed at the vessel side wall. They have been widely promoted and applied in the sterile pharmaceutical industry.

The spraying device is another very important vessel auxiliary for a sanitary pressure vessel. In pharmaceutical systems, the complete wetting of the internal surface of the vessel can help the automatic cleaning of the system and prevent any microbial growth. At the same time it can also ensure a homogeneous temperature within the entire vessel. The functions of the spraying device mainly include spray cleaning and vessel internal surface wetting, such as the initial spray cleaning of a PW storage and distribution systems after pickling and passivation, and the complete wetting of the WFI distribution during its operation.

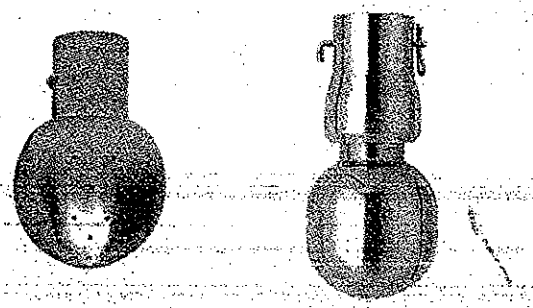
The spraying devices used in a pharmaceutical system are mainly used to realize the mechanical actions of cleaning or surface wetting. Based on the differences in the working pressure, the spraying devices used in pharmaceutical water vessels mainly include fixed spray balls and rotating spray balls (Fig 3.8). Based on the cleaning angle, spraying balls can be divided into 90°, 180° upward, 180° downward, 270° upward, 360° and 360° high throughput. Based on the installation mode, washing balls can be divided into welded, threaded, and plug-in washing balls.

Fixed cleaning balls [Fig 3.8(a)] are medium and low pressure high flow rate cleaning balls. They are the earliest spraying devices invented by human beings. They have been widely used in the pharmaceutical, food and beverage industries because they are easy to install, can have flexible holes, with a low cost and a long service life. The working principle of fixed cleaning balls is that small streams of the cleaning liquid are continuously sprayed out of each of the holes of the cleaning ball towards fixed points on the internal tank wall, and the cleaning liquid is distributed to the internal surface of the storage tank in a type of laminar flow. The theoretical working pressure of a fixed cleaning ball is medium (1.5 to 6 bar). The usually used working pressure is from 2 to 4 bar. At the time of cleaning the impact force is relatively weak. In order to ensure the cleaning effect, a large amount of the cleaning liquid is required. It is mainly used for cleaning tasks with lower requirements or for surface wetting. In pharmaceutical systems, fixed cleaning balls are accepted by some enterprises because they are not rotating. However, the return water pressure and



(a) Clamp connection (b) NA clamp connection (c) Kest sterile connection

Fig 3.7 Sanitary sterile connections



(a) Fixed (b) Rotating

Fig 3.8 Spray devices for tank

flow rate for WFI are restricted by the design and the operation of the water systems. So the cleaning effect is not very satisfactory. The cleaning pressure is required to be rather high, the water consumption and the cleaning reagent consumption are high, the cleaning holes can be easily blocked and rouge can develop. So they have been gradually replaced by tangent cleaning balls.

Tangent cleaning balls [Fig 3.8(b)] are also called rotary cleaning balls. They are low pressure and low flow rate cleaning balls. A tangent cleaning ball is composed of a tangent water spraying ball and a connecting rod that can be rotated rapidly. The impact force of the water flow is used to make the tangent water spraying ball rotate rapidly. Its working principle is that the cleaning liquid is continuously sprayed tangentially in a type of fan-shaped vortex flow. The combination of vibration and physical impact is used to spray the cleaning liquid evenly onto the tank internal wall. The tangent cleaning balls have medium working pressure (0.5 to 10 bar). The commonly used working pressure is 1 to 5 bar. The impact force at the time of cleaning is relatively strong. Only a small amount of cleaning reagent is required to obtain an ideal cleaning effect. They are mainly used for tanks that are easy to clean. At the same time, the surface wetting action from a tangent spraying device is very significant. They have been widely accepted in the pharmaceutical industry because they are easy to install, economic, energy saving and water saving.

Different from fixed cleaning balls, tangent cleaning balls are water lubricating spraying devices. Professional rotary cleaning ball abrasion test show that about 17,300 m^3 of cleaning water will go through the spraying device if it is run at 2.7bar continuously for 1,100 hours, and the loss of mass of the spraying device is 0.09 g, which is equivalent to a theoretical shed iron chip concentration of 0.0052 ppb. This concentration is far lower than the quality criteria for iron in the pharmaceutical industry. However, particulate contamination risks caused by dry frictions of spraying devices rotating at a high speed must be avoided. It is not allowed to blow with compressed air or other inert gases, or severe rouge and particulate contamination can be caused. High attention is required for the use of a tangent spraying cleaning ball.

3.1.5 Sanitary Heat Exchangers

In a typical application of pharmaceutical water systems, the heat exchanger is usually a pressure ves-

sel. It is a type of energy saving equipment that realizes the transfer of heat between two or more flowing liquids. The heat is transferred from the fluid with a higher temperature to the fluid with a lower temperature to raise it to the required temperature to meet the process requirements. At the same time, a heat exchanger is also a major type of equipment for the improvement of the energy utilization rate.

Heat exchangers can be divided into heating/cooling heat exchangers, pre-heaters, over-heaters and evaporators based on their uses. Heating/cooling heat exchangers are used to heat/cool a liquid to the required temperature. However, there is no change of phase for the liquid to be heated/cooled. For example, the major function of the heat exchanger in a PW distribution system is to maintain the temperature of the system and for periodic sanitization of the system. It is generally placed at the return pipe at the end of the distribution systems. And the heat exchangers at the user point distribution loop are mainly used to lower the water temperature. The pre-heaters are used to heat up a fluid to ensure the standard process parameters of a process, such as the pre-heater of a multi-effect still. The over-heaters are used to heat a fluid (process gas or steam) to the over-heated status. For example, the heat exchanger of WFI distribution systems is mainly used to maintain the water temperature within the systems and for the periodic sterilization of the systems with over-heated water. Evaporators are used to heat a type of fluid to a temperature above its boiling point so that the fluid evaporates. There is generally a phase change. The most typical evaporators used in pharmaceutical water systems include multi-effect stills and thermocompression water stills.

In pharmaceutical water systems, the often used heat exchangers include shell and tube heat exchangers, plate heat exchangers and tube in tube heat exchangers. Other heat exchangers (such as displacement heat exchangers) are also used in the soft ware systems.

a. Shell and tube heat exchangers. A shell and tube heat exchanger is mainly composed of the shell, the tube bundle, the tube sheet and the head (Fig 3.9). The shell is round in most cases. Parallel or spiral tube bundles are installed within the shell and the two ends of the tube bundles are fixed on the tube sheets. For the two types of fluid used for the transfer of heat within a shell and tube heat exchanger, one flows within the tubes, which is called tube pass. The other type of fluid flows outside the tube, which is called the shell pass. The tube bundle walls are used as the heat transfer surface. Most shell and tube heat exchangers are metal structures using 316 L stainless steel as the major material. They are divided into straight ones and U ones. Shell and tube heat exchangers are easy to clean and can effectively inhibit the microbial growth. They have become the most widely used heat exchangers in pharmaceutical water systems.

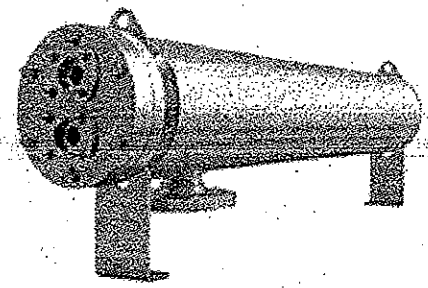


Fig 3.9 Double plate tube heat exchangers

In order to prevent any cross contamination, the *Inspection Guide for High Purity Water* of the US FDA suggests that the following two methods should be used. First, double tube sheet (DTS) heat exchangers should be used. Second, the differential pressure between the two sides should be monitored continuously to ensure that the pressure at the clean side is always higher than that at the non-clean side. The double tube sheet design has become the mainstream for the heat exchangers used in pharmaceutical water systems, such as the pre-heater and the evaporation columns of multi-effect stills, the heat exchangers of storage and distribution systems, and the cooling heat exchangers at points of use. Fig 3.10 shows the design schematic drawing of a typical double tube sheet heat exchanger. There is an inspection port for the easy leakage inspection between two plate sheets. When there is a leak at the connection between a tube and a tube sheet, the leakage of fluid will go to the atmosphere, not the process flow. However, it should be noted that this type of design cannot solve any issues caused by the pipe failures. If it can be ensured that a higher pressure is always maintained at the fluid of higher purity, such as between the second effect and the final effect of a multi-effect still, single tube sheet heat exchangers can also be used. In these evaporators, the design of the multi-effect still determines whether the pure steam is at higher pressure.

The combination of hydraulic expansion and

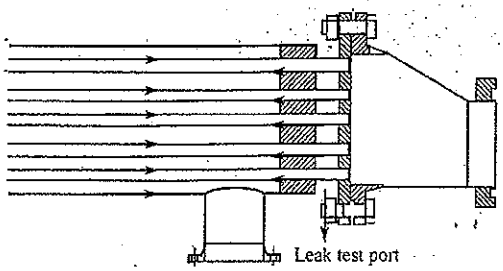


Fig 3.10 Design schematic drawing of double tube sheet heat exchangers

welding is used for shell and tube heat exchangers, which maximally ensures the process safety. Some suppliers can provide products using double expansion connection technology. For a shell and tube heat exchanger, there is an O ring conforming to the US FDA requirements at each end of the head to facilitate maintenance and spare part replacement activities. The seal ring materials are usually EPDM, Silicon, Vition and Teflon, and the temperature can reach as high as 250 ℃. Seamless steel tubes of different sizes, such as 8×1, 10×1 and 12×1 are used for the tube pass heat exchange internal tubes. Stainless steel tubes are also used as the sleeve tubes at the shell pass. The cold medium and the hot medium flow within the inner tube and the sleeve tube gap respectively. And the heat exchange is completed during the flow. The cold medium and the hot medium flow within their respective passes and will not be mixed together, which can completely avoid any cross contamination (Fig 3.11).

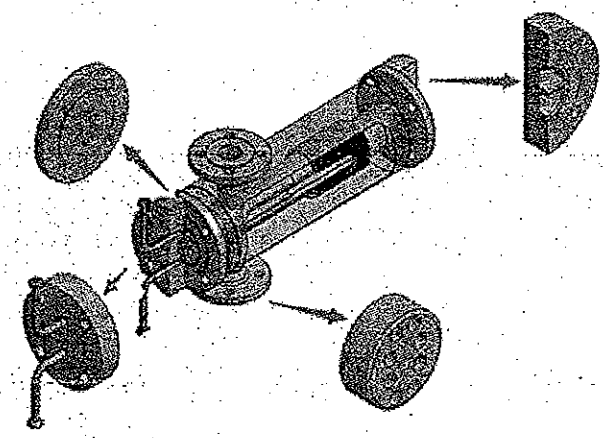


Fig 3.11 Structure of double tube shell heat exchangers

Because of the temperature difference between the shell pass medium and the tube pass medium, the expansions are different at the two sides. The higher the temperature difference, the higher the thermal stress of the shell and the tube bundle will be. The installation of expansion joints on the shell can effectively prevent any leakage or damages caused by the different thermal expansions, to improve and reduce the load of each of the components. In order to improve the performance of a single expansion joint, a bellow expansion joint can be installed on a heat exchanger. It can effectively remove any stresses and prolong the service life of the heat exchanger. The cost of a bellow expansion joint is high and its structure is very precise. There are certain requirements on the dimensions and the material. Special care should be taken at the time of manufacturing to avoid any defects such as perforation, damages or loss of stability. It must be ensured that the entire clean side of the heat exchanger can be completely self drained to facilitate SIP/CIP.

b. Plate heat exchangers. Plate heat exchangers are typical dividing wall heat exchangers (Fig 3.12). They have a long history of application in the industry. And they still play a leading role. The main structures of a plate heat exchanger include the heat exchange plates and the rubber bars between the plates. They are mainly used for the heat exchange between liquids or between liquid and steam. In order to improve the heat transfer coefficient of the fluid outside the tube, a certain number of transverse deflection baffles are installed within the shell. The deflection baffles can not only prevent any short-cut of the fluid flow and increase the fluid flow rate, but also force the fluid to pass the tube bundle for multiple times following specified paths, which greatly increases the turbulence of the flow.

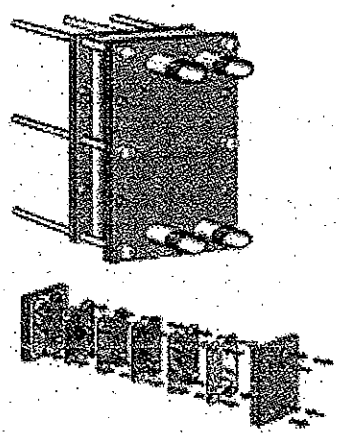


Fig 3.12 Structure of plate heat exchangers

Plate heat exchangers are smaller and easy to maintain and install. The number of plates can be increased easily to increase the heat exchange area of the heat exchanger. Plate heat exchangers can also be designed with a double plate structure (Fig 3.13). Al-

though a double-plate plate heat exchanger is relatively lower in price, it has certain microbial contamination risk because it cannot be emptied by itself. So the ISPE recommends that plate heat exchangers are not allowed in the storage and distribution systems. However, they can be used in the pretreatment and purification steps of a PW system.

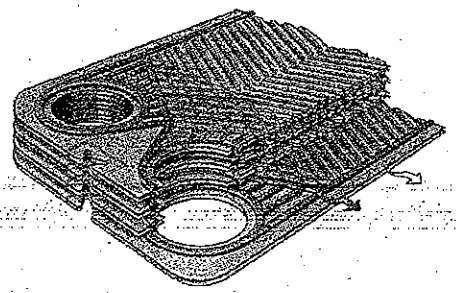


Fig 3.13 Design schematic drawing of double-plate plate heat exchangers

c. Tube in tube heat exchangers. The tube in tube heat exchangers are a reasonable application of U tubes. The most typical application is the single point WFI cooling module (Fig 3.14). This equipment is a sub-loop cooling system with a modular design. The design concept of a pitot tube is used to ensure the back pressure of the main loop. The design is compact and the installation, operation and maintenance activities can be very convenient. They are especially suitable for the point of use cooling of WFI for such simple and open applications as sinks and QC sampling points.

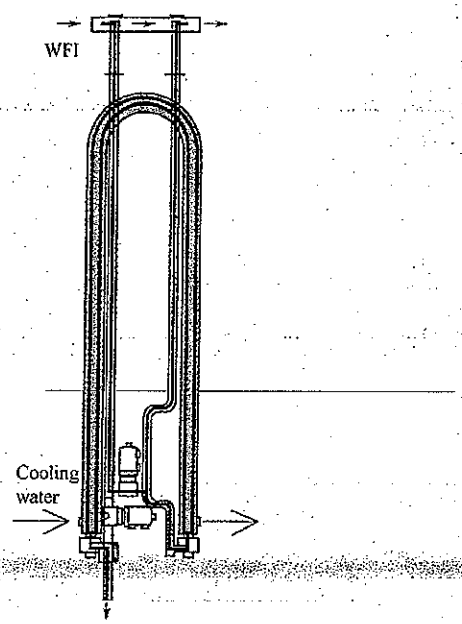


Fig 3.14 Application of tube in tube heat exchangers

3.2 Centrifuge Pumps

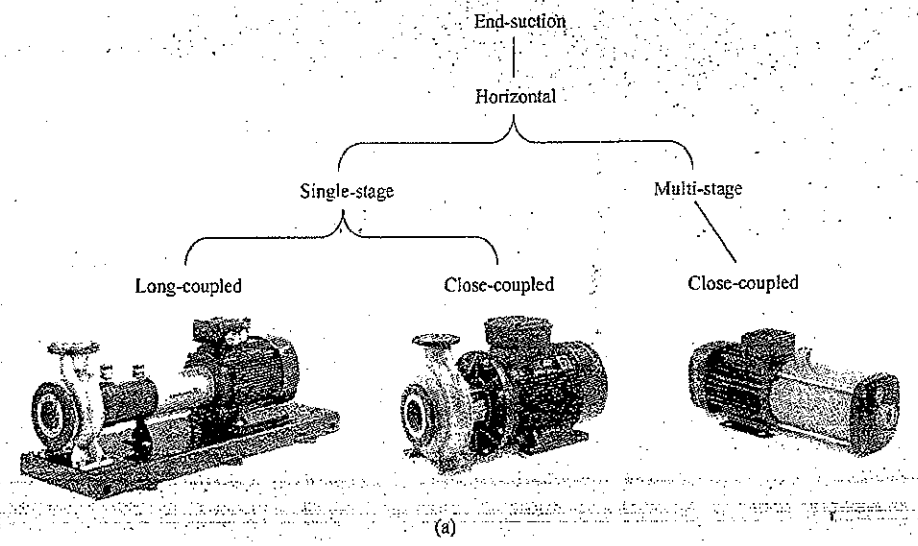
The centrifugal pump is the most common pumps of all types. It is widely used in such industries as dairy products, beer, beverage, pharmaceuticals, biologicals, cosmetics and fine chemicals. The working principle of a centrifugal pump is that the pump chamber is first filled with liquid, then the motor drives the shaft and the impellers to rotate, during which process a centrifugal force is generated, and the liquid is thrown away from the center of the impellers during a circular motion. At the same time, a low pressure area is created at the center of the impellers, a differential pressure is created between the low pressure area and the surface of the liquid sucked in. So the liquid is continuously sucked in and expelled out at a certain pressure, which allows the continuous transfer of the liquid. Fig 3.15 shows the classification of centrifugal pumps by the connection mode, the installation mode and the number of impellers.

According to the working conditions, the centrifugal pumps used in the pharmaceutical industry are divided into ordinary centrifugal pumps and self-priming centrifugal pumps. The ordinary centrifugal pumps are further divided into single stage centrifugal pumps and multistage centrifugal pumps according to their flow and head. Based on the different cleanness requirements of the pharmaceutical industry, centrifugal pumps are divided into non-sanitary pumps, sanitary centrifugal pumps and sterile centrifugal pumps (Fig 3.16).

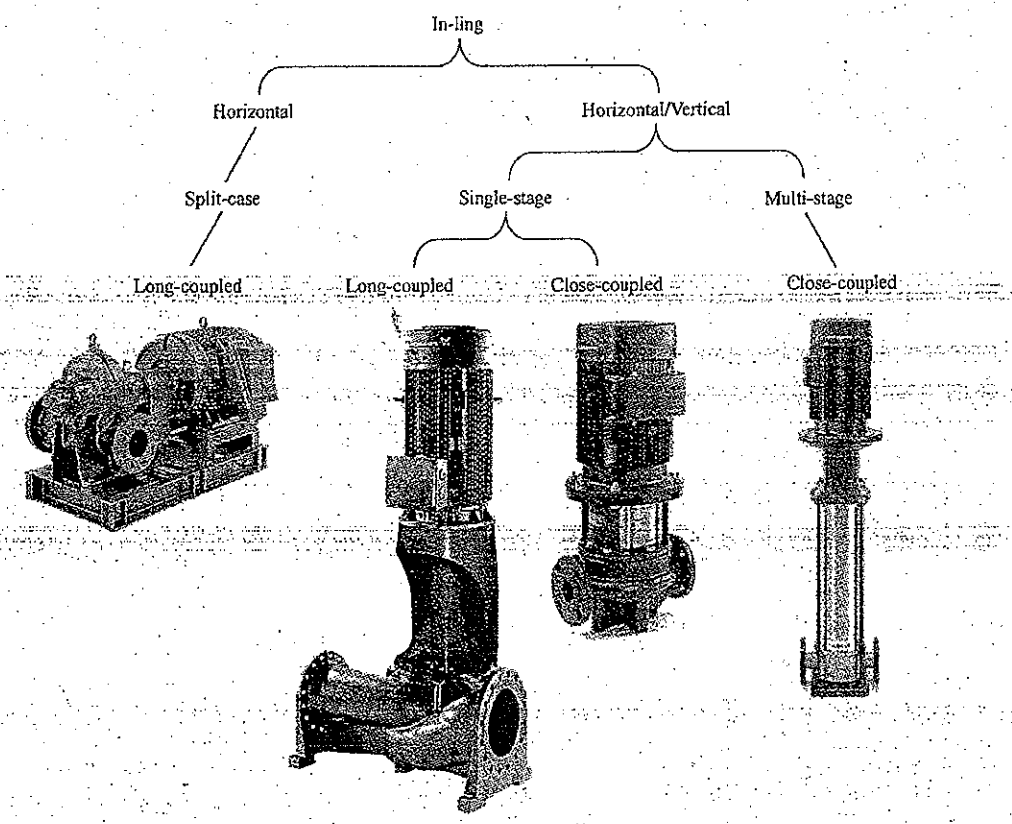
3.2.1 Multistage Centrifugal Pumps

The multistage centrifugal pumps are those with two or more rows of impellers placed side by side within the pump chamber to increase the head. In the pharmaceutical industry, in some cases centrifugal pumps with a low flow rate (of no more than 15 t/h) and a high head (of more than 12 bar) are required. Multistage centrifugal pumps can meet this type of requirement.

Multistage centrifugal pumps are divided into industry type and sanitary type. An industry type multistage pump has many deadleg by design and cannot be cleaned through CIP. A sanitary multi-stage centrifugal pump has a type of open and deadleg free design, which can meet the CIP requirements and effectively



(a)



(b)

Fig 3. 15 Centrifugal pump classification

ensure the cleanness within the pump chamber. And at the same time, a sanitary multistage centrifugal pump needs to meet the material requirements for a single stage centrifugal pump by design, conforms to the open design requirements of a sanitary single stage centrifugal pump, and uses the internal mechanical seal design (Fig 3. 17).

In the pharmaceutical industry, when a sterile multistage centrifugal pump is used for the transfer of a type of liquid, the pump must meet the following design requirements: Stainless steel press forged parts should be used and no casted parts are allowed. Open or partially open impellers should be used. Sterile connectors should be used. Higher level sterile mechanical seals should be used. The springs should be built-in and not in contact with the material. The pump internal surface should be electropolished and passivated. The surface roughness *Ra* should be no more than 0. 5

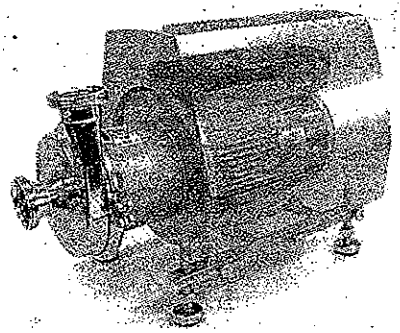
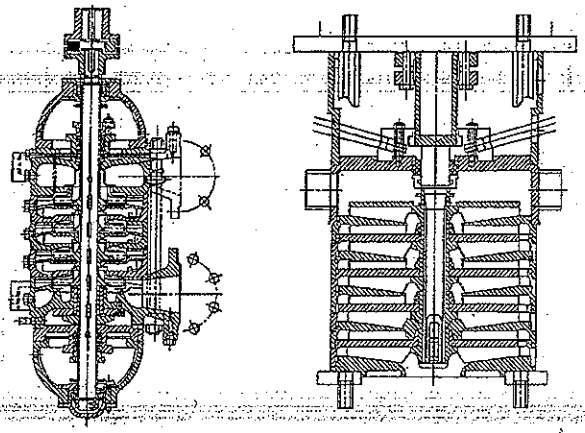


Fig 3. 16 Sterile centrifugal pumps



(a) industry type (b) sanitary type

Fig 3. 17 Multistage centrifugal pumps

μm. It should be installed vertically with the inlet at the bottom. It should be possible for the pump to be emptied when it is not running (Fig 3. 18).

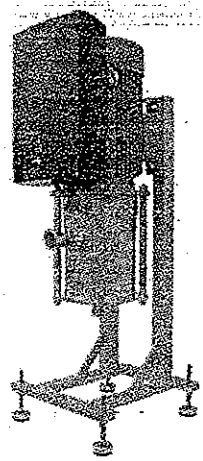


Fig 3. 18 Sterile multistage centrifugal pumps

In pharmaceutical water systems, industrial vertical multistage centrifugal pumps are used more widely; the booster pump before the RO membrane and the water supplementation pump between the multi-effect still and the pure steam generation are all vertical multistage centrifugal pumps. The major components of a vertical multistage centrifugal pump include motor, shaft seal, sleeve, chamber stake, base and connectors (Fig 3. 19).

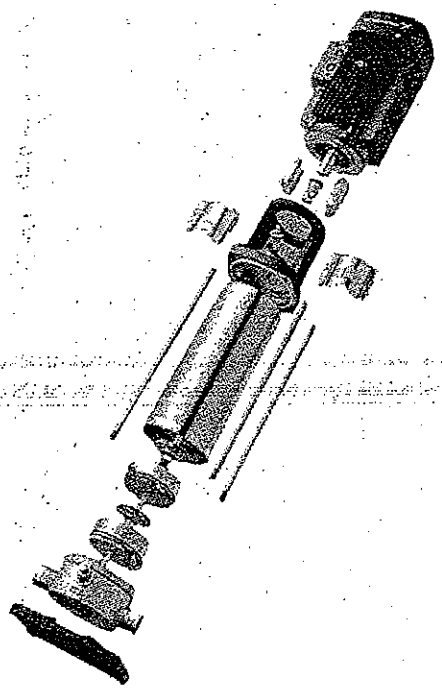


Fig 3. 19 Vertical multistage centrifugal pumps

a. Motor. Motors are used in many applications all over the world. The purpose of the electric motor is to create rotation, that is to convert electric energy into mechanical energy, to drive the pump.

NEMA and IEC are the two major international standards for motors. The National Electrical Manufacturers Association (NEMA) sets standards for a wide range of electric products, including motors. NEMA is primarily associated with motors used in North America. The standards represent general industry practices and are supported by the manufacturers of electric equipment. The standards can be found in NEMA Standard Publication No. MG1. Some large motors may not fall under NEMA standards. The International Electrotechnical Commission (IEC) sets standards for motors used in many countries around the world. The IEC 60034 standard contains recommended electrical practices that have been developed by the participating IEC countries.

Three different ways of mounting the motor exist: Foot-mounted motor, flange-mounted motor with free-hole flange (FF) and flange-mounted motor with tapped-hole flange (FT). Fig 3. 20 shows the different ways of mounting a motor and the standards that apply for the mountings.

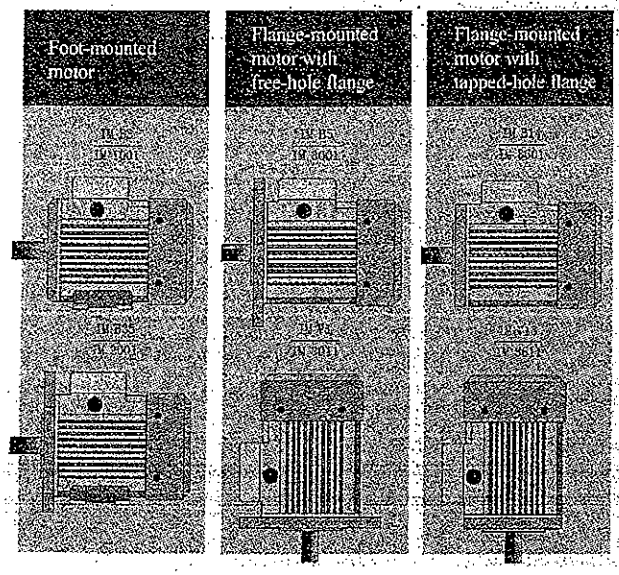


Fig 3.20 Motor mounting ways

The enclosure class states the degrees of protection of the motor against ingress of solid objects and water. The enclosure class is stated by means of two letters IP followed by two digits, for example IP55. The first digit stands for protection against contact and ingress of solid objects and the second digit stands for protection against ingress of water (Table 3.1). Drain holes enable the escape of water which has entered the stator housing, for instance through condensation. When the motor is installed in a damp environment, the bottom drain hole should be opened. Opening the drain hole changes the motor's enclosure class from IP55 to IP44.

Fig 3.21 gives an overview of the relation between frame size, shaft end, motor power and flange type and size. For motors in frame sizes 63 up to and including 315M, the relationship is specified in EN 50347. For motors with frame size 315 L and larger, no standard covers this relation. Flanges and shaft ends comply with EN 50347 and IEC 60072-1. Some pumps have a coupling, which requires a smooth motor shaft end or a special shaft extension which is not defined in the standards.

The insulation class is defined in the IEC 60085 standard (Fig 3.22) and tells something about how robust the insulation system is to temperatures. The life of an insulation material is highly dependent on the temperature to which it is exposed. The various insulation materials and systems are classified into insulation classes depending on their ability to resist high temperatures.

Table 3.1 Motor enclosure class specifications

First digit		Second digit	
Protection against contact and ingress of solid objects		Protection against ingress of water0.	
0	No special protection	0	No special protection
1	The motor is protected against solid objects larger than 55 mm, e. g. a hand	1	The motor is protected against vertically falling drops of water, such as condensed water
2	The motor is protected against objects larger than 12 mm, e. g. anger	2	The motor is protected against vertically falling drops of water, even if the motor is tilted at an angle of 15°
3	The motor is protected against solid objects larger than 25 mm, i. e. wires, tools, etc.	3	The motor is protected against water spray falling at an angle of 60° from vertical
4	The motor is protected against solid objects larger than 1 mm, e. g. wires	4	The motor is protected against water splashing from any direction
5	The motor is protected against ingress of dust	5	The motor is protected against water being projected from a nozzle from any direction
6	The motor is completely dustproof	6	The motor is protected against heavy seas or high-pressure water jets from any direction
		7	The motor is protected when submerged from 15 cm to 1 m in water for a period specified by the manufacturer
		8	The motor is protected against continuous submersion in water under conditions specified by the manufacturer

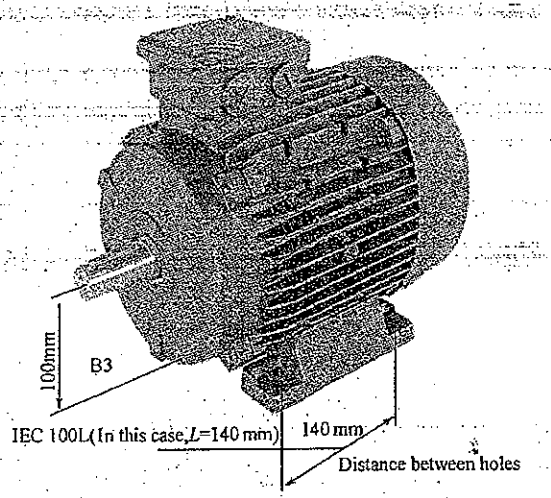
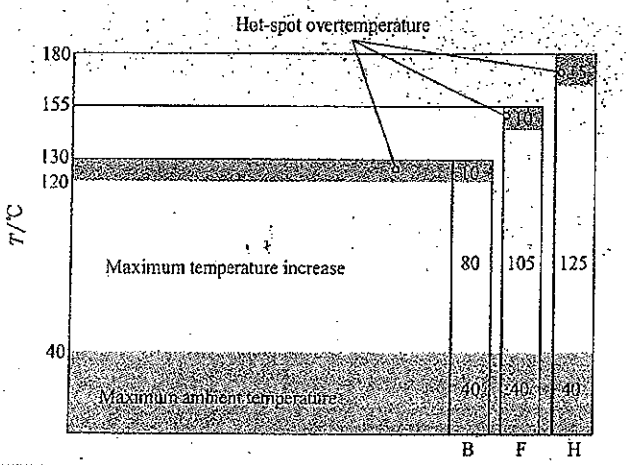


Fig 3.21 Motor dimensions overview

The motor's rated voltage lies within a certain voltage range. According to the international standard IEC 60038, the motor has to be able to operate with a main voltage tolerance of ±10%. For motors that are designed according to the IEC 60034—1 standard with a wide voltage range, e. g. 380-415 V, the main voltage may have a tolerance of ±5%. The permissible maximum temperature for the actual insulation class should not be exceeded when the motor is operated within the rated voltage range. For conditions at the extreme boundaries the temperature typically rises approx. 10K.

Generally speaking, electric motors are quite effi-



Class	Maximum ambient temperature/℃	Maximum temperature rise/K	Hot-spot overtemperature/K	Maximum winding temperature/℃
B	40	80	10	130
F	40	105	10	155
H	40	125	10	180

Fig 3.22 Motor insulation classes

cient. Some motors have electricity-to-shaft power efficiencies of 80-93% depending on the motor size and sometimes even higher for larger motors. Two types of energy losses in electric motors exist: Load-dependent losses and load-independent losses. Load-dependent losses vary with the square of the current and cover, which mainly include stator winding losses (copper losses), rotor losses (slip losses), and stray losses (in different parts of the motor). Load-independent losses in the motor include iron losses (core losses) and mechanical losses (friction).

On July 23rd, 2009, the EU passed a resolution, deciding to make IE2 the mandatory minimum energy performance standard for motors by June 16th, 2011, IE3 the minimum energy performance standard for the 7.5-375 kW motor by January 1st, 2015, and IE3 the mandatory minimum energy performance standard for motors by January 1st, 2017.

On the basis of the national standard, GB 18613—2006 version, (the energy performance fixed value and the grading standard of small and mid-sized three-phase asynchronous motor), our country decided to make the 2nd level energy performance (equivalent to IE2) the mandatory minimum energy performance from January 1st, 2012. On September 1st of the same year, the national standard was upgraded. The new national standard, GB 18613—2012 version, lowers the level of the motor energy performance standard, with the original 1st level downgrading to 2nd level. And the 3rd level energy performance (equivalent to IE2) is regarded as the mandatory minimum energy performance in the standard. According to the new standard, the 2nd level energy performance (equivalent to IE3) will be regarded as the minimum energy performance standard for the 7.5-315 kW motors four years later (beginning from September 1, 2016), and five years later it (equivalent to IE3) will be regarded as the minimum energy performance standard for motors with a power less than 7.5 kW.

b. Motor stool. The motor stool is used for fixing the motor and pump head. As an interconnecting piece of two main units, the production of the motor stool demands very high machining accuracy, especially for concentricity. The pump head, as the name implies, is the top part of the pump body. Usually, a mechanical seal is installed on the top of pump head. And normally there are also an airvent and a filling opening on the pump head.

Motor stools and pump heads can be integrated, but also separated. Fig 3.23 shows the separated pump head and motor stool usually used for stainless steel vertical multistage centrifuge pumps. The pump head material is stainless steel and the motor stool material is cast iron.

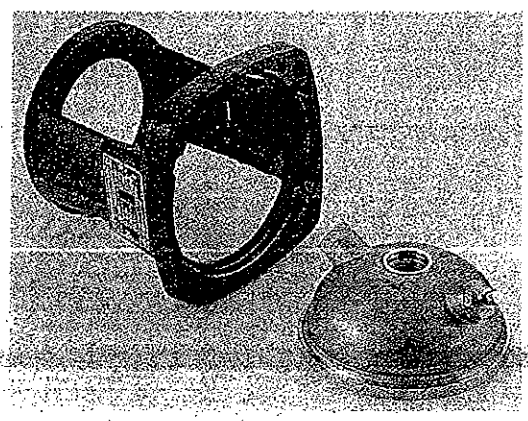


Fig 3.23 Motor stool and pump head

c. Shaft seal. From the middle of the 1950s mechanical shaft seals gained ground in favor of the traditional sealing method-the stuffing box. Compared to stuffing boxes, mechanical shaft seals provide the following advantages:

- They keep tight at smaller displacements and vibrations in the shaft.
- They do not require any adjustment.
- Seal faces provide a small amount of friction and thus, minimize the power loss.
- The shaft does not slide against any of the seal's components and thus, is not damaged because of wear (reduced repair costs).

The mechanical shaft seal is the part of a pump that separates the liquid from the atmosphere. Fig 3.24 shows an example of a shaft seal which is installed on a vertical multi-stage centrifugal pump. The majority of mechanical shaft seals are produced according to the European standard EN 12756. Before choosing a shaft seal, there are certain things that are needed to be known about the liquid, like the seal's resistance to the liquid, including the type of liquid, the pressure that the shaft seal is exposed to, the speed that the shaft seal is exposed to, and the built-in dimensions.

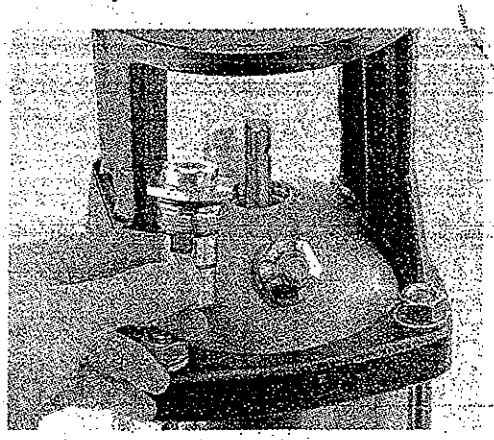


Fig 3.24 Shaft seal

The mechanical shaft seal is made of two main components, a rotating part and a stationary part. Fig 3.25 shows the parts of the mechanical seal and where the different parts are placed in the seal. The stationary part of the seal is fixed in the pump housing. The rotating part of the seal is fixed on the pump shaft and rotates when the pump operates.

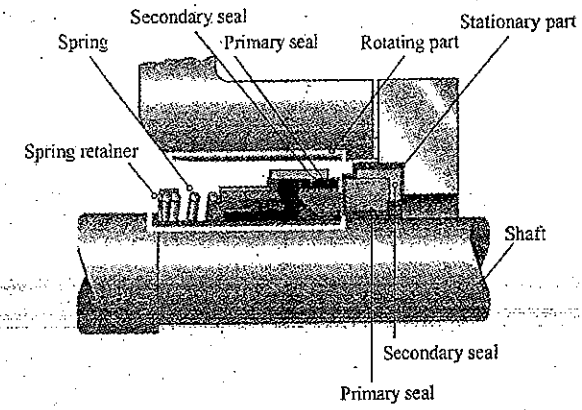


Fig 3.25 Schematic drawing of mechanical seal

The two primary seal faces are pushed against each other by the spring and the liquid pressure. During operation a liquid film is produced in the narrow gap between the two seal faces. This film evaporates before it enters the atmosphere, making the mechanical shaft seal liquid tight. During operation the liquid forms a lubricating film between the seal faces. This lubricating film consists of a hydrostatic and a hydrodynamic film. The thickness of the lubricating film depends on the pump speed, the liquid temperature, the viscosity of the liquid and the axial forces of the mechanical shaft seal.

Fig 3.26 shows the optimum ratio between fine lubrication properties and limited leakage. As you can tell, the optimum ratio is when the lubricating film covers the entire seal gap, except for a very narrow evaporation zone close to the atmospheric side of the mechanical shaft seal.

Leakage due to deposits on the seal faces is often observed. When using coolant agents, deposits are built up quickly by the evaporation at the atmosphere side of the seal. When the liquid evaporates in the evap-

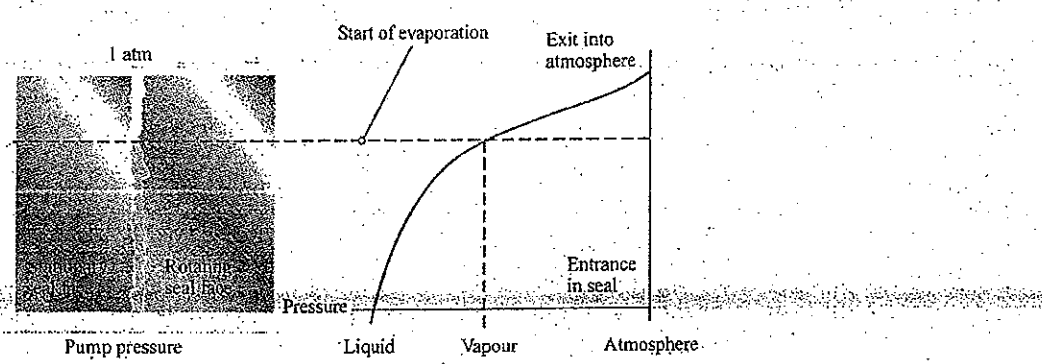


Fig 3.26 Schematic drawing of lubricating film

oration zone, microscopic solids in the liquid remain in the seal gap as deposits creating wear.

These deposits are seen in connection with most types of liquid. But when the pumped liquid has a tendency to crystallize, it can become a problem. The best way to prevent wear is to select seal faces made of hard material, such as tungsten carbide (WC) or silicon carbide (SiC). The narrow seal gap between these materials (app. 0.3 μm *Ra*) minimizes the risk of solids entering the seal gap and thereby minimizes the amount of deposits building up.

The main types of mechanical shaft seals are O-ring seal, bellows seal, and the one-unit seal - the cartridge seal. In an O-ring seal, sealing between the rotating shaft and the rotating seal face is done by an O-ring (below figure). The O-ring must be able to slide freely in the axial direction to absorb axial displacements as a result of changes in temperatures and wear. Incorrect positioning of the stationary seat may result in rubbing and thus unnecessary wear on the O-ring and on the shaft. O-rings are made of different types of rubber material, such as NBR, EPDM and FKM, depending on the operating conditions. A common feature of bellows seals is a rubber or metal bellows which functions as dynamic sealing element between the rotating ring and the shaft. In a cartridge mechanical shaft seal, all parts form a compact unit on a shaft sleeve, ready to be installed. A cartridge seal offers many benefits compared to conventional mechanical shaft seals.

In certain applications it is possible to extend the performance of the mechanical shaft seal by installing flushing. Flushing can lower the temperature of the mechanical shaft seal and prevent deposits from occurring. Flushing can be installed either internally or externally. Internal flushing is done when a small flow from the pump's discharge side is bypassed to the seal area. Internal flushing is primarily used to prevent further heat generation from the seal in heating applications. External flushing is done by a flushing liquid and is used to ensure trouble-free operation when handling liquids that are abrasive or contain clogging solids. The deposit rate is reduced to the minimum.

Double mechanical shaft seals are used when the life span of single mechanical shaft seals is insufficient due to wear caused by solids or too high/low pressure and temperature. Further, double mechanical shaft seals are used in connection with toxic, aggressive and explosive liquids to protect the surroundings. Two types of double mechanical shaft seals exist, the double seal in a tandem arrangement and the double seal in a back-to-back arrangement.

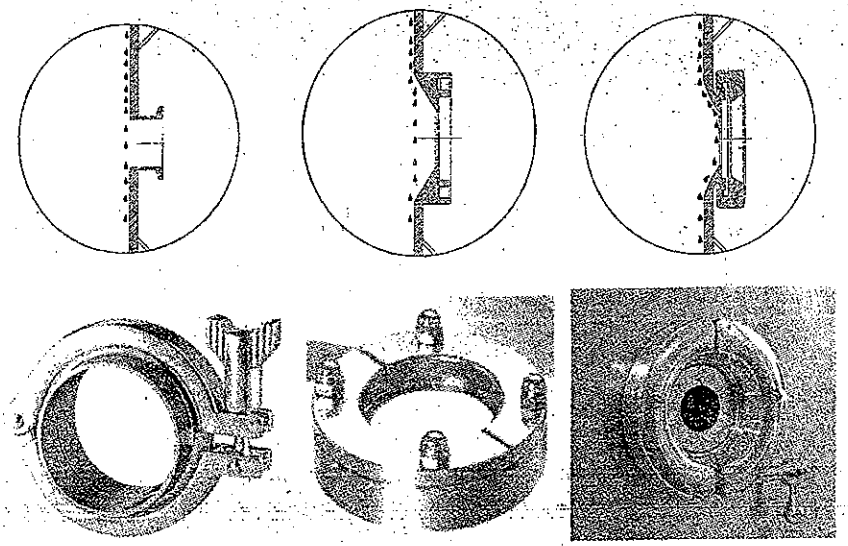
The major materials used in mechanical shaft seals include tungsten carbide/tungsten carbide (WC/WC), silicon carbide/silicon carbide (SiC/SiC) and carbon/tungsten carbide or carbon/silicon carbide.

Cemented tungsten carbide covers the type of hard metals that are based on a hard tungsten carbide (WC) phase and usually a softer metallic binder phase. The correct technical term is cemented tungsten carbide, however, the abbreviated term tungsten carbide (WC) is used for convenience. Cobalt-bonded (Co) WC is only corrosion resistant in water if the pump incorporates base metal, such as cast iron. Chromium-nickel-molybdenum-bounded WC has a corrosion resistance equal to EN 14401. Sintered binderless WC has the highest corrosion resistance. However, its resistance to corrosion in liquids, such as hypochlorite, is not as high. The material pairing WC/WC is extremely wear resistant, very robust, and has poor dry-running properties. In case of dry-running, the temperature increases to several hundred degrees Celsius in very few minutes and consequently damages the O-rings.

If a certain pressure and a certain temperature are exceeded, the seal may generate noise. Noise is an indication of poor seal operating conditions that in the long term may cause wear of the seal. The limits of use depend on seal face diameter and design. To a WC/WC seal face pairing, the running-in wear period where noise is to be expected may last 3-4 weeks, although typically, no noise occurs during the first 3-4 days.

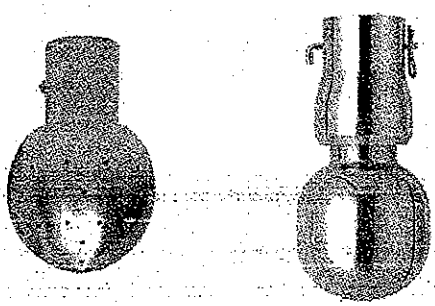
Silicon carbide/silicon carbide (SiC/SiC) is an alternative to WC/WC and is used where higher corrosion resistance is required. The SiC/SiC material pairing is very brittle and extremely wear resistant. SiC ($Q1^S$, $Q1^P$ and $Q1^G$) hardly corrodes, irrespective of the pumped liquid type. However, an exception is water with very poor conductivity, such as demineralised water, which attacks the SiC variants $Q1^S$ and $Q1^P$, whereas $Q1^G$ is corrosion resistant also in this liquid. In general, these material pairings have poor dry-running properties. However, the $Q1^G$/ $Q1^G$ material withstands a limited period of dry-running on account of the graphite content of the material. For different purposes, various SiC/SiC variants exist.

Carbon/tungsten carbide or carbon/silicon carbide has a carbon seal, which is very brittle, can be worn by liquids containing solid particles, has good corrosion resistance and good dry-running properties (temporary dry-running). The self-lubricating properties of carbon make the seal suitable for use even with poor lubricating conditions (high temperature) without generating noise. However, such conditions will cause wear of the car-



(a) Clamp connection (b) NA clamp connection (c) Kest sterile connection

Fig 3.7 Sanitary sterile connections



(a) Fixed (b) Rotating

Fig 3.8 Spray devices for tank

flow rate for WFI are restricted by the design and the operation of the water systems. So the cleaning effect is not very satisfactory. The cleaning pressure is required to be rather high, the water consumption and the cleaning reagent consumption are high, the cleaning holes can be easily blocked and rouge can develop. So they have been gradually replaced by tangent cleaning balls.

Tangent cleaning balls [Fig 3.8 (b)] are also called rotary cleaning balls. They are low pressure and low flow rate cleaning balls. A tangent cleaning ball is composed of a tangent water spraying ball and a connecting rod that can be rotated rapidly. The impact force of the water flow is used to make the tangent water spraying ball rotate rapidly. Its working principle is that the cleaning liquid is continuously sprayed tangentially in a type of fan-shaped vortex flow. The combination of vibration and physical impact is used to spray the cleaning liquid evenly onto the tank internal wall. The tangent cleaning balls have medium working pressure (0.5 to 10 bar). The commonly used working pressure is 1 to 5 bar. The impact force at the time of cleaning is relatively strong. Only a small amount of cleaning reagent is required to obtain an ideal cleaning effect. They are mainly used for tanks that are easy to clean. At the same time, the surface wetting action from a tangent spraying device is very significant. They have been widely accepted in the pharmaceutical industry because they are easy to install, economic, energy saving and water saving.

Different from fixed cleaning balls, tangent cleaning balls are water lubricating spraying devices. Professional rotary cleaning ball abrasion test show that about 17,300 m^3 of cleaning water will go through the spraying device if it is run at 2.7bar continuously for 1,100 hours, and the loss of mass of the spraying device is 0.09 g, which is equivalent to a theoretical shed iron chip concentration of 0.0052 ppb. This concentration is far lower than the quality criteria for iron in the pharmaceutical industry. However, particulate contamination risks caused by dry frictions of spraying devices rotating at a high speed must be avoided. It is not allowed to blow with compressed air or other inert gases, or severe rouge and particulate contamination can be caused. High attention is required for the use of a tangent spraying cleaning ball.

3.1.5 Sanitary Heat Exchangers

In a typical application of pharmaceutical water systems, the heat exchanger is usually a pressure ves-

sel. It is a type of energy saving equipment that realizes the transfer of heat between two or more flowing liquids. The heat is transferred from the fluid with a higher temperature to the fluid with a lower temperature to raise it to the required temperature to meet the process requirements. At the same time, a heat exchanger is also a major type of equipment for the improvement of the energy utilization rate.

Heat exchangers can be divided into heating/cooling heat exchangers, pre-heaters, over-heaters and evaporators based on their uses. Heating/cooling heat exchangers are used to heat/cool a liquid to the required temperature. However, there is no change of phase for the liquid to be heated/cooled. For example, the major function of the heat exchanger in a PW distribution system is to maintain the temperature of the system and for periodic sanitization of the system. It is generally placed at the return pipe at the end of the distribution systems. And the heat exchangers at the user point distribution loop are mainly used to lower the water temperature. The pre-heaters are used to heat up a fluid to ensure the standard process parameters of a process, such as the pre-heater of a multi-effect still. The over-heaters are used to heat a fluid (process gas or steam) to the over-heated status. For example, the heat exchanger of WFI distribution systems is mainly used to maintain the water temperature within the systems and for the periodic sterilization of the systems with over-heated water. Evaporators are used to heat a type of fluid to a temperature above its boiling point so that the fluid evaporates. There is generally a phase change. The most typical evaporators used in pharmaceutical water systems include multi-effect stills and thermocompression water stills.

In pharmaceutical water systems, the often used heat exchangers include shell and tube heat exchangers, plate heat exchangers and tube in tube heat exchangers. Other heat exchangers (such as displacement heat exchangers) are also used in the soft ware systems.

a. Shell and tube heat exchangers. A shell and tube heat exchanger is mainly composed of the shell, the tube bundle, the tube sheet and the head (Fig 3. 9). The shell is round in most cases. Parallel or spiral tube bundles are installed within the shell and the two ends of the tube bundles are fixed on the tube sheets. For the two types of fluid used for the transfer of heat within a shell and tube heat exchanger, one flows within the tubes, which is called tube pass. The other type of fluid flows outside the tube, which is called the shell pass. The tube bundle walls are used as the heat transfer surface. Most shell and tube heat exchangers are metal structures using 316 L stainless steel as the major material. They are divided into straight ones and U ones. Shell and tube heat exchangers are easy to clean and can effectively inhibit the microbial growth. They have become the most widely used heat exchangers in pharmaceutical water systems.

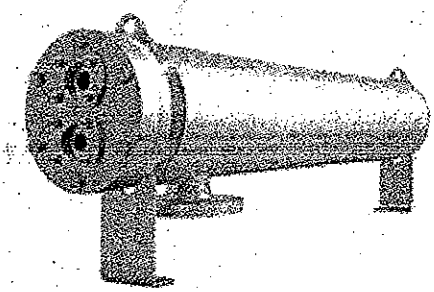


Fig 3. 9 Double plate tube heat exchangers

In order to prevent any cross contamination, the *Inspection Guide for High Purity Water* of the US FDA suggests that the following two methods should be used. First, double tube sheet (DTS) heat exchangers should be used. Second, the differential pressure between the two sides should be monitored continuously to ensure that the pressure at the clean side is always higher than that at the non-clean side. The double tube sheet design has become the mainstream for the heat exchangers used in pharmaceutical water systems, such as the pre-heater and the evaporation columns of multi-effect stills, the heat exchangers of storage and distribution systems, and the cooling heat exchangers at points of use. Fig 3. 10 shows the design schematic drawing of a typical double tube sheet heat exchanger. There is an inspection port for the easy leakage inspection between two plate sheets. When there is a leak at the connection between a tube and a tube sheet, the leakage of fluid will go to the atmosphere, not the process flow. However, it should be noted that this type of design cannot solve any issues caused by the pipe failures. If it can be ensured that a higher pressure is always maintained at the fluid of higher purity, such as between the second effect and the final effect of a multi-effect still, single tube sheet heat exchangers can also be used. In these evaporators, the design of the multi-effect still determines whether the pure steam is at higher pressure.

The combination of hydraulic expansion and

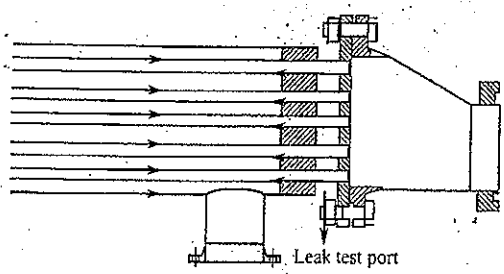


Fig 3.10 Design schematic drawing of double tube sheet heat exchangers

welding is used for shell and tube heat exchangers, which maximally ensures the process safety. Some suppliers can provide products using double expansion connection technology. For a shell and tube heat exchanger, there is an O ring conforming to the US FDA requirements at each end of the head to facilitate maintenance and spare part replacement activities. The seal ring materials are usually EPDM, Silicon, Vition and Teflon, and the temperature can reach as high as 250 ℃. Seamless steel tubes of different sizes, such as 8×1, 10×1 and 12×1 are used for the tube pass heat exchange internal tubes. Stainless steel tubes are also used as the sleeve tubes at the shell pass. The cold medium and the hot medium flow within the inner tube and the sleeve tube gap respectively. And the heat exchange is completed during the flow. The cold medium and the hot medium flow within their respective passes and will not be mixed together, which can completely avoid any cross contamination (Fig 3.11).

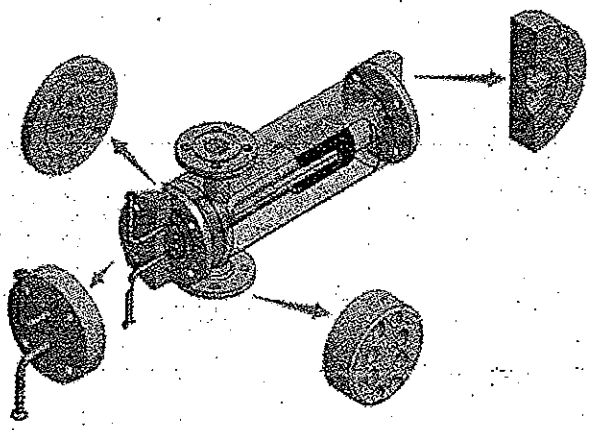


Fig 3.11 Structure of double tube shell heat exchangers

Because of the temperature difference between the shell pass medium and the tube pass medium, the expansions are different at the two sides. The higher the temperature difference, the higher the thermal stress of the shell and the tube bundle will be. The installation of expansion joints on the shell can effectively prevent any leakage or damages caused by the different thermal expansions, to improve and reduce the load of each of the components. In order to improve the performance of a single expansion joint, a bellow expansion joint can be installed on a heat exchanger. It can effectively remove any stresses and prolong the service life of the heat exchanger. The cost of a bellow expansion joint is high and its structure is very precise. There are certain requirements on the dimensions and the material. Special care should be taken at the time of manufacturing to avoid any defects such as perforation, damages or loss of stability. It must be ensured that the entire clean side of the heat exchanger can be completely self drained to facilitate SIP/CIP.

b. Plate heat exchangers. Plate heat exchangers are typical dividing wall heat exchangers (Fig 3.12). They have a long history of application in the industry. And they still play a leading role. The main structures of a plate heat exchanger include the heat exchange plates and the rubber bars between the plates. They are mainly used for the heat exchange between liquids or between liquid and steam. In order to improve the heat transfer coefficient of the fluid outside the tube, a certain number of transverse deflection baffles are installed within the shell. The deflection baffles can not only prevent any short-cut of the fluid flow and increase the fluid flow rate, but also force the fluid to pass the tube bundle for multiple times following specified paths, which greatly increases the turbulence of the flow.

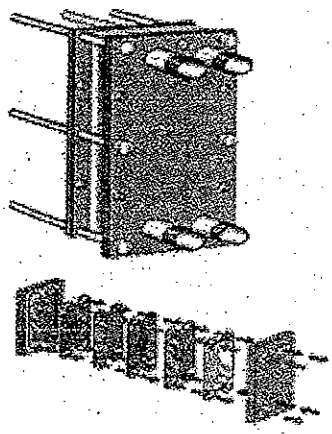


Fig 3.12 Structure of plate heat exchangers

Plate heat exchangers are smaller and easy to maintain and install. The number of plates can be increased easily to increase the heat exchange area of the heat exchanger. Plate heat exchangers can also be designed with a double plate structure (Fig 3.13). Al-

though a double-plate plate heat exchanger is relatively lower in price, it has certain microbial contamination risk because it cannot be emptied by itself. So the ISPE recommends that plate heat exchangers are not allowed in the storage and distribution systems. However, they can be used in the pretreatment and purification steps of a PW system.

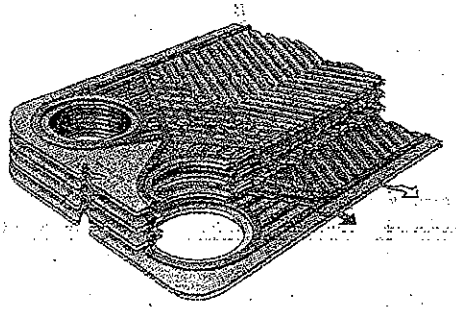


Fig 3.13 Design schematic drawing of double-plate plate heat exchangers

c. Tube in tube heat exchangers. The tube in tube heat exchangers are a reasonable application of U tubes. The most typical application is the single point WFI cooling module (Fig 3.14). This equipment is a Sub-loop cooling system with a modular design. The design concept of a pitot tube is used to ensure the back pressure of the main loop. The design is compact and the installation, operation and maintenance activities can be very convenient. They are especially suitable for the point of use cooling of WFI for such simple and open applications as sinks and QC sampling points.

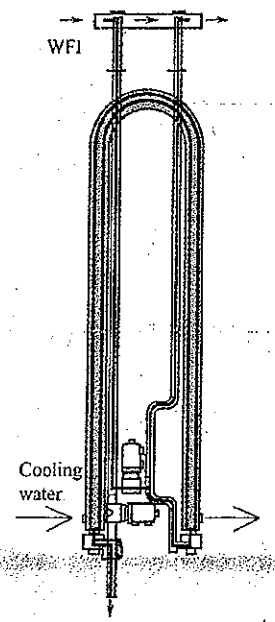


Fig 3.14 Application of tube in tube heat exchangers

3.2 Centrifuge Pumps

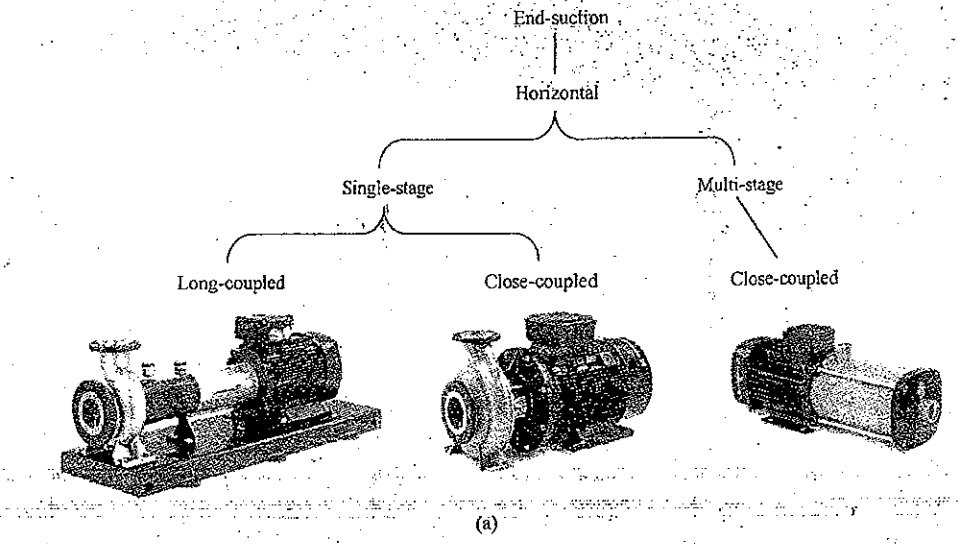
The centrifugal pump is the most common pumps of all types. It is widely used in such industries as dairy products, beer, beverage, pharmaceuticals, biologicals, cosmetics and fine chemicals. The working principle of a centrifugal pump is that the pump chamber is first filled with liquid, then the motor drives the shaft and the impellers to rotate, during which process a centrifugal force is generated, and the liquid is thrown away from the center of the impellers during a circular motion. At the same time, a low pressure area is created at the center of the impellers, a differential pressure is created between the low pressure area and the surface of the liquid sucked in. So the liquid is continuously sucked in and expelled out at a certain pressure, which allows the continuous transfer of the liquid. Fig 3.15 shows the classification of centrifugal pumps by the connection mode, the installation mode and the number of impellers.

According to the working conditions, the centrifugal pumps used in the pharmaceutical industry are divided into ordinary centrifugal pumps and self-priming centrifugal pumps. The ordinary centrifugal pumps are further divided into single stage centrifugal pumps and multistage centrifugal pumps according to their flow and head. Based on the different cleanness requirements of the pharmaceutical industry, centrifugal pumps are divided into non-sanitary pumps, sanitary centrifugal pumps and sterile centrifugal pumps (Fig 3.16).

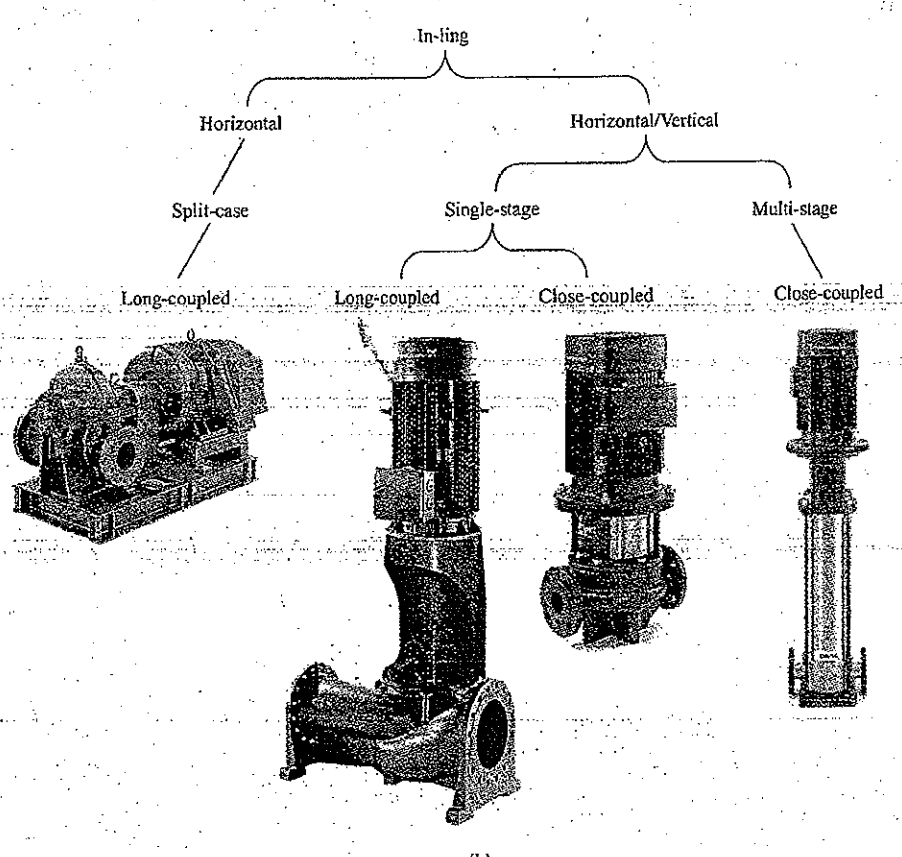
3.2.1 Multistage Centrifugal Pumps

The multistage centrifugal pumps are those with two or more rows of impellers placed side by side within the pump chamber to increase the head. In the pharmaceutical industry, in some cases centrifugal pumps with a low flow rate (of no more than 15 t/h) and a high head (of more than 12 bar) are required. Multistage centrifugal pumps can meet this type of requirement.

Multistage centrifugal pumps are divided into industry type and sanitary type. An industry type multistage pump has many deadleg by design and cannot be cleaned through CIP. A sanitary multi-stage centrifugal pump has a type of open and deadleg free design, which can meet the CIP requirements and effectively



(a)



(b)

Fig 3.15 Centrifugal pump classification

ensure the cleanness within the pump chamber. And at the same time, a sanitary multistage centrifugal pump needs to meet the material requirements for a single stage centrifugal pump by design, conforms to the open design requirements of a sanitary single stage centrifugal pump, and uses the internal mechanical seal design (Fig 3.17).

In the pharmaceutical industry, when a sterile multistage centrifugal pump is used for the transfer of a type of liquid, the pump must meet the following design requirements: Stainless steel press forged parts should be used and no casted parts are allowed. Open or partially open impellers should be used. Sterile connectors should be used. Higher level sterile mechanical seals should be used. The springs should be built-in and not in contact with the material. The pump internal surface should be electropolished and passivated. The surface roughness *Ra* should be no more than 0.5

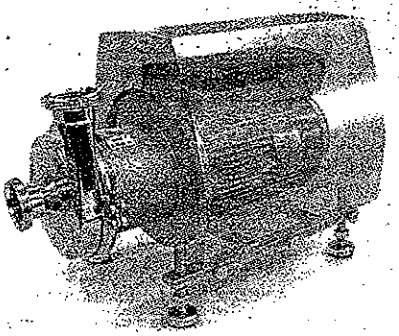
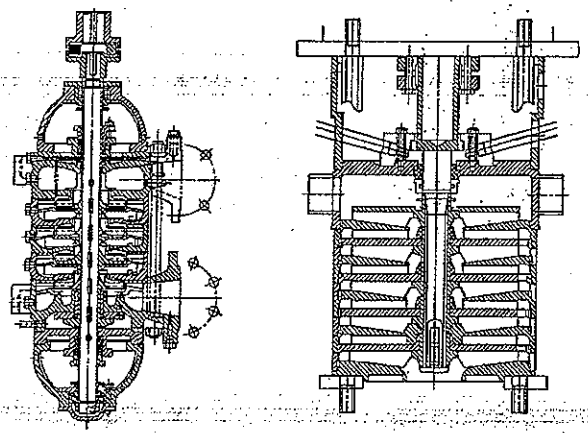


Fig 3. 16 Sterile centrifugal pumps



(a) industry type (b) sanitary type

Fig 3. 17 Multistage centrifugal pumps

μm. It should be installed vertically with the inlet at the bottom. It should be possible for the pump to be emptied when it is not running (Fig 3. 18).

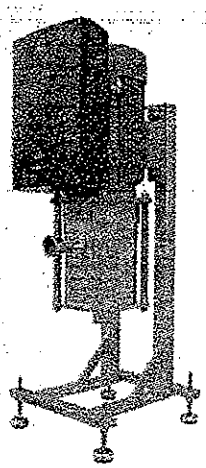


Fig 3. 18 Sterile multistage centrifugal pumps

In pharmaceutical water systems, industrial vertical multistage centrifugal pumps are used more widely; the booster pump before the RO membrane and the water supplementation pump between the multi-effect still and the pure steam generation are all vertical multistage centrifugal pumps. The major components of a vertical multistage centrifugal pump include motor, shaft seal, sleeve, chamber stake, base and connectors (Fig 3. 19).

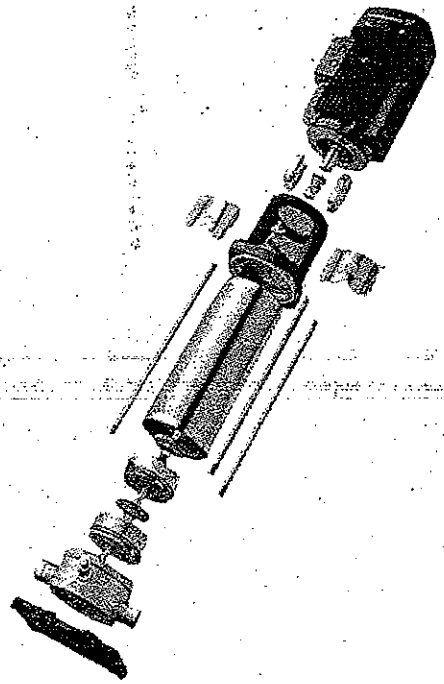


Fig 3. 19 Vertical multistage centrifugal pumps

a. Motor. Motors are used in many applications all over the world. The purpose of the electric motor is to create rotation, that is to convert electric energy into mechanical energy, to drive the pump.

NEMA and IEC are the two major international standards for motors. The National Electrical Manufacturers Association (NEMA) sets standards for a wide range of electric products, including motors. NEMA is primarily associated with motors used in North America. The standards represent general industry practices and are supported by the manufacturers of electric equipment. The standards can be found in NEMA Standard Publication No. MG1. Some large motors may not fall under NEMA standards. The International Electrotechnical Commission (IEC) sets standards for motors used in many countries around the world. The IEC 60034 standard contains recommended electrical practices that have been developed by the participating IEC countries.

Three different ways of mounting the motor exist: Foot-mounted motor, flange-mounted motor with free-hole flange (FF) and flange-mounted motor with tapped-hole flange (FT). Fig 3. 20 shows the different ways of mounting a motor and the standards that apply for the mountings.

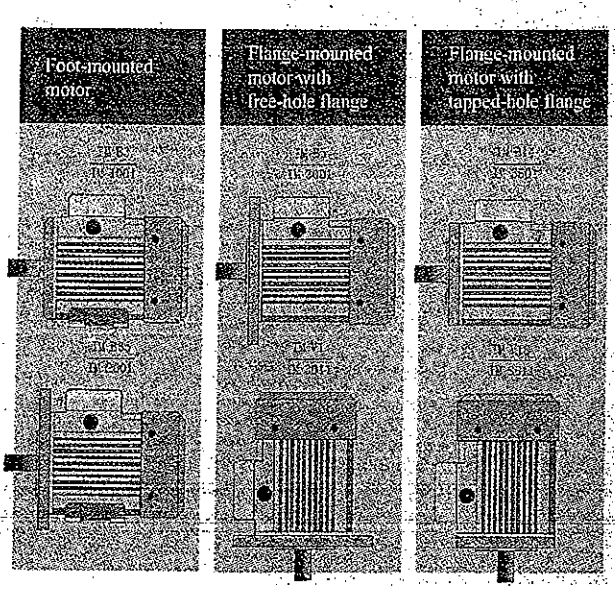


Fig 3.20 Motor mounting ways

The enclosure class states the degrees of protection of the motor against ingress of solid objects and water. The enclosure class is stated by means of two letters IP followed by two digits, for example IP55. The first digit stands for protection against contact and ingress of solid objects and the second digit stands for protection against ingress of water (Table 3.1). Drain holes enable the escape of water which has entered the stator housing, for instance through condensation. When the motor is installed in a damp environment, the bottom drain hole should be opened. Opening the drain hole changes the motor's enclosure class from IP55 to IP44.

Fig 3.21 gives an overview of the relation between frame size, shaft end, motor power and flange type and size. For motors in frame sizes 63 up to and including 315M, the relationship is specified in EN 50347. For motors with frame size 315 L and larger, no standard covers this relation. Flanges and shaft ends comply with EN 50347 and IEC 60072-1. Some pumps have a coupling, which requires a smooth motor shaft end or a special shaft extension which is not defined in the standards.

The insulation class is defined in the IEC 60085 standard (Fig 3.22) and tells something about how robust the insulation system is to temperatures. The life of an insulation material is highly dependent on the temperature to which it is exposed. The various insulation materials and systems are classified into insulation classes depending on their ability to resist high temperatures.

Table 3.1 Motor enclosure class specifications

First digit		Second digit	
Protection against contact and ingress of solid objects		Protection against ingress of water0.	
0	No special protection	0	No special protection
1	The motor is protected against solid objects larger than 55 mm, e. g. a hand	1	The motor is protected against vertically falling drops of water, such as condensed water
2	The motor is protected against objects larger than 12 mm, e. g. anger	2	The motor is protected against vertically falling drops of water, even if the motor is tilted at an angle of 15°
3	The motor is protected against solid objects larger than 25 mm, i. e. wires, tools, etc.	3	The motor is protected against water spray falling at an angle of 60° from vertical
4	The motor is protected against solid objects larger than 1 mm, e. g. wires	4	The motor is protected against water splashing from any direction
5	The motor is protected against ingress of dust	5	The motor is protected against water being projected from a nozzle from any direction
6	The motor is completely dust-proof	6	The motor is protected against heavy seas or high-pressure water jets from any direction
		7	The motor is protected when submerged from 15 cm to 1 m in water for a period specified by the manufacturer
		8	The motor is protected against continuous submersion in water under conditions specified by the manufacturer

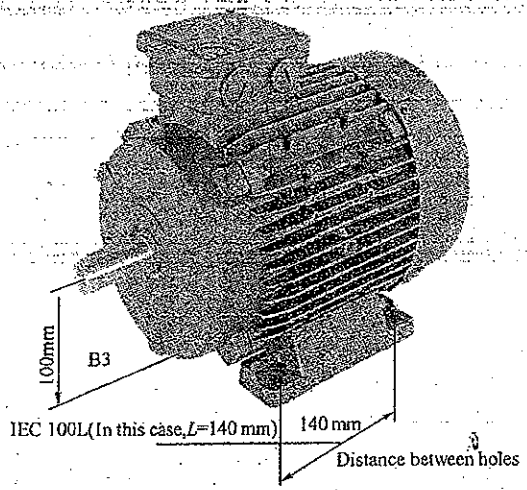
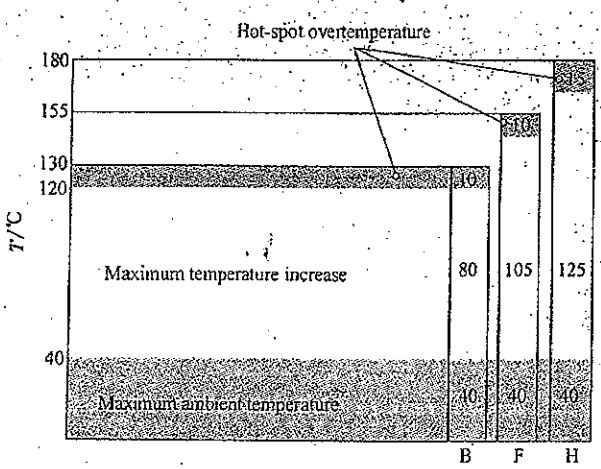


Fig 3.21 Motor dimensions overview

The motor's rated voltage lies within a certain voltage range. According to the international standard IEC 60038, the motor has to be able to operate with a main voltage tolerance of ±10%. For motors that are designed according to the IEC 60034—1 standard with a wide voltage range, e. g. 380-415 V, the main voltage may have a tolerance of ±5%. The permissible maximum temperature for the actual insulation class should not be exceeded when the motor is operated within the rated voltage range. For conditions at the extreme boundaries the temperature typically rises approx. 10K.

Generally speaking, electric motors are quite effi-



Class	Maximum ambient temperature/℃	Maximum temperature increase/K	Hot-spot overtemperature/K	Maximum winding temperature/℃
B	40	80	10	130
F	40	105	10	155
H	40	125	15	180

Fig 3.22 Motor insulation classes

cient. Some motors have electricity-to-shaft power efficiencies of 80-93% depending on the motor size and sometimes even higher for larger motors. Two types of energy losses in electric motors exist: Load-dependent losses and load-independent losses. Load-dependent losses vary with the square of the current and cover, which mainly include stator winding losses (copper losses), rotor losses (slip losses), and stray losses (in different parts of the motor). Load-independent losses in the motor include iron losses (core losses) and mechanical losses (friction).

On July 23rd, 2009, the EU passed a resolution, deciding to make IE2 the mandatory minimum energy performance standard for motors by June 16th, 2011, IE3 the minimum energy performance standard for the 7.5-375 kW motor by January 1st, 2015, and IE3 the mandatory minimum energy performance standard for motors by January 1st, 2017.

On the basis of the national standard, GB 18613—2006 version, (the energy performance fixed value and the grading standard of small and mid-sized three-phase asynchronous motor), our country decided to make the 2nd level energy performance (equivalent to IE2) the mandatory minimum energy performance from January 1st, 2012. On September 1st of the same year, the national standard was upgraded. The new national standard, GB 18613—2012 version, lowers the level of the motor energy performance standard, with the original 1st level downgrading to 2nd level. And the 3rd level energy performance (equivalent to IE2) is regarded as the mandatory minimum energy performance in the standard. According to the new standard, the 2nd level energy performance (equivalent to IE3) will be regarded as the minimum energy performance standard for the 7.5-315 kW motors four years later (beginning from September 1, 2016), and five years later it (equivalent to IE3) will be regarded as the minimum energy performance standard for motors with a power less than 7.5 kW.

b. Motor stool. The motor stool is used for fixing the motor and pump head. As an interconnecting piece of two main units, the production of the motor stool demands very high machining accuracy, especially for concentricity. The pump head, as the name implies, is the top part of the pump body. Usually, a mechanical seal is installed on the top of pump head. And normally there are also an airvent and a filling opening on the pump head.

Motor stools and pump heads can be integrated, but also separated. Fig 3.23 shows the separated pump head and motor stool usually used for stainless steel vertical multistage centrifuge pumps. The pump head material is stainless steel and the motor stool material is cast iron.



Fig 3.23 Motor stool and pump head

c. Shaft seal. From the middle of the 1950s mechanical shaft seals gained ground in favor of the traditional sealing method the stuffing box. Compared to stuffing boxes, mechanical shaft seals provide the following advantages:

- They keep tight at smaller displacements and vibrations in the shaft.
- They do not require any adjustment.
- Seal faces provide a small amount of friction and thus, minimize the power loss.
- The shaft does not slide against any of the seal's components and thus, is not damaged because of wear (reduced repair costs).

The mechanical shaft seal is the part of a pump that separates the liquid from the atmosphere. Fig 3.24 shows an example of a shaft seal which is installed on a vertical multi-stage centrifugal pump. The majority of mechanical shaft seals are produced according to the European standard EN 12756. Before choosing a shaft seal, there are certain things that are needed to be known about the liquid, like the seal's resistance to the liquid, including the type of liquid, the pressure that the shaft seal is exposed to, the speed that the shaft seal is exposed to, and the built-in dimensions.

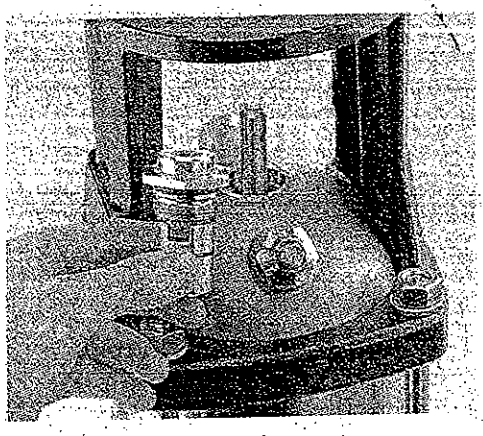


Fig 3.24 Shaft seal

The mechanical shaft seal is made of two main components, a rotating part and a stationary part. Fig 3.25 shows the parts of the mechanical seal and where the different parts are placed in the seal. The stationary part of the seal is fixed in the pump housing. The rotating part of the seal is fixed on the pump shaft and rotates when the pump operates.

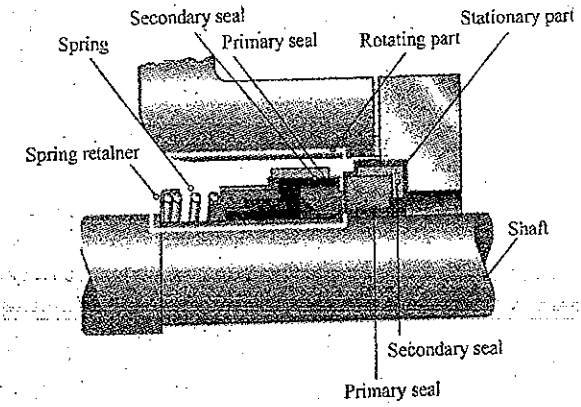


Fig 3.25 Schematic drawing of mechanical seal

The two primary seal faces are pushed against each other by the spring and the liquid pressure. During operation a liquid film is produced in the narrow gap between the two seal faces. This film evaporates before it enters the atmosphere, making the mechanical shaft seal liquid tight. During operation the liquid forms a lubricating film between the seal faces. This lubricating film consists of a hydrostatic and a hydrodynamic film. The thickness of the lubricating film depends on the pump speed, the liquid temperature, the viscosity of the liquid and the axial forces of the mechanical shaft seal.

Fig 3.26 shows the optimum ratio between fine lubrication properties and limited leakage. As you can tell, the optimum ratio is when the lubricating film covers the entire seal gap, except for a very narrow evaporation zone close to the atmospheric side of the mechanical shaft seal.

Leakage due to deposits on the seal faces is often observed. When using coolant agents, deposits are built up quickly by the evaporation at the atmosphere side of the seal. When the liquid evaporates in the evap-

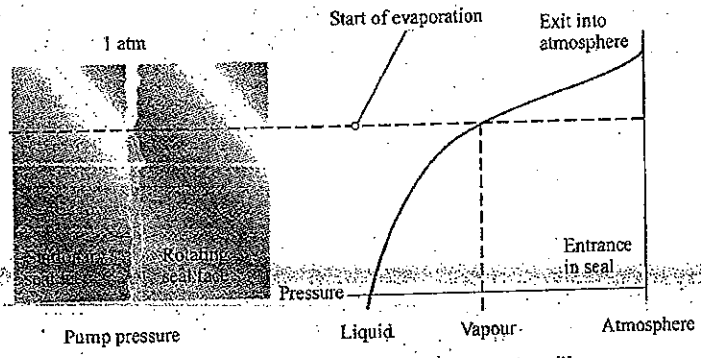


Fig 3.26 Schematic drawing of lubricating film

oration zone, microscopic solids in the liquid remain in the seal gap as deposits creating wear.

These deposits are seen in connection with most types of liquid. But when the pumped liquid has a tendency to crystallize, it can become a problem. The best way to prevent wear is to select seal faces made of hard material, such as tungsten carbide (WC) or silicon carbide (SiC). The narrow seal gap between these materials (app. 0.3 μm Ra) minimizes the risk of solids entering the seal gap and thereby minimizes the amount of deposits building up.

The main types of mechanical shaft seals are O-ring seal, bellows seal, and the one-unit seal - the cartridge seal. In an O-ring seal, sealing between the rotating shaft and the rotating seal face is done by an O-ring (below figure). The O-ring must be able to slide freely in the axial direction to absorb axial displacements as a result of changes in temperatures and wear. Incorrect positioning of the stationary seat may result in rubbing and thus unnecessary wear on the O-ring and on the shaft. O-rings are made of different types of rubber material, such as NBR, EPDM and FKM, depending on the operating conditions. A common feature of bellows seals is a rubber or metal bellows which functions as dynamic sealing element between the rotating ring and the shaft. In a cartridge mechanical shaft seal, all parts form a compact unit on a shaft sleeve, ready to be installed. A cartridge seal offers many benefits compared to conventional mechanical shaft seals.

In certain applications it is possible to extend the performance of the mechanical shaft seal by installing flushing. Flushing can lower the temperature of the mechanical shaft seal and prevent deposits from occurring. Flushing can be installed either internally or externally. Internal flushing is done when a small flow from the pump's discharge side is bypassed to the seal area. Internal flushing is primarily used to prevent further heat generation from the seal in heating applications. External flushing is done by a flushing liquid and is used to ensure trouble-free operation when handling liquids that are abrasive or contain clogging solids. The deposit rate is reduced to the minimum.

Double mechanical shaft seals are used when the life span of single mechanical shaft seals is insufficient due to wear caused by solids or too high/low pressure and temperature. Further, double mechanical shaft seals are used in connection with toxic, aggressive and explosive liquids to protect the surroundings. Two types of double mechanical shaft seals exist, the double seal in a tandem arrangement and the double seal in a back-to-back arrangement.

The major materials used in mechanical shaft seals include tungsten carbide/tungsten carbide (WC/WC), silicon carbide/silicon carbide (SiC/SiC) and carbon/tungsten carbide or carbon/silicon carbide.

Cemented tungsten carbide covers the type of hard metals that are based on a hard tungsten carbide (WC) phase and usually a softer metallic binder phase. The correct technical term is cemented tungsten carbide, however, the abbreviated term tungsten carbide (WC) is used for convenience. Cobalt-bonded (Co) WC is only corrosion resistant in water if the pump incorporates base metal, such as cast iron. Chromium-nickel-molybdenum-bounded WC has a corrosion resistance equal to EN 14401. Sintered binderless WC has the highest corrosion resistance. However, its resistance to corrosion in liquids, such as hypochlorite, is not as high. The material pairing WC/WC is extremely wear resistant, very robust, and has poor dry-running properties. In case of dry-running, the temperature increases to several hundred degrees Celsius in very few minutes and consequently damages the O-rings.

If a certain pressure and a certain temperature are exceeded, the seal may generate noise. Noise is an indication of poor seal operating conditions that in the long term may cause wear of the seal. The limits of use depend on seal face diameter and design. To a WC/WC seal face pairing, the running-in wear period where noise is to be expected may last 3-4 weeks, although typically, no noise occurs during the first 3-4 days.

Silicon carbide/silicon carbide (SiC/SiC) is an alternative to WC/WC and is used where higher corrosion resistance is required. The SiC/SiC material pairing is very brittle and extremely wear resistant. SiC ($Q1^S$, $Q1^P$ and $Q1^G$) hardly corrodes, irrespective of the pumped liquid type. However, an exception is water with very poor conductivity, such as demineralised water, which attacks the SiC variants $Q1^S$ and $Q1^P$, whereas $Q1^G$ is corrosion resistant also in this liquid. In general, these material pairings have poor dry-running properties. However, the $Q1^G$/ $Q1^G$ material withstands a limited period of dry-running on account of the graphite content of the material. For different purposes, various SiC/SiC variants exist.

Carbon/tungsten carbide or carbon/silicon carbide has a carbon seal, which is very brittle, can be worn by liquids containing solid particles, has good corrosion resistance and good dry-running properties (temporary dry-running). The self-lubricating properties of carbon make the seal suitable for use even with poor lubricating conditions (high temperature) without generating noise. However, such conditions will cause wear of the car-

bon seal face leading to reduced seal life. The wear depends on pressure, temperature, liquid type and seal design.

Low speeds reduce the lubrication between the seal faces, as a result, increased wear may be expected. However, this is normally not the case because the distance that the seal faces have to move is reduced. Metal-impregnated carbon offers limited corrosion resistance, but improved mechanical strength, heat conductivity and thus reduced wear. With reduced mechanical strength, but higher corrosion resistance, synthetic resin-impregnated carbon covers a wide application field. Synthetic resin-impregnated carbon is approved for drinking water. The use of carbon/SiC for hot water applications may cause heavy wear of the SiC, depending on the quality of the carbon and water. This type of wear primarily applies to $Q1^S$/carbon. The use of $Q1^P$, $Q1^G$ or a carbon/WC pairing causes far less wear. Thus, carbon/WC, carbon/$Q1^P$ or carbon/$Q1^G$ are recommended for hot water systems.

d. Sleeve. The sleeve, also called outer sleeve (Fig 3.27), is the shell of the vertical multistage centrifugal pump. The outer sleeve always uses stainless steel. Usually, there are two types of manufacturing techniques, one is welding the stainless steel plate, and the other is stretching the stainless steel pipe. The welded sleeve, due to the seam, has many defects, such as poor machining accuracy, poor static indentation, poor thermal adaptability, and poor corrosion resistance. Correspondingly, the stretched sleeve outperforms the one welded in above properties.

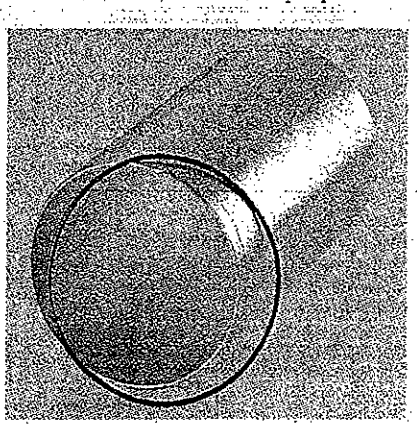


Fig 3.27 Sleeve

e. Chamber stack. The chamber stack (Fig 3.28), also called rotary components, is the main part of the vertical multistage centrifugal pumps. It is composed of shaft, impeller, chamber, bearing ring, spacer and other parts, which are assembled according to a certain principle and sequence. The chamber stack and the design, material, processing and assembling quality of its components directly decide the efficiency of the pump.

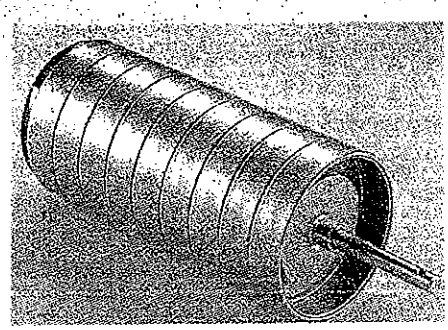


Fig 3.28 Chamber stack

The shaft, as the spine of the whole chamber stack, has high requirements on its design, material and processing. The vertical, multistage centrifugal pump is usually made of stainless steel to ensure the high rigidity, corrosion resistance and abrasion resistance of the pump (Fig 3.29). In design, the small-size vertical multistage centrifugal pump usually uses the star section structure and oval section structure. As for the overall performance, the design of star section is much better than that of the oval section. The picture below presents the star section design. The large-size vertical multistage centrifugal pump usually uses the round optical axis. As for the machining accuracy, the shaft is the basis for other components' installation, as well as the key component for the transfer of mechanical forces. So shaft should have high rigidity and machining accuracy to minimize the radial wobbles and to support other components well when the chamber stack spins at high speed.

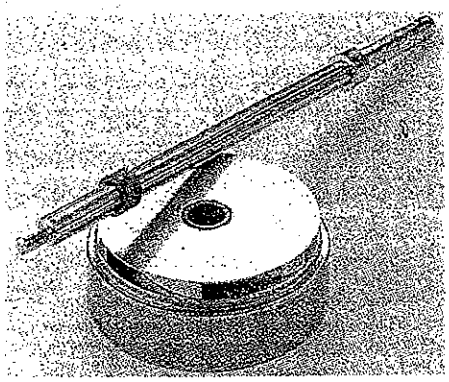


Fig 3.29 Shaft

The bearing ring and bearing chamber are installed in pairs in the chamber stack. Usually, the higher the stage (the number of impellers) of the pump, the more bearing ring and bearing chambers are installed. They are paired balanced and installed inside the chamber stack. The main function of the bearing

ring and bearing chamber is to absorb radial forces, and to ensure that the shaft always maintains a high concentricity while spinning in a high speed. So, in most cases, the vertical multistage centrifugal pump equipped with bearing ring and bearing chamber has a much longer service life and better stability than those without this type of design. The bearing ring inset in the bearing chamber is called static bearing ring. The bearing ring on the shaft is called rotary bearing ring. The rotary bearing ring should rotate synchronously with the shaft, so it must have good contact with the shaft. The material selection of the rotary bearing ring and the static bearing ring should give priority to good rigidity and abrasion resistance. SiC and WC are appropriate materials.

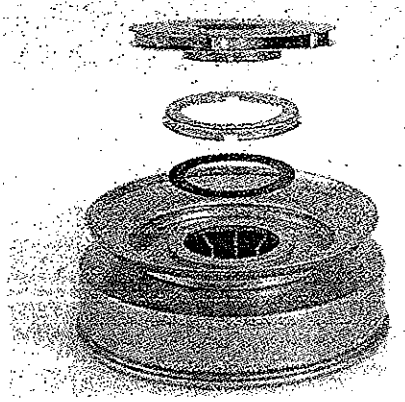


Fig 3. 30 Impeller and chamber

The impeller and chamber are key components of vertical multistage centrifugal pumps. Their material, design and precision will directly affect the efficiency of pumps. The impeller and chamber are usually made of stainless steel above SS304 (Fig 3. 30). And as for the selection of stainless steel sheet, there is relatively high demand for the sheet's thickness, flatness, density and smooth finish. The design of the impeller and chamber's channel decides the pump's basic hydraulic efficiency. In vertical multistage centrifugal pumps, generally, the larger the impeller's channel, the larger the pump's flow, and the more impellers, the higher the pump's hydraulic head. The chamber is the only component in the chamber stack that does not rotate. Normally, only multistage pumps have this part. Its main function is flow leading. Of course, to enhance the pump's hydraulic efficiency, there are corresponding channels in the chamber. The production of impeller and chamber mainly uses stamping and welding. The impeller of the small-size vertical multistage centrifugal pumps usually is made using the spot welding technique. The impellers of the large-size vertical multistage centrifugal pumps are usually made using the laser welding technique.

The centrifugal pumps' impeller usually is an open impeller, semi-open impeller or closed impeller type. In order to gain the optimal efficiency, the vertical multistage centrifugal pumps usually use the closed impeller. Due to variations of material's thickness and density, every impeller must go through a balance test in production. Only the impeller that meets the dynamic balance requirements can ensure the pump having the due hydraulic balance and high efficiency.

The main function of the spacer (Fig 3. 31) is positioning every stage of impellers. Usually, the spacer is only used in multistage pumps with star section shaft. And it is always made of stainless steel.

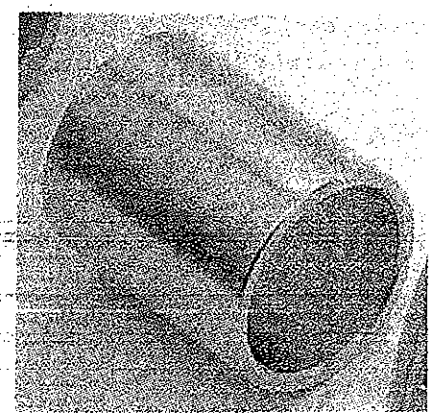


Fig 3. 31 Spacer

f. Base. In the vertical multistage centrifugal pumps of pipeline installation, there are both a suction side and a discharge side of the pump on the base. Good hydraulic design and good sealing design between the high-pressure chamber and the low-pressure chamber is the key to ensure the pump's high design efficiency. The base is usually equipped with a connector that connects the pipe (Fig 3. 32). Common connection types are

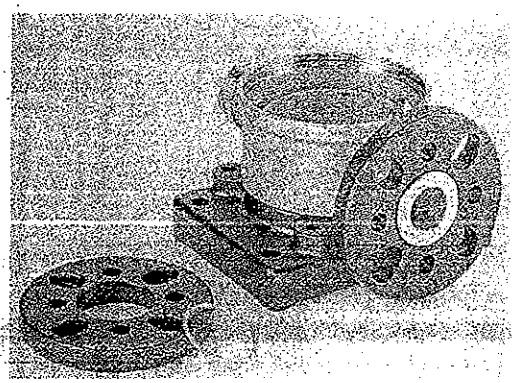


Fig 3. 32 Base and connection

flange, thread, clamp and so on. Among which the most common one is the flanged connection, whose frequently-used standards include DIN (Germany), JIS (Japan) and ANSI (the US). Some small-size vertical multistage centrifugal pumps could be equipped with the multipurpose flange with elliptical hole, which fits all the three standards mentioned above. The base also needs a drain for maintenance and freeze-proofing.

On a multistage centrifugal pump, some components may use cast iron materials for the motor shell, motor stool, pump head, base and flanges. For the sake of anti-corrosion and aesthetics, these components will be coated on the surface. At present, the most commonly used coating techniques are spray paint and Cathode Electro-deposition (CED). Out of the two the CED is better. Fig 3.33 shows an iron casting after CED treatment.

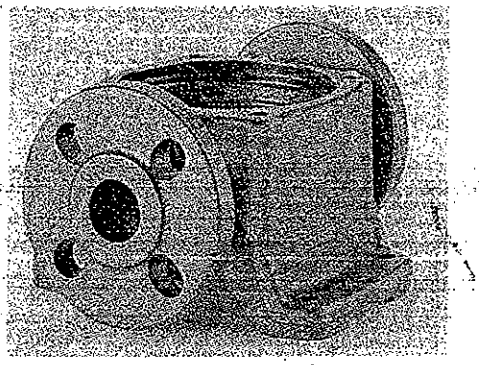


Fig 3.33 Cast ion part treated with CED

Cathode electro-deposition (CED) is a highly efficient, low-emission, non-toxic and widely applied decoration or protection technology for metal surface developed in the late 1980s. It is usually used in the coating of auto parts. After going through the CED coating, the iron casting will be pasted with a layer of epoxy (the thickness of which is usually about 30 μm), and the epoxy will permeate into the iron casting. This type of coating not only makes the external surface smooth, beautiful and not likely to fall off, it also has an excellent performance in corrosion resistance.

3.2.2 Single Stage Centrifugal Pump

There is only one impeller within the pump chamber of a single stage centrifugal pump. For the transfer of material within a fluid process system, sanitary single stage centrifugal pumps are widely used in the pharmaceutical industry for the transfer of water and drug solution and CIP. The material and the design of a sanitary centrifugal pump conform to the CIP and SIP requirements. The self-cleaning and self-cooling of the system is possible. And the degree of self-cleaning capacity is also a parameter for the determination of the degree of sanitary design.

The horizontal design is mainly adopted for sanitary centrifugal pumps. During operation the flow rate is comparatively slow and it is suitable for the transfer of such sensitive materials as sterile drug solutions and biological products, for they can reduce the damages to the solution ingredients. This type of pumps will not affect the odor or the color of the material. No such non-acceptable mechanical seal materials as graphite should be used. This type of pumps will not affect the cleanness of the material. For example, the risks of any contaminants or rust sediments within the pump chamber can be avoided. This type of pumps must conform to the requirements for in situ cleaning in place. This type of pumps must conform to the requirements for in situ steam in place. They should be resistant to high temperatures, acidic solutions or alkaline solutions. A good sanitary centrifugal pump should conform to the requirements in all such areas as the construction material, the pump design and certification.

a. Material requirements. The material contact parts should be made of AISI 316L stainless steel and its carbon content should be less than 0.02%. This is because during welding or at a temperature as high as 450-850 ℃, carbon can react with the chromium in the stainless steel to form chromium carbide and cause some areas that are poor in chromium, which can result in the decrease in the corrosion resistance of the steel material. So low carbon stainless steel materials should be used as much as possible. Stainless steel obtains its corrosion resistance by forming a very thin layer of firm, dense and stable chromium rich oxidation film (protection film) that can prevent the further penetration of oxygen and further oxidation. If this thin film is damaged, the oxygen in the air or the fluid can further penetrate into the metal and the iron will be released continuously to form a type of loose ferric oxide, and the surface will be continuously corroded.

The seal rings made of such materials as EPDM VITON, NBR, PTFE and KALREZ are all conforming to FDA requirements. Ethylene propylene terpolymer (EPDM) is highly resistant to high temperatures and can be used for long periods of time at 120 ℃ or intermittently at 130-150 ℃. It can well tolerate vapor and

its tolerance to over heated water is even better than its tolerance to hot water. So it is very suitable for SIP. It has excellent corrosion resistance and can well tolerate the acids, the bases and the cleaning reagents used during CIP. VITON (fluororubber) was first manufactured by Du Pont in 1956. It has excellent tolerance to high temperatures (for FDA grade up to 170 ℃) and resistance to chemical corrosion. Nitrile-butadiene rubber. (NBR) has excellent resistance to oils. However, it can only tolerate a temperature as high as 100 ℃. Polytetrafluoroethylene (PTFE) is excellent in corrosion resistance, insulation properties, resistance to high and low temperatures, self wetting, non-adhesive and resistance to atmospheric aging. However, its elasticity is rather poor. So it is seldom used in pumps. KALREZ (elastic rubber with full perfluorination) can satisfy almost all the material and temperature requirements of the pharmaceutical industry. Its maximum working temperature is as high as 250 ℃.

For the manufacturing of a centrifugal pump, the mechanical seal materials conforming to food grade requirements include SiC/SiC, WC/WC and stainless steel/special carbon. The mechanical seal materials conforming to pharmaceutical grade requirements include SiC/SiC and WC/WC. Any mechanical seal that requires the addition of a type of lubricant does not conform to the sanitary design requirements, even if the lubricant used is food grade. This is because it does not comply with the design concept for a sanitary pump.

Punching is a type of processing method that uses external forces applied on a stainless steel sheet or profile using a press machine and patterns to obtain a type of plastic deformation or separation, to get the work pieces (punched parts) with the required shape and dimensions. Forging is a processing method that uses external forces applied on a stainless steel piece to obtain the required shape through plastic deformation. This type of force is applied by a hammer or press. During the forging process, a type of dense granule structure is obtained and the physical properties of the stainless steel are improved. Punching and forging are all plastic processing methods and they are collectively called press forging. Press forged pieces have higher strength, denser internal granules, less holes or spare faces, less inclusions or other impurities and smoother surfaces. It is easier for them to meet the surface roughness requirements for a sterile pump used in the pharmaceutical industry.

When observing and comparing the surface of a press forged component and that of a cast component under a microscope it can be found that the gaps between the surface uneven areas are higher on the surface of a cast component than on that of a press forged component. A smaller space can effectively avoid the trapping and the retaining of particles. The higher gaps between the uneven areas on the surface of a cast component have more risks in retaining any particles. At the same time, the surface cleaning difficulty for a cast component is increased (Fig 3. 34). So cast components should be avoided for the selection of the pump materials.

b. Design requirements. The traditional industrial centrifuge pumps mainly pursue higher efficiency to satisfy the requirements on higher flow rate and higher head. With the more and more attention paid to safety and sanitary requirements, and more and more prominent problems in cleaning and cross contamination during the actual uses, open and deadleg free have become the aim for the design of sanitary centrifugal pumps.

An open and deadleg free design means that there is no deadleg at any part of the pump chamber, every part can be completely and sufficiently wetted by fluid, so that every part can be cleaned during the CIP process. And this type of design can also allow the maximum self-cooling of the mechanical seals (Fig 3. 35).

EPDM O-rings conforming to FDA requirements are used at both the front and the back of the impellers of a sanitary centrifugal pump. There will be no residual microbes at the pump shaft. The O-rings are placed inside open nut flutes and they can be automati-

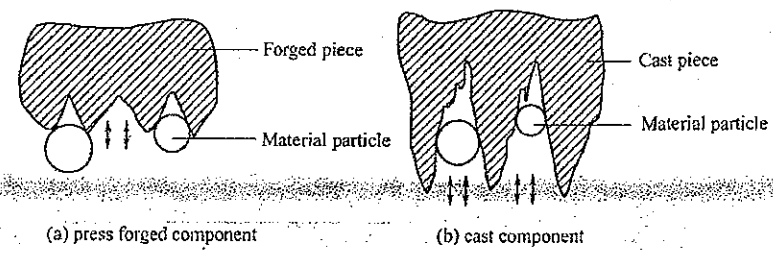


Fig 3. 34 Press forged components and cast components

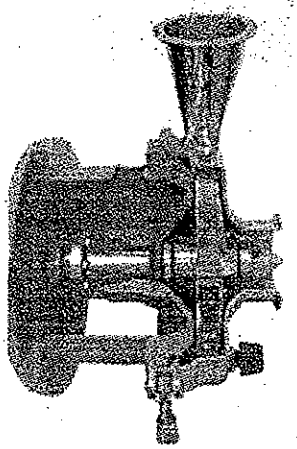


Fig 3.35 Open and deadleg free design

cally cleaned when transferring the medium. Because of the use of a turbine pump shell around the O-ring of the pump shell, its material contact area is increased, which significantly improves its automatic cleaning capacity. In order to ensure the automatic emptying of the pump chamber, a small drainage port is usually provided at bottom of the pump chamber for the automatic draining of the system through a valve installed here (Fig 3.36). At the same time, the 45° out feeding water flow can help eliminate any non-condensable gases in the WFI to avoid anyoperation risks caused by the long term accumulation of non-condensable gases within the pump chamber.

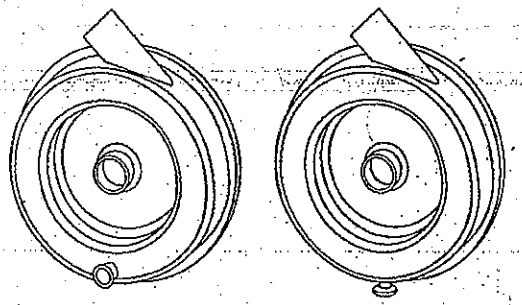
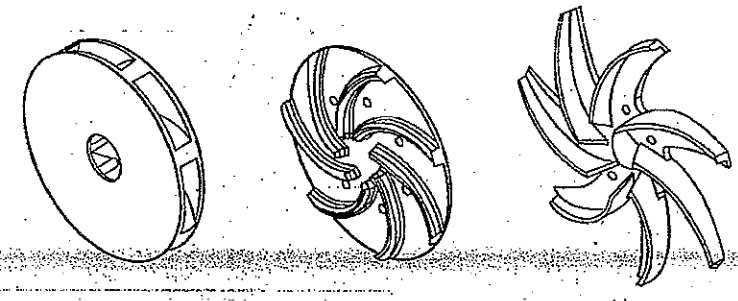


Fig 3.36 Pump chamber design with a bottom drainage port and 45 degree out feeding flow

The efficiency is one of the important parameters of a centrifugal pump. The design of the impellers of a centrifugal pump includes the closed type, semi-open type and open type (Fig 3.37). Closed impellers are the impellers typically designed for industry use. The semi-open impellers are typically designed for the food and pharmaceutical use. And open impellers are designed for sterile applications. The advantages of closed impellers include a high flow rate and a high efficiency. They can meet the requirements of high flow rate and high head applications. The maximum working efficiency of an industrial centrifuge pump can be as high as 88% . The characteristics of semi-open impellers are that the design requirements for the flow rate, the efficiency and the sanitary design are all taken into consideration. The maximum working efficiency is no more than 60% and they are often used on the food, beverage and pharmaceutical industries. In such high sterility requirement industries as the pharmaceutical industry, the open design is often used to ensure the sterility requirements of the centrifuge pumps. The working efficiency will be greatly reduced. Generally speaking, the efficiency of a sterile centrifugal pump is only about 30%.

At present, the high efficiency, environmental protection and energy saving demands bring new requirements on centrifuge pumps. During recent years, the use of IE2 and IE3 high efficiency motors has become compulsory in Europe. The combination of the reasonable use high efficiency motors and the improved efficiency of sanitary centrifugal pump design will provide material help in meeting the high efficiency, environmental protection and energy saving targets. So improving the efficiency of sanitary centrifugal pumps has become one of the major subjects of research for pump suppliers. Fig 3.38 shows the latest high efficiency and energy saving centrifuge developed in Germany. This pump retained the original AISI 316L/1.4404 forging design, the turbine design pump shell and the internal mechanical



(a) closed (b) semi-open (c) open

Fig 3.37 Impeller classifications

seals. In addition, the working efficiency of the pump is greatly improved. The core of its innovation is that a type of semi-open Double-Fin design is adopted for the impellers.

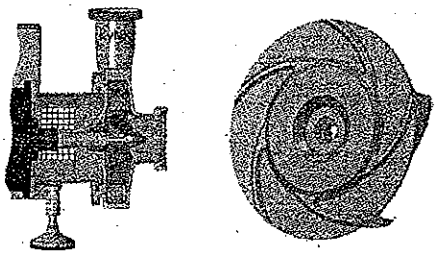


Fig 3. 38 Centrifuge with a double-fin design

The Double-Fin design can improve the efficiency by 10% compared with the ordinary design for a sanitary centrifugal pump and it can be more than 70% in extreme cases. This pump can have parameter values that normal centrifugal pump cannot reach under sanitary conditions. And a persistent fixation force can be obtained around the mechanical seal. A dry running of the mechanical seal will not result even under the liquid vaporizing pressure near this area, so that the service life of the mechanical seal can be prolonged. At the same time, the overall net positive suction head (NPSH) of the centrifugal pump will also be significantly reduced with this new impeller design. This can more effectively avoid the damages to the centrifugal pump by the cavitation phenomena. This new design perfectly combines the IE2/IE3 high efficiency motor and the high efficiency Double-Fin design and effectively satisfies the requirements of the modern industry on high efficiency, environmental protection, energy saving and sanitary.

Although open impeller centrifugal pumps have lower working efficiency, flow rate and head compared with closed impeller centrifugal pumps, which to some extent restricts their uses, they have slower flows and relatively softer transfer of materials. The deadleg free design and the surface roughness can meet the production requirements of the pharmaceutical industry. There is sufficient space at the part in contact with the mechanical seal, which allows optimal automatic cleaning and automatic cooling. The impellers processed by forging the base metal and high pressure water cutting technology (Fig 3. 39) can effectively ensure that the impeller material can be with higher density, strength and precision. And there is no thermal treatment during the processing and no secondary plastic deformation can result for the material and the internal structure of the material will not be affected.

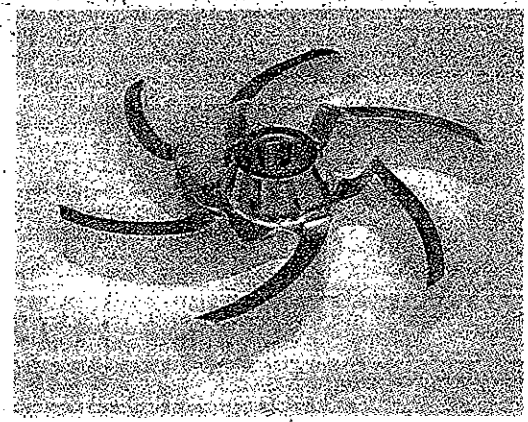


Fig 3. 39 Open impellers processed by high pressure water cutting

At present, the mechanical seal design of sanitary pumps mainly includes the external type and the internal type. At the same time, as restricted by the material properties or the actual use conditions, they can be divided into single end mechanical seals and double end mechanical seals (or flush type mechanical seal).

• External mechanical seal design. The external mechanical seal design is the earliest sanitary pump mechanical seal design. During the time when only graphite could be used for the mechanical seal, the fine graphite particles could be easily shed into the fluid and pass through the sterile filter. An external mechanical seal can effectively prevent the graphite particles generated when the pump is running from entering into the fluid, to avoid any particulate contamination cause by the mechanical seal. From Fig 3. 40 we can see that the static ring part of the external mechanical seal is completely submerged in the fluid and such components as the dynamic ring are exposed outside the pump.

With the development of science and technology, such sealing materials as graphite have been replaced by high strength materials like silicon carbide. The external mechanical seal design can also bring some problems that cannot be solved. The gap between the pump cover and the impeller is very small, which will not cause any problem if water is to be transferred. However, if the medium to be transferred is a type of drug solution containing any particles, syrups or crystals, the material can be easily stuck within this small space, thus causing cross contamination and affect the cleaning effect of the pump chamber. At the same time, the gap between the static ring and the pump shaft is very small. A high temperature will result from the friction between the static ring and the dynamic ring of the me-

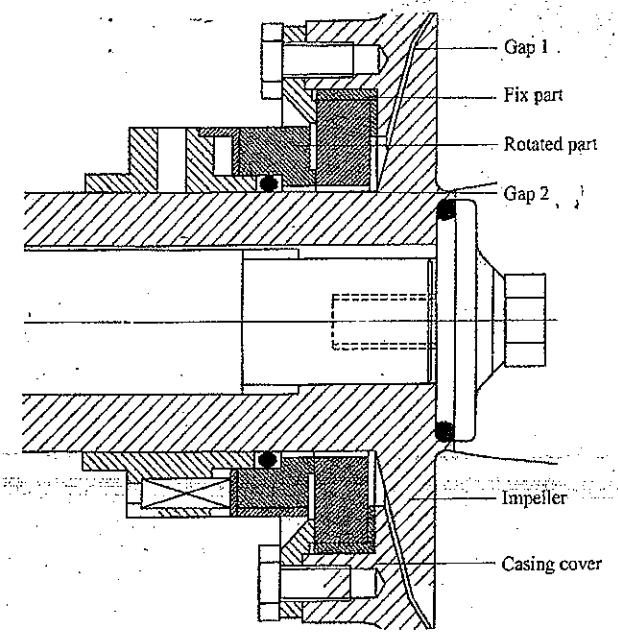


Fig 3.40 External mechanical seal design

chanical seal when it is working. This gap can ensure that it is rinsed and cooled by a medium (such as WFI) of a relatively lower temperature. If the gap is blocked, the cooling of the sealing surface can be affected and a type of condition similar to that of "dry running" can result for the mechanical seal, and the service life of the mechanical seal can be reduced. In addition, the action of the material pressure and the elastic force of the mechanical seal are contrary to each other. When there is a fluctuation of the material pressure or when the spring compensation is insufficient, the loss of stability of the mechanical seal and even leaks can result in severe cases. In order to solve the above problems, only the external double mechanical seal design can be used for compensation when external mechanical design is used for the centrifugal pump to transfer materials for a formulation system.

The external double mechanical seal design can increase the pump cost, the installation of the solution pipeline is more complex, and the operation cost and the subsequent maintenance cost will also be increased. At the same time, when the mechanical seal at the fluid side is damaged and the external mechanical seal is not damaged, the problem cannot be directly and rapidly identified from the appearance. When the pump is running normally, the pump chamber pressure is quite high and the fluid can leak into the chamber between the internal mechanical seal and the external mechanical seal, which will not cause any influences on the cleanness of the pump chamber. When the pump is stopped, the rinsing solution within the chamber between the internal and external mechanical seals can penetrate into the pump chamber, and cause unnecessary contaminations.

• Internal mechanical seal design. The internal mechanical seal design (Fig 3.41) is a type of advanced mechanical seal design. The dynamic and the static rings of the mechanical seal are completely submerged in the fluid. They can be well cleaned and cooled automatically. The fluid pressure is used to provide satisfactory sealing effects. Its advantages are outstanding for uses in clean pharmaceutical water systems.

With the improvements in the sealing materials, silicon carbide is used to replace the graphite, which makes it possible to change the mechanical seal design to the internal design. This solved the problems of the

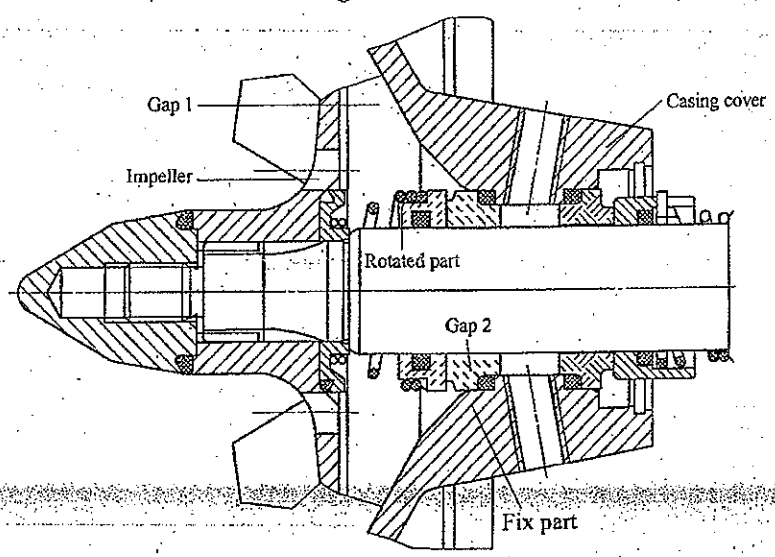


Fig 3.41 Internal mechanical seal design

external mechanical design. Silicon carbide is very brittle. When it is damaged, large pieces usually result, which can be retained by the sterile filter. This can avoid the contamination of the product by the very fine graphite particles. The gap between the mechanical seal and the pump cover and the impellers for an internal mechanical seal is larger, and it can be used to transfer almost all types of materials of a sanitary industry, including drug solutions containing small amounts of crystals or materials containing small amounts of active carbon particles, without worrying about any accumulation of particles.

Even for an internal mechanical seal design, a double end mechanical seal design is required in some special cases to allow the washing solution to enter and wash the surfaces of the dynamic and static rings and prolong the service life of the mechanical seals. For example, when the fluid is dangerous or corrosive, the internal double end mechanical seal can provide double protection to reduce the risk of fluid leakage. When there is a large amount of sugar crystals or particulate matters in the material, the double end mechanical seal should be used so that the gap can be cleaned in a timely manner. The pipeline connections for a double end mechanical seal (Fig 3.42) are relatively simpler. We only need to connect the external flexible or hard pipe to the pipeline of the double mechanical seal of the pump.

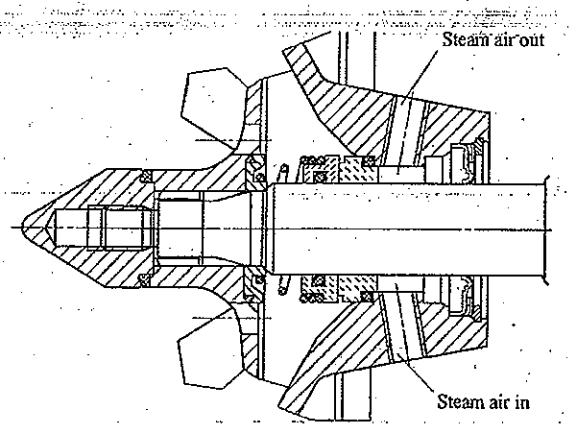


Fig 3.42 Installation of double mechanical seals

c. Regulatory certification. The regulatory certifications involved for sanitary centrifugal pumps mainly include 3.1B material certificates, US 3A certification, US 3A TPV certification and EP EHEDG certification.

For a 3.1B material certificate, the original documents should be provided for the materials of the sanitary pump parts in contact with the material to ensure the traceability of the materials. For the US 3A certification, written design drawings need to be submitted to the US 3A certification organization and the certificate can only be obtained after passing the strict inspection by that organization. In 2003, the 3A certification organization expanded its application scope. New third party verification (TPV) inspections are used to improve the integrity of the 3A certification. The EU EHEDG certification is a real on-line assessment and certification for sanitary pumps. Its inspection process is briefly described below.

- The pump to be inspected and two specially polished straight pipes (with a surface roughness $\leqslant 0.5\ \mu m$) form a closed system with the circulation system.
- Such activities as de-greasing, oil removal, acid washing, alkaline washing, hot water washing, cold water washing and 30-minute steam sterilization are performed for the circulated system to ensure the initial cleanness of the system.
- Add bacteria containing spores into spoiled milk to allow the spore concentration to be $10^5/cm^3$, and add the dye.
- Blow the mixed milk solution into the pipeline with 5 bar compressed air, maintain the pressure for 2 minutes each time and perform the test for three cycles.
- Empty the materials within the pump chamber, blow the pipeline dry with filtered air at a speed of 1.0 m/s for 2-4 hours until the humidity reaches no more than $0.5\% \pm 0.3\%$.
- Ensure that a very difficult to clean environment is created within the pipeline. Perform the CIP of the system. Open the pump chamber, and measure the quantity of the residual dyed milk particles that have not been removed from the pump chamber and compare it with the quantity of the residual dyed milk particles that have not been removed from the two connected straight pipes. It is acceptable only if the former is less than the latter. Then it can be concluded that the cleanability of the pump is at least no less than that of the connected straight pipes.
- The EHEDG certification mark with a specified number of years of validity can be obtained only after the results are determined to be acceptable.

In the bio-pharmaceutical industry, sterile single stage centrifugal pumps are often used for the transfer of liquids to ensure the sterility of the system. For this type of pumps, forged components are used and cast

components are forbidden, open impellers are used, sterile connectors are used, higher level sterile mechanical seals are used (Fig 3.43), the springs are built-in and not in contact with the material, a drainage port or a diaphragm valve is installed at the bottom of the pump chamber, and the bottom drainage port length should be no more than 3 times of the pipe diameter, the pump internal surface should be electropolished and passivated and the surface roughness Ra should be no more than 0.5 μm.

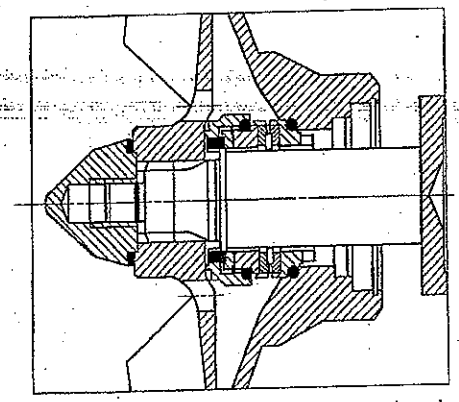


Fig 3.43 Design of sterile mechanical seals

3.2.3 Performance Parameters

When selecting a centrifugal pump, special attention should be paid to the flow rate, the head, the net positive suction head, the material properties and the working environment.

a. Flow rate. The flow rate is one of the important performance data for pump selection. It is related to the production capacity and the transferring capacity of the entire device. The normal, minimum and maximum flow rates of the pump should be calculated during the process design. The maximum flow rate should be based when selecting the pump, and the normal flow rate should also be considered. When the maximum flow rate is not available, the 1.1 times of the normal flow rate can be taken as the maximum flow rate.

b. Head. The head is also called the pressure loss. The calculation covers all the components from the pump outlet to the last user point. The head required by the system is another important performance value for pump selection. Generally the pump should be selected based on the head with 5%-10% redundancy.

c. Net positive suction head (NPSH). The calculation of the net positive suction head covers all the components before the pump inlet. The net positive suction head of the system should be higher than the net positive suction head of the selected pump to ensure its normal running.

d. Fluid properties. The fluid properties include the working temperature, the viscosity, the specific gravity, and the existence of granules.

e. Working environment. The working environment includes the altitude, the operation time, the local electric requirements, etc.

Fig 3.44 shows the typical centrifugal pump selection curve. When a frequency converter is used for the adjustment of the system, the conversion relationships among the flow rate (Q), the head (H), the power (P), the frequency (N) and the rotation speed (n) is very important. The detailed formulas are as listed below.

$$\begin{aligned} Q_1/Q_2 &= N_1/N_2 = n_1/n_2 \\ H_1/H_2 &= (N_1/N_2)^2 = (n_1/n_2)^2 \\ P_1/P_2 &= (N_1/N_2)^3 = (n_1/n_2)^3 \end{aligned} \qquad (3.5)$$

The performance curve of a centrifugal pump is fixed. It is provided by the manufacturer and generally will not change. The working curve of a centrifugal pump is determined by the pipeline system. When the actual duty point and the theoretical duty point coincide with each other, the pump will operate normally. When there is a deviation between the actual duty point and the theoretical duty point, the system cannot work as designed. This can be shown from some of the abnormal performances of the pump. As shown in Fig 3.45, when there is a deviation between the two points, a series of problems as a lower actual flow rate, a higher power required, an increased NPSH value can be caused because the actual pressure loss in the pipeline is lower than that of the calculated pressure loss. The most directly perceivable phenomena are that there are noises, motor overload and high temperature the pump.

The method for solving the above problem includes lowering the head to change the working curve of the pump so that it can coincide with the system, using a frequency converter to lower the frequency, reducing the impeller diameter, regulating the outlet valve to change the working curve of the system so that it can coincide with the pump, increasing the pressure loss, reducing the flow rate, reducing the power and reducing the NPSH.

When selecting a pump for a given application, it is crucial to select a pump with a duty point within its

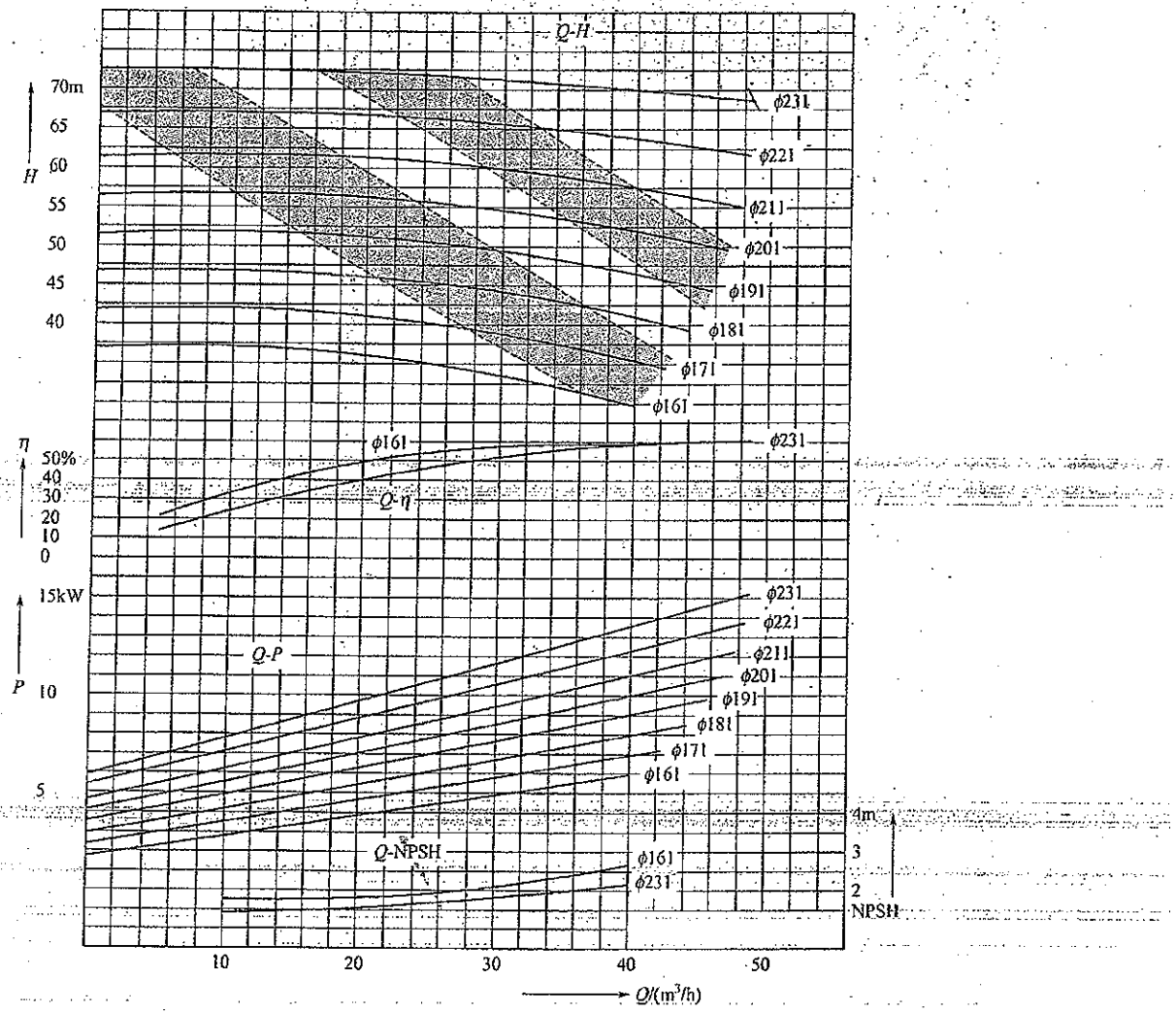


Fig 3.44 Centrifugal pump selection curve

highly efficient area. Otherwise, the power consumption of the pump can be unnecessarily high (Fig 3.46).

However, in some cases it is not possible to select a pump that is suitable to the optimal duty point because of a system requirement or a changing system curve. So it is necessary to adjust the pump performance to meet the changing requirements. The most common methods of changing pump performance are throttle control, bypass control, modifying impeller diameter, and speed control. Choosing a method of adjusting the pump performance is based on an evaluation of the initial investment together with the operating costs of the pump. All methods can be carried out continuously during operation apart from the modifying impeller diameter method. Often, oversized pumps are selected for the system and therefore it is necessary to limit the performance-first of all, the flow rate and in some applications the maximum head.

a. Throttle control. A throttle valve is placed in series with the pump making it possible to adjust the duty point. The throttling results in a reduction of flow. The throttle valve adds resistance to the system and raises the system curve to a higher position. Without the throttle valve, the flow is Q_2. With the throttle valve connected in series with the pump, the flow is reduced to Q_1. Throttle valves can be used to limit the maximum flow. By adding the valve, the maximum possible flow in the system is limited. In the example, the flow will never be higher than Q_3, even if the system curve is completely flat-meaning no resistance at all in the system. When the pump performance is adjusted by the throttling method, the pump will deliver a higher head than necessary for that particular system. $H_p = H_s + H_v$. If the pump and the throttle valve are replaced by a smaller pump, the pump will be able to meet the wanted flow Q_1, but at a lower pump head and consequently a lower power consumption (Fig 3.47).

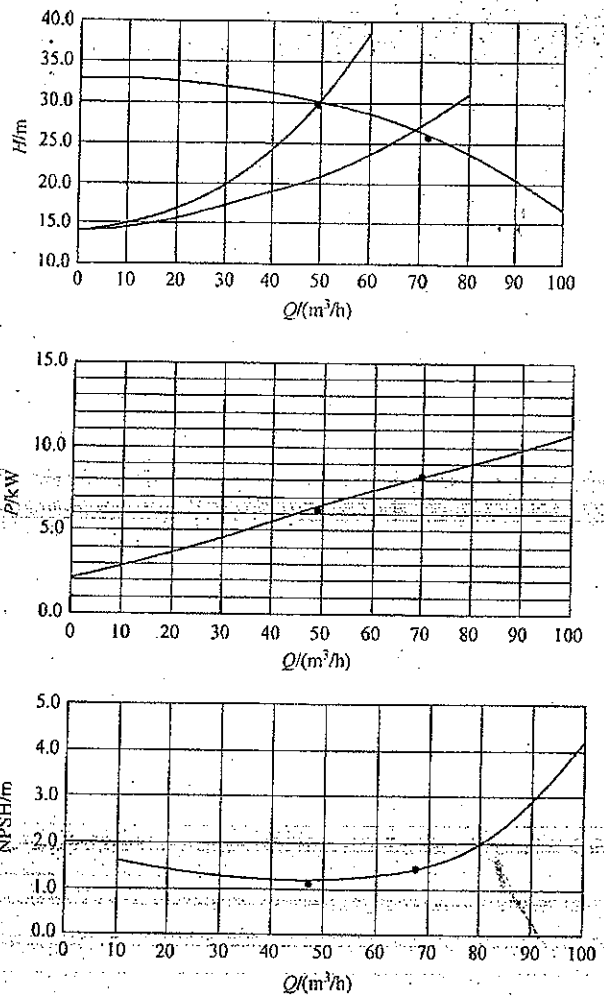


Fig 3.45 Performance curve and working curve of a centrifugal pump

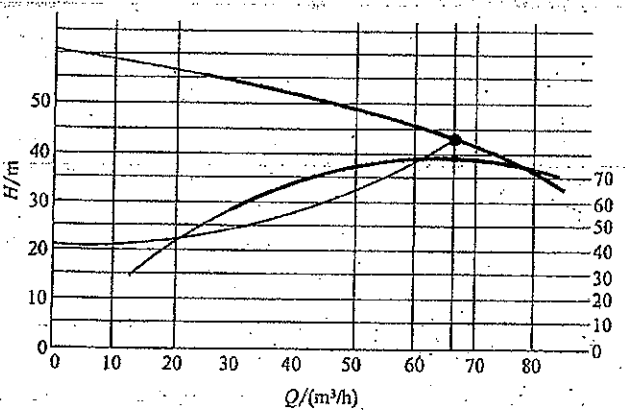


Fig 3.46 Selection centrifugal pump

b. Bypass control. Instead of connecting a valve in series with the pump, a bypass valve across the pump can be used to adjust the pump performance (Fig 3.48).

Compared to the throttle valve, installing a bypass valve will result in a certain minimum flow Q_{BP} in the pump, independent on the system characteristics. The flow Q_P is the sum of the flow in the system

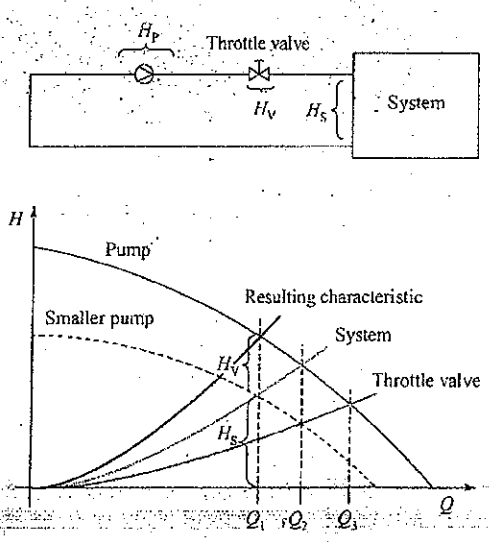


Fig 3.47 Schematic drawing of throttle control

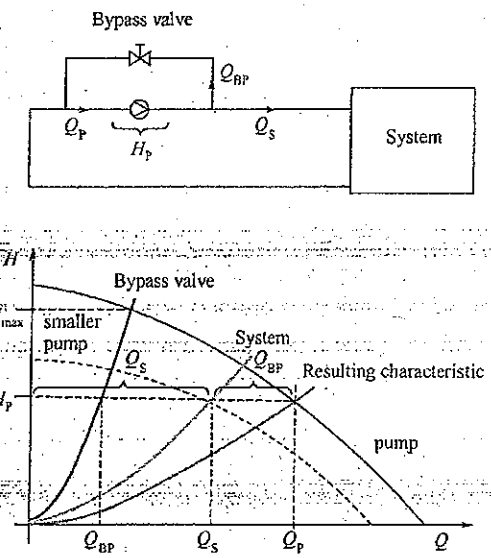


Fig 3.48 Schematic drawing of bypass control

Q_S and the flow in the bypass valve Q_{BP}. $Q_P = Q_S + Q_{BP}$. The bypass valve will introduce a maximum limit of head supplied to the system H_{max}. Even when the required flow in the system is zero, the pump will never run against a closed valve. Like it was in the case with the throttling valve, the required flow Q_S can be met by a smaller pump and no bypass valve. The result being a lower flow and consequently a lower energy consumption.

c. Modifying impeller diameter. Another way of adjusting the performance of a centrifugal pump is by modifying the impeller diameter (Fig 3.49) in the pump meaning reducing the diameter and consequently reducing the pump performance. Obviously, reducing the impeller diameter cannot be done while the pump is operating. Compared to the throttling and bypass meth-

ods, which can be carried out during operation, modifying the impeller diameter has to be done in advance before the pump is installed or in connection with service.

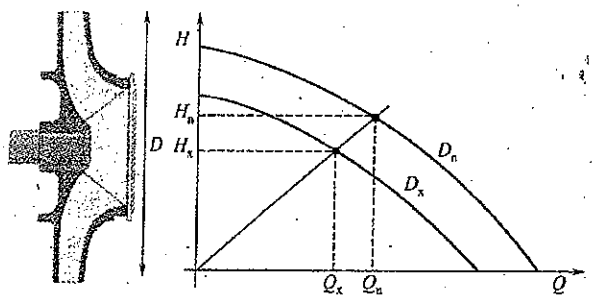


Fig 3.49 Schematic drawing of modifying impeller diameter

The following formulas show the relation between the impeller diameter and the pump performance.

$$\frac{Q_n}{Q_x}=\left(\frac{D_n}{D_x}\right);\frac{H_n}{H_x}=\left(\frac{D_n}{D_x}\right)^2;\frac{P_n}{P_x}=\left(\frac{D_n}{D_x}\right)^3;\frac{\eta_n}{\eta_x}=1 \tag{3.6}$$

Please note that the formulas are an expression of an ideal pump. In practice, the pump efficiency decreases when the impeller diameter is reduced. For minor changes of the impeller diameter $D_x > 0.8 \cdot Dn$, the efficiency is only reduced by a few %-points. The degree of efficiency reduction depends on pump type and duty point (check specific pump curves for details).

As it appears from the formulas, the flow and the head change with the same ratio-that is the ratio change of the impeller diameter to the second power. The duty points following the formulas are placed on a straight line starting at (0, 0). The change in power consumption is following the diameter change to the third power.

d. Speed control. Speed control by means of a frequency converter is without any doubt the most efficient way of adjusting the performance of a pump exposed to variable flow requirements (Fig 3.50). The following equations apply with close approximation to how the change of speed of centrifugal pumps influences the performance of the pump.

$$\frac{Q_n}{Q_x}=\frac{n_n}{n_x};\frac{H_n}{H_x}=\left(\frac{n_n}{n_x}\right)^2;\frac{P_n}{P_x}=\left(\frac{n_n}{n_x}\right)^3;\frac{\eta_n}{\eta_x}=1 \tag{3.7}$$

The affinity laws apply on condition that the system characteristic remains unchanged for n_n and n_x and forms a parabola through (0, 0). The power equation furthermore implies that the pump efficiency

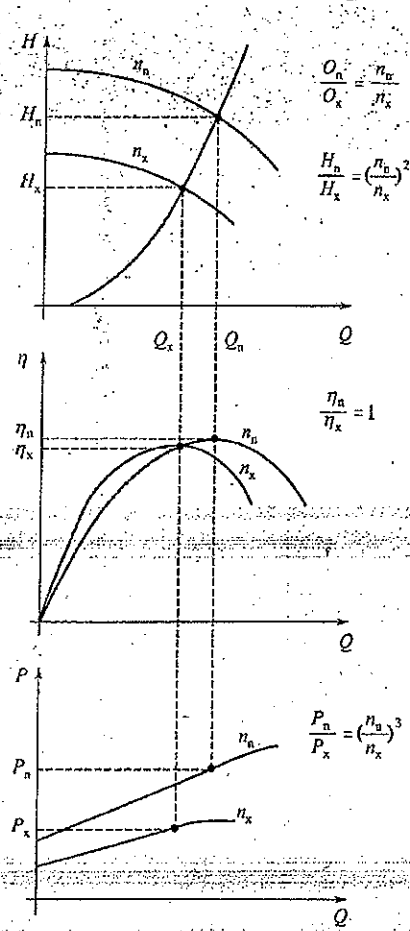


Fig 3.50 Schematic drawing of Speed control

is unchanged at the two speeds.

The formulas in the above figure show that the pump flow (Q) is proportional to the pump speed (n). The head (H) is proportional to the second power of the speed (n) whereas the power (P) is proportional to the third power of the speed (n). In practice, a reduction of the speed will result in a slight fall in efficiency. The efficiency at reduced speed (n_x) can be estimated by the following formula, which is valid for speed reduction down to 50% of the maximum speed.

$$\eta_x=1-(1-\eta_n)\times\left(\frac{n_n}{n_x}\right)^{0.1} \tag{3.8}$$

Now we have seen the four different methods for changing the performances of a centrifugal pump. When we consider the pump and its performance changing device as one unit, we can observe the resulting QH-characteristic of this device and compare the result of the different systems.

The throttling method implies a valve connected in series with a pump, see Fig 3.51(a). This connection acts as a new pump at unchanged maximum head but reduced flow performance. The pump curve H_n, the

valve curve and the curve covering the complete system-H_x, see Fig 3.51(b).

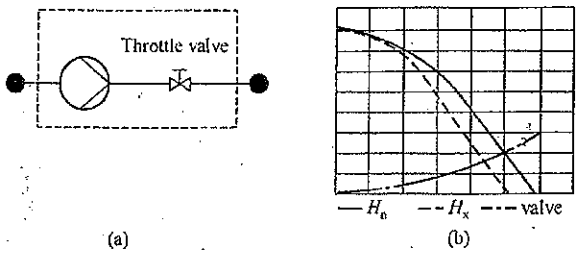


Fig 3.51 Throttle control

When a valve is connected across the pump, see Fig 3.52(a), this connection acts as a new pump at reduced maximum head and a QH curve with a changed characteristic. The curve will tend to be more linear than quadratic, see Fig 3.52(b).

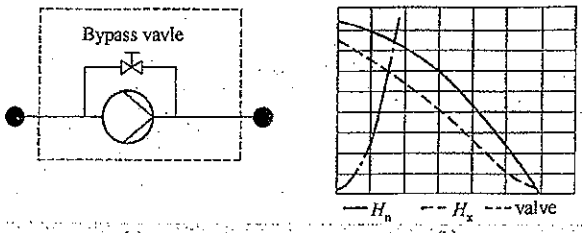


Fig 3.52 Bypass control

The impeller-reducing method does not imply any extra components. Fig 3.53 shows the reduced QH curve (H_x) and the original curve characteristics (H_n).

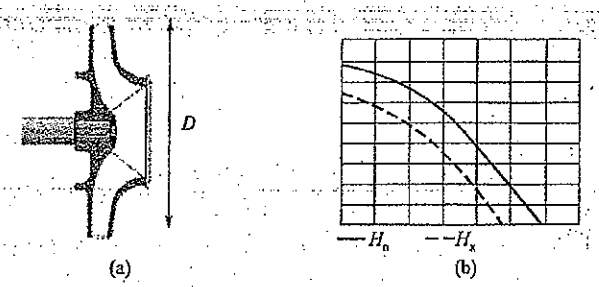


Fig 3.53 Modifying impeller diameter

The speed control method (Fig 3.54) results in a new QH curve at reduced head and flow. The characteristics of the curves remain the same. However, when speed is reduced the curves become more flat, as the head is reduced to a higher degree than the flow. Compared to the other methods the speed control method also makes it possible to extend the performance range of the pump above the nominal QH curve, simply by increasing the speed above the nominal speed level of the pump, see the H_y curve in below figure. If this over synchronous operation is used, the size of the motor has to be taken into account.

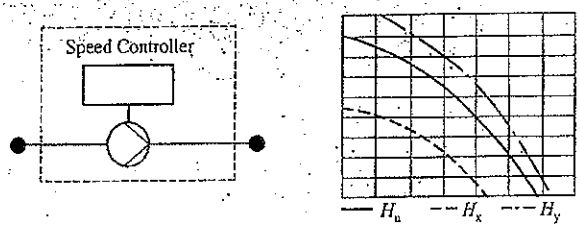


Fig 3.54 Speed control

In summary, both the throttling and the bypass method introduce some hydraulic power losses in the valves ($P_{loss} = kQH$). Therefore, the resulting efficiency of the pumping system is reduced. Reducing the impeller size in the range of $D_x/D_n \geq 0.8$ does not have a significant impact on the pump efficiency. Therefore, this method does not have a negative influence on the overall efficiency of the system. The efficiency of speed-controlled pumps is only affected to a limited extent, as long as the speed reduction does not drop below 50% of the nominal speed. Studies show that the efficiency was only reduced by a few percentage points, and that it does not have an impact on the overall running economy of speed-controlled solutions.

3.2.4 Frequency Control

A large number of pump applications do not require full pump performance 24 hours a day. Therefore, it is an advantage to be able to adjust the pump's performance in the system automatically. The best possible way of adapting the performance of a centrifugal pump is by means of speed control of the pump. The speed control of pumps is normally done by a frequency converter unit.

Controlling a centrifugal pump through a frequency converter has many advantages. Speed-controlled pumps only use the amount of energy needed for a specific pump job. Compared to other control methods, frequency-controlled speed control offers the highest efficiency and thus the most efficient utilization of the energy. Second, the energy consumption of a pump is a very important factor when considering a pump's life cycle costs. Therefore, it is important to keep the operating costs of a pumping system at the lowest possible level. Efficient operation leads to lower energy consumption and thus to lower operating costs. Compared to fixed speed pumps, it is possible to reduce the energy consumption by up to 50% with a speed-controlled pump. At the same time, energy efficient

pumps pollute less and thus are better for the environment. Speed control in different pumping systems is quieter. For example, in water supply systems, automatic pressure control and soft-start of pumps reduce water hammer and noise generated by a too high pressure in the system. In circulating systems, speed-controlled pumps ensure that the differential pressure is kept at a level so that noise in the system is minimized. Speed-controlled pumps can reduce the need for commissioning and control valves in the system. Therefore, the total system costs can be reduced.

Pumps with integrated frequency converters are the optimum solution. The reason is that these pumps combine the benefits of a speed-controlled pump solution with the benefits gained from combining a pump, a frequency converter, a PI-controller and sometimes also a sensor/pressure transmitter in one single unit (Fig 3.55). A pump with integrated frequency converter is not just a pump, but a system which is able to solve application problems or save energy in a variety of pump installations. Pumps with integrated frequency converter can be installed instead of fixed speed pumps at no extra installation cost. All that is required is a power supply connection and a fitting of the pump with integrated frequency converter in the pipe system, and then the pump is ready for operation. All the installer has to do is to adjust the required set point (pressure) after which the system is operational.

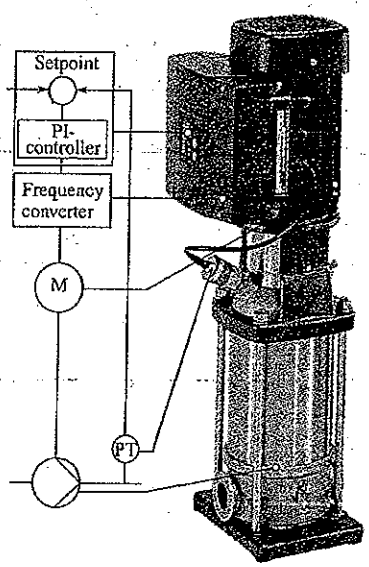


Fig 3.55 Centrifugal pump with integrated frequency converter

Because the pump, the motor and the frequency converter are designed for compatibility, the operation of the pump system reduces power consumption. They have a very broad performance range, which enables them to perform efficiently under widely varied conditions and to meet a wide range of requirements. Thus, fewer pumps can replace many fixed speed pump types with narrow performance capabilities.

Fig 3.56 shows an example of the performance curves of a speed-controlled pump. The first curve shows the QH curve and the second curve shows the corresponding power consumption curve. The performance curves are given for every 10% decrease in speed from 100% down to 50%. Likewise, the minimum curve represented by 25% of the maximum speed is also shown. As we have indicated in the diagram, a specific duty point QH, the speed at which the duty point can be reached and what the power consumption P_1 is, can be determined.

The change in pump performance and consequently the potential energy savings depend on the system in question. Speed-controlled pumps are used in a wide range of systems. The characteristic of a system is an indication of the required head needed in order to transport a certain quantity of liquid through the system. Fig 3.57 shows the performance curve and the system characteristic of a closed and an open system.

In closed systems, like heating and air-conditioning systems, the pump has only to overcome the friction losses in the pipes, valves, heat exchangers, etc. Fig 3.58 shows an example with a speed-controlled pump in a closed system. The total friction loss by a full flow of 15 m^3/h is 18 m.

As shown in Fig 3.59, the system characteristic of a closed variable frequency system starts at the point (0,0). The control valves in the system always need a certain operating pressure, so the pump cannot work according to the system characteristic. That is why some speed-controlled pumps offer the proportional pressure control function, which ensures that the pump will operate according to the discontinuity line shown in the figure. As can be seen from the figure, the minimum performance is around 57% of the full speed. In a circulating system, operation at the minimum curve (25% of the full speed) can be relevant in some situations, for example when we deal with night-time duty in heating systems.

The system characteristics of an open variable frequency system as well as the operating range of the

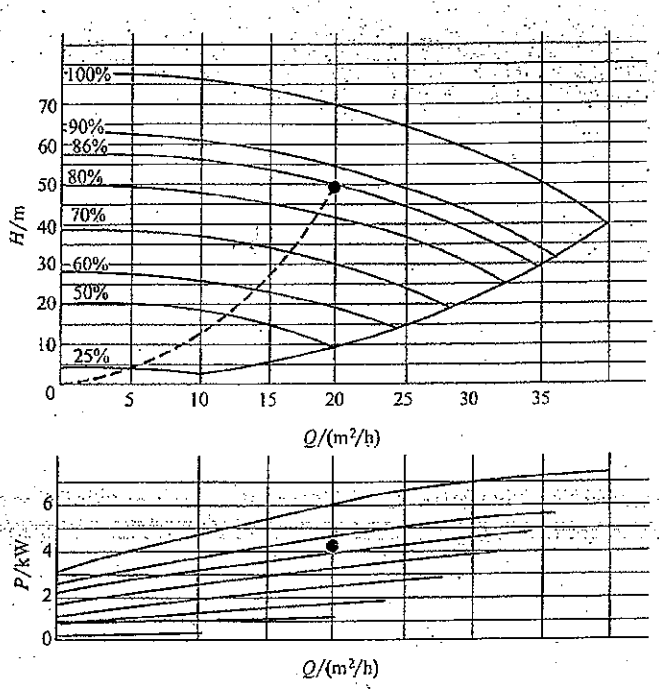


Fig 3.56 Variable frequency pump performance curves

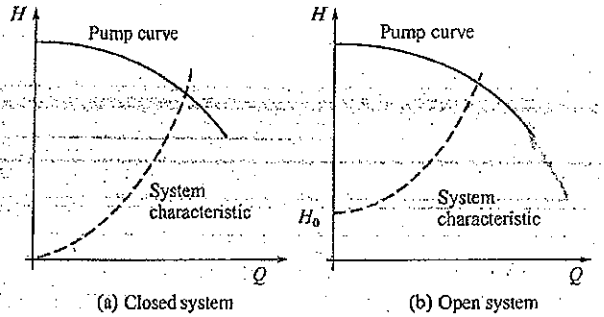


Fig 3.57 Closed system and open system

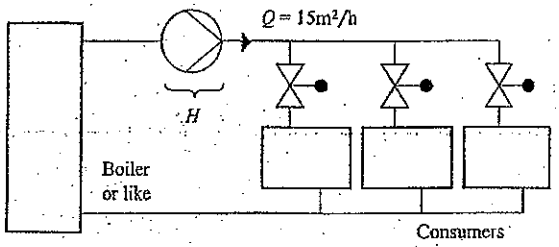


Fig 3.58 Closed variable frequency system

pump depend on the type of system in question. Fig 3.60 shows a pump in a pressure boosting/water supply system. The pump has to supply $Q=6.5$ m³/h to the tap, which is placed $h=20$ m above the pump. The inlet pressure to the pump P_s is 1 bar, the pressure at the tap P_t has to be 2 bar and the total friction loss in the system at full flow P_f is 1.3 bar.

Fig 3.61 shows the QH curve of a pump, which is able to meet the requirements described before. You can calculate the required head at zero flow (H_0) using the equation on your right.

If you need to calculate the maximum head at a flow (Q) of 6.5 m³/h, this is the equation to use:

$$H_{max}=H_0+\frac{P_f}{\rho \cdot g}=30.2+\frac{1.3\times10^5}{998\times9.81}=43.5\ \text{m}$$

To cover this application from zero flow to maximum flow $Q=6.5$ m³/h the pump operates in a relative narrow speed band (from about 65% of the full speed up to 99% of the full speed). In systems with less friction loss the variation in speed will be even smaller. If there is no friction loss, the minimum speed in the above case is about 79% speed. In summary, the possible variation in speed and consequently in power consumption is highest in closed systems. Therefore, the closed systems account for the highest energy saving potential.

3.2.5 Installation and Maintenance

When installing and using a centrifugal pump, manual valves should be installed at both the inlet pipe and the outlet pipe to facilitate the necessary manual regulation of the flow and the pressure during operation. At the same time, closing the valves can allow the independent disassembling and replacement of the pump. It should be ensured that the pump will be running within the selected range and overloads should be strictly forbidden. Care should be taken with respect to safety when disassembling or moving a pump. Special tools should be used if necessary. It should be

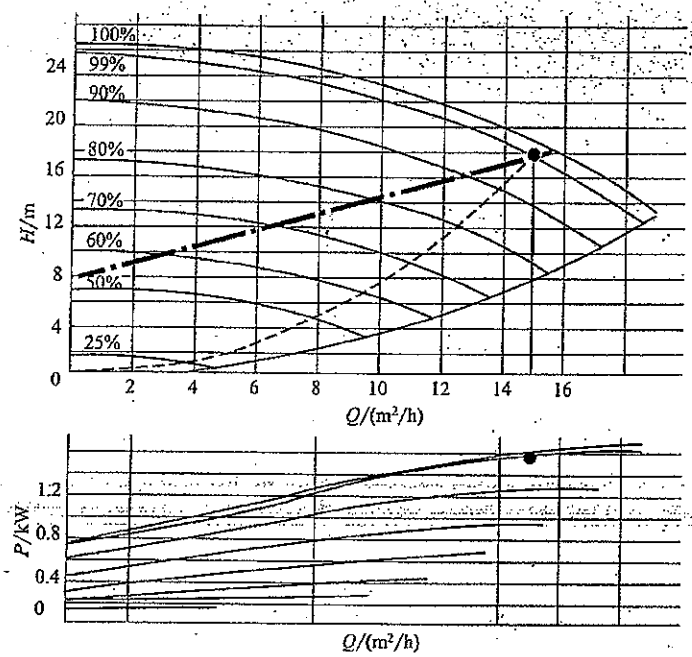
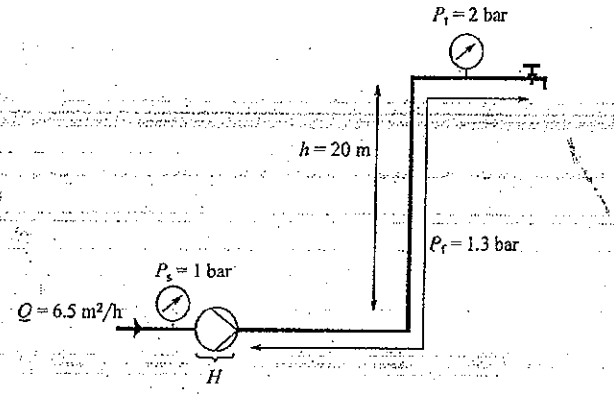


Fig 3. 59 Performance curve of a closed variable frequency system



P_t — Pressure at tapping point
P_s — Suction pressure
P_f — Friction loss
Q — Flow rate
h — Static lift

$$H_0 = h + \frac{P_t - P_s}{\rho \cdot g} = 20 + \frac{(2-1)\times 10^5}{998\times 9.81} = 30.2 \text{ m}$$

Fig 3. 60 Performance curve of an open variable frequency system

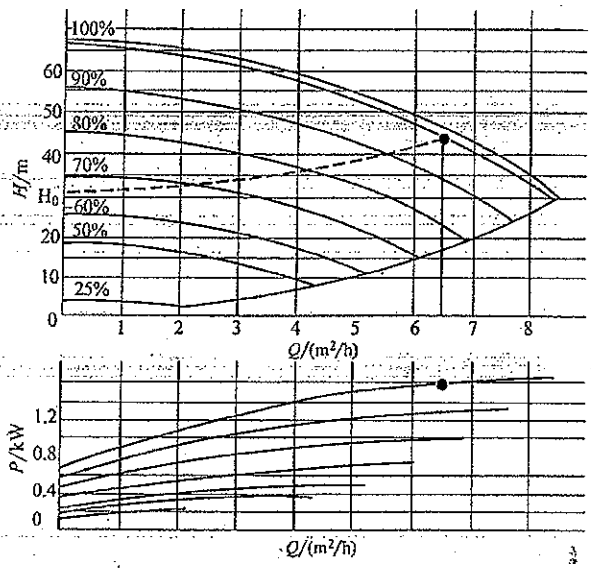


Fig 3. 61 QH curve of a variable frequency pump

ensured that the pump and the pipe connections are appropriately installed and there is no tension. It should be ensured that the load of the pipeline will not be placed on the pump to avoid damaging the pump shell or the seal ring. Verify whether the nominal power of the motor is compatible with other electrical components. Verify that there is sufficient space around the pump and there is nothing obstructing the fan. Manually rotate the shaft before correctly starting the pump. It should be ensured that there are no foreign matters within the pump chamber and there are no foreign matters in the materials to be transferred. The gap between the impeller and the pump chamber of a centrifugal pump is very small (0.2 to 0.4 mm). Special care should be taken to prevent introducing any foreign matter to avoid any abrasion of the pump chamber components, or any contamination of the fluid by any stainless steel chips resulted from the friction. The correct power supply connection and starting method should be selected. The direct starting method can be used below 4 kW and star (380 V) and triangle (220 V) connection and appropriate starting methods should be used above 4 kW.

Variable frequency starting is preferred. Excellent starting, protection and operation adjustment devices should be installed. Necessary and effective protection measures, such as over temperature protection and current protection, should be taken for the motor. It should be verified that the motor fan is rotating clockwise. The outlet valve of the centrifugal pump must be always open during operation. The inlet valve of the centrifugal pump can be closed for a short period of time during operation (only if the centrifuge pump inlet is vertical, if it is horizontal, it is forbidden to close it during operation). Start the pump only after verifying that all the pipeline systems are safe. Before starting, the pump chamber must be filled with liquid. Any dry running because of insufficient supply material should be forbidden. The mechanical seal can be damaged within a short period of time. The power supply must be cut before any maintenance inspections. The temperature of the pump and the motor must be checked before any installation, operation or maintenance activities to avoid any high temperature risks. It is strictly forbidden to transfer any highly corrosive materials to avoid any corrosion or pitting of the surfaces. The open and close of the inlet valve during operation should be slow to avoid any water hammer.

When the flow or the head is insufficient, the common methods that can be used include, fastening the seal when there is a leakage at the inlet, replace the mechanical seal when the mechanical seal is with abrasion, replace the pump cover seal ring if aging of the pump cover seal ring is noticed. When no liquid is transferred out of the pump, the common methods that can be used include, open the inlet device if it is closed, remove any foreign matters if the inlet pipe is blocked, reinstall the valve to the correct direction if it is installed at a wrong direction. When there is a leakage at the mechanical seal, the commonly methods that can be used include, replace the sealing material if it is aged, replace it when carbonization resulted because of a dry run, reinstall if the installation is not correct. When the motor is hot or trips, the common methods that can be used include, adjust the flow and pressure within the normal range if the load or the current is too high, repair or replace the motor if the motor coil is broken, remove the foreign matters if any foreign matters are introduced and stuck in the pump chamber.

When there are abnormal noises at the centrifugal pump, the common methods that can be used include, open the pump chamber for inspection and maintain and replace it if necessary if there is a mechanical fault of the pump head, replace the motor bearing if it is aged, adjust the outlet valve to the nominal pressure and flow if the flow is increased suddenly, remove the gas if any gas enters the pump chamber.

Cavitation is an abnormal phenomenon that often occurs in the pharmaceutical industry. This phenomenon is especially prominent in a WFI system operating at a high temperature or a concentrate solution preparation system. For example, a large noise can often be heard from within the pump chamber during overheated water sterilization. Generally speaking, when the pump is running, if the absolute pressure of the liquid to be pumped is lowered below the vaporizing pressure of that type of liquid under the corresponding temperature because of any reason at the local areas with the over flow of liquid (usually somewhere a little behind the inlet of the impellers), the liquid starts vaporize at that place. And a large amount of vapor can be generated to form bubbles. When the liquid carrying a large amount of bubbles moves through the impellers to the high pressure areas, the high pressure liquid around the bubbles make them shrink rapidly and collapse.

The hazard of cavitation if very significant. When the bubble is broken, liquid particles fill the cavity at a very high speed. And a very high impact force is generated instantly and impacts the metal surface at a very high frequency. The impact stress can be as high as several hundred to several thousand times the atmospheric pressure. And the impact frequency can be several tens of thousand times per second. After a period of time, fatigue of the metal will result, honeycomb structures will be formed at the metal surface, and the stress will be more concentrated, and cracks and peel off areas will result on the impellers. At the same time, because of the intermittent contact with the water and the honeycomb structures, a potential difference is generated between the side wall and the bottom of the honeycomb structure, which can cause electrochemical corrosion and the widening of the cracks. At the end, several cracks connect to each other to result in complete destruction (Fig 3.62).

It is easy to have a cavitation in the pump in the following conditions: ① The material temperature is too high, such as the overheated water sterilization of WFI, the high temperature CIP and the high tempera-

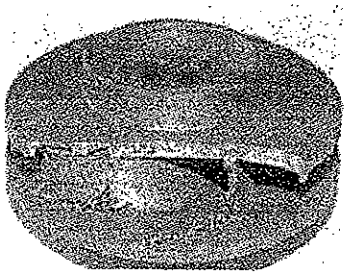


Fig 3. 62 Cavitation

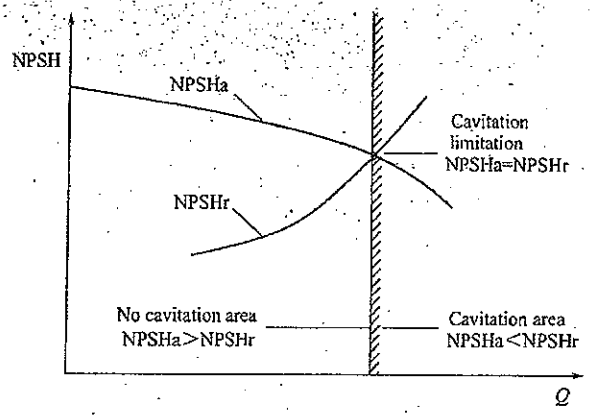


Fig 3. 63 Schematic drawing for cavitation

ture fluid solutions. ②Any system with vacuum, such as a deoxygenated water systems. ③ With the continuous consumption of the pharmaceutical water, the tank level drops gradually, if the WFI supplementation speed is insufficient and the transient water consumption is very high, the water level drops rapidly.

In the engineering industry, the following formula can help the analysis of cavitation of the pump. NPSHa is a type of actual working condition value. NPSHa=A value (tank pressure, usually the atmospheric pressure)+B value (height difference from the level to the pump inlet)−C value (pipeline resistance loss at the pump inlet)−D value (saturated steam pressure at a certain temperature). NPSHr is the design net positive suction head of the pump. It is a fixed value for the pump from the time it is released from the factory. Usually, when NPSHa< NPSHr, a cavitation will result within the system. When NPSHa is 0.6 to 1.0 m higher than NPSHr, cavitation will not happen in the centrifugal pump (Fig 3. 63).

Taking the cavitation of a pump during the overheated water sterilization of WFI as an example, the following methods can help solve the problem of cavitation within a WFI pump.

• Increasing the A value. Increase the pressure within the tank by introducing clean gas to ensure the tank gas phase pressure is increased appropriately. Install an inducer at the pump inlet. Install a vortex prevention baffle at the bottom of the tank.

• Increasing the B value. appropriately increase the level within the tank during the early phase of overheated water sterilization. Reduce the pump installation height appropriately. Reasonably design the water generator capacity and the storage tank volume to avoid a rapid dropping of the tank level during the operation.

• Decreasing the C value. Appropriately increase the pump inlet pipe diameter. Reduce the pump inlet pipe length. Ensure that the pump inlet pipe is smooth and reduce the number of bends. Approximately reduce the flow of the overheated water circulation of the pump.

• Reducing the D value. Maintain the water temperature at 70 to 80 ℃, when the WFI system is working normally and the temperature should not exceed 85 ℃.

An inducer (Fig 3. 64) is a type of device similar to a propeller installed at the front of the pump shaft. The major functions of an inducer include increasing the inlet pressure of a transfer pump, reducing the net positive suction head of a transfer pump, reducing the cavitation to the minimum, maximally reducing the component height and satisfying the site installation

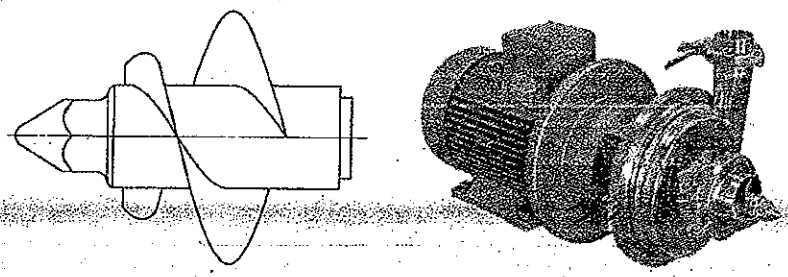


Fig 3. 64 Inducer

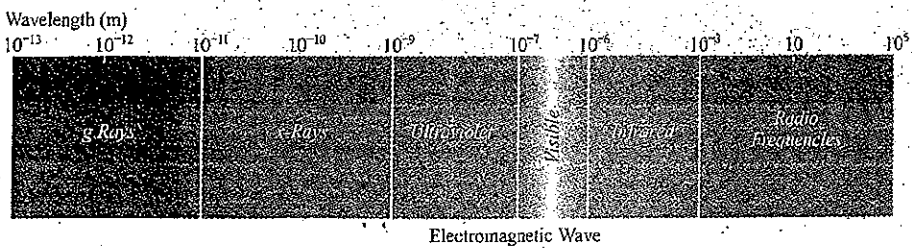


Fig 3.65 Electromagnetic wave spectrum

space restrictions in a new system.

3.3 UV Light

3.3.1 UV Introduction

UV light is a type of electromagnetic wave between X rays and visible light. Its wavelength is between 10 nm and 400 nm (Fig 3.65).

The UV light can be divided into four sections based on the wavelength. The first section is VUV with a wavelength from 10-200 nm. The second section is UVC with a wavelength from 200-280 nm. The third section is UVB with a wavelength from 280-315 nm. The fourth section is UVA with a wavelength from 315-400 nm. UV light is a type of electromagnetic wave, the shorter the wavelength the higher the energy and the weaker the penetration capacity, the longer the wavelength the lower the energy and the stronger the penetration capacity (Fig 3.66).

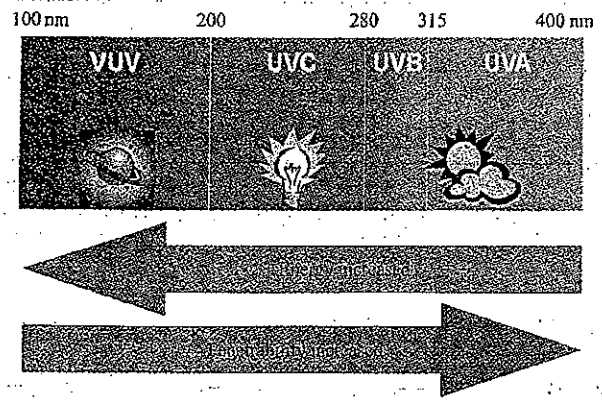


Fig 3.66 Types and properties of UV light

Ordinary glass cannot transmit UV light; UV light is usually generated by a mercury vapor arc lamp. The shell is made of quartz glass or other materials with a high UV light transmittance and a certain amount of inert gas and mercury are filled within the tube. The electrode is heated to emit electrons when the UV lamp is working. Some of the electrons in the mercury vapor atoms are excited and transition to a higher orbit. The atoms also reach a higher energy state. The se atoms with higher energy states are instable and can easily return to their original base state. Because the energy level difference between the electron orbits is a fixed value, when a higher energy state atom returns to the base state the electrons at higher energy level will also return to the original orbit. At the same time, the absorbed energy is released in the form of a light wave with a fixed wavelength (Fig 3.67). For example, the wavelength corresponding to the electron transition energy level of most of the mercury atom in a low pressure UV lamp is 253.7 nm.

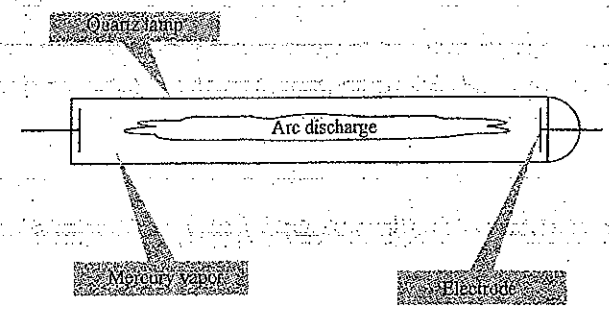


Fig 3.67 UV light generation principles

There are three types of UV lamps used for water treatment: traditional low pressure UV lamps, low pressure amalgam UV lamps and medium pressure UV lamps. The mercury vapor pressure is less than 10^3 Pa in a traditional low pressure UV lamp, UV light is only generated at 185nm and 254 nm, and the power of a single lamp is generally less than 100 W. A low pressure amalgam UV lamp is similar to a traditional low pressure UV lamp, but the power of a single lamp can be as high as 800 W. The mercury vapor pressure is between 10^3 Pa and 10^6 Pa in a medium pressure UV lamp, and the power of a single lamp can be as high as 7,000W.

The sanitization action of UV light is mainly exerted by damaging the core genetic material (DNA) of the microbes. The absorption wavelength of UV light

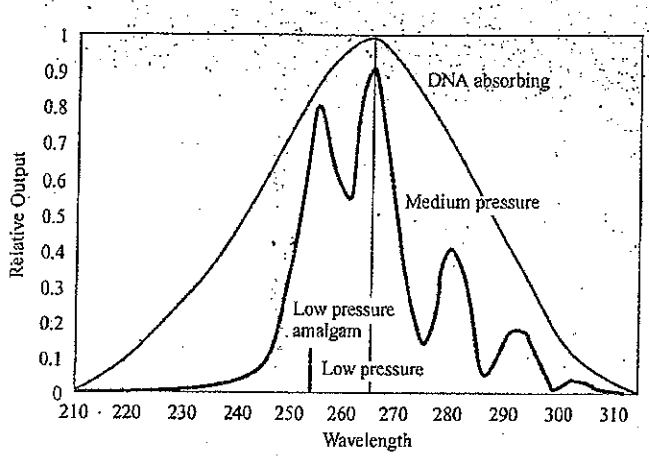


Fig 3.68 Characteristics of spectral output of different UV technologies

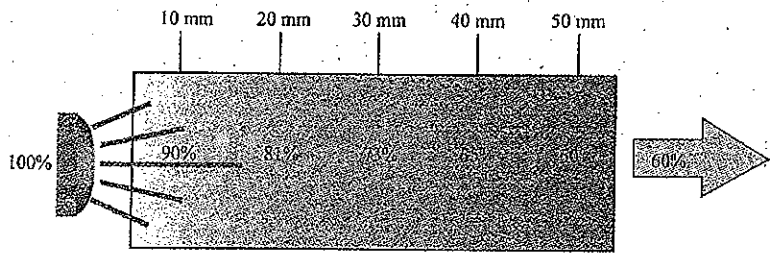


Fig 3.69 UV light transmittance definition

by DNA is from 200-300 nm and the absorption peak is at about 265 nm. The output wavelength range is concentrated at 185 nm and 254 nm for traditional low pressure UV lamps and low pressure amalgam UV lamps. And only the 254 nm wavelength light has sanitization effect. At the same time, the relative output intensity of low pressure vapor UV lamp is higher than that of traditional low pressure UV lamp. The output wavelength of a medium pressure UV lamp is from 200 nm to 400 nm and its relative output intensity is far higher than that of a low pressure UV lamp or a low pressure amalgam UV lamp (Fig 3.68).

The UV light transmittance is used to indicate the ability of UV light to be transmitted through a medium. The UV light transmittance is one of the parameters that must be considered when selecting a UV light water treatment system. For a medium, it is assumed that the UV light from the UV lamp and the quartz tube surface is attenuated to 90% of the initial intensity after 10mm distance, the UV light transmittance of the medium UV T_{10} is 90%. If it is attenuated to 81% of the initial intensity after 20 mm, the UV light transmittance of the medium UV T_{20} is 81%. Likewise, the UV light transmittance of the medium UV T_{40} will be 73% and the UV T_{50} will be 65% (Fig 3.69).

For a pharmaceutical water system, the municipal water is generally treated through a multimedia filter, an active carbon filter and a softener. At this stage the UV light transmittance UV T_{10} can achieve 90% to 95%. And after a single pass RO or a double-pass RO, the UV light transmittance UV T_{10} can achieve more than 98%.

The D_{10} value of a type of microbe is the UV light dose required to kill 90% of this type of microbe. For example, if the UV light dose required to kill 90% (1 lg) of MS2 phage is 16 mJ/cm^2, the D_{10} value of MS2 phage is defined as 16 mJ/cm^2. The relationship between the UV light dose and the killing efficiency of MS2 phage is approximately linear. The UV light dose required for killing 99% (2 lg) of MS2 phage is about 34 mJ/cm^2, that for killing 99.9% (3 lg) of MS2 phage is about 52 mJ/cm^2.

The D_{10} value is significantly different for different microbes. The D_{10} value of *Escherichia Coli*, a representative gram negative bacterium, is 3.0 mJ/cm^2. For other common bacteria, the D_{10} of *Shigella Dysenteriae* is 4.2 mJ/cm^2, of *Vibrio Cholerae* is 6.5 mJ/cm^2, of *Staphylococcus Aureus* is 2.6 mJ/cm^2 and of *Pseudomonas Aeruginosa* is 5.5 mJ/cm^2 (Table 3.2).

Table 3.2 D_{10} Values of common bacteria

Bacteria	D_{10}/(mJ/cm²)
Bacillus Subtilis (spores)	28
Clostridium Tetani	4.9
Clostridium Botulinum	12
Dysentery Bacilli	2.2(1)
Escherichia Coli	3.0
Leptospira SPP (Jaundice)	3
Legionella Pneumophila	2.04
Listeria Monocytogenes	3.4
Pseudomonas Aeruginosa	5.5
Salmonella Enteritidis	7.6
Shigella Dysenteriae	4.2
Shigella Paradysenteriae	1.68
Staphylococcus Albus	1.84
Staphylococcus Aureus	2.6
Streptococcus Salivarius	2
Streptococcus Faecalis	4.5
Tuberculose Bacillus	10
Vibrio Comma	3.1
Vibrio Cholerae	6.5

The D_{10} values of other types of microbes, such as viruses, moulds and yeasts, are as listed in Table 3.3.

Table 3.3 D_{10} Values of common viruses, moulds and yeasts

Virus	D_{10}/(mJ/cm²)
MS2 phage	16
Bacteriophage(*E Coli* Virus)	3
Hepatitus B Virus	11
Infectious Hepatitus Virus	5.8/8
Influenza	3.4
Poliovirus(Poliomyelitis)	3.1/6.5
Mould(Spores)	**D_{10}/(mJ/cm²)**
Aspergillus Niger	132
Penicillium Chrysogenum	30-50
Penicillium Roqueforti	13
Rhizopus Nigricans	110
Scopulariopsis Breicaulis(Cheese)	50-80
Yeast	**D_{10}/(mJ/cm²)**
Bakers	3.9
Brewers	10

3.3.2 UV Light Dose

The UV light dose (mJ/cm²) is the product of UV light intensity (mW/cm²) and the retention time (s). The UV light intensity is related to the lamp output power and the water quality, the higher the lamp output power, the higher the UV intensity. And the higher the water quality, the higher the UV light transmittance. The retention time is related to the treatment flow and the UV chamber dimensions. If the chamber dimensions are the same, the higher the treatment flow, the shorter the retention time. If the treatment flow is the same, the larger the chamber dimensions, the longer the retention time (Fig 3.70).

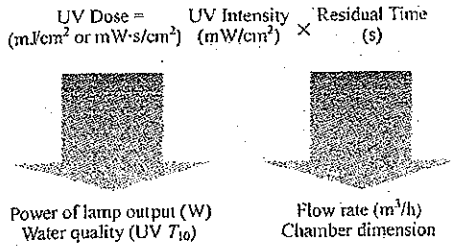


Fig 3.70 Definition of UV light dose

The UV light dose is used to indicate the processing capacity of an UV light water treatment equipment under certain process conditions. The commonly used doses include the CFD average dose, the CFD RED dose and the bio-validated dose. For example, for sanitization and disinfection, assume the flow of a process is 5 m³/h, the UV transmittance of the medium UV T_{10} is 98%, the equipment selected is A, the effective UV dose of A under the process conditions is RED 30 mJ/cm², then the sanitization capacity of A is a microbial inactivation efficiency of ≥99.9% (taking *E. coli* as the reference). Assume the process conditions are changed, the flow is increased to 10 m³/h, the UV transmittance of the medium UV T_{10} is kept the same, the equipment selected is A, the effective UV dose of A under the process conditions is reduced to RED 10 mJ/cm², then the sanitization capacity of A is reduced to a microbial inactivation efficiency of ≥90% (taking *E. coli* as the reference).

The mathematic ave rage dose assumes that all the microbes passing different paths (within the UV light treatment equipment chamber) receive the same UV light intensity and the same contact time (Fig 3.71). The mathematic average dose does not sufficiently consider the hydraulic factors within the UV light water

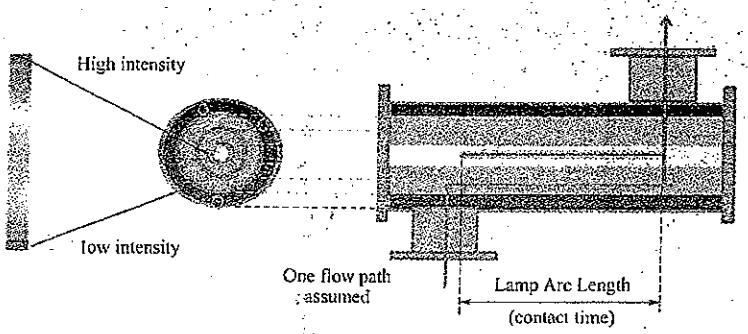


Fig 3.71 Calculation of mathematic average dose

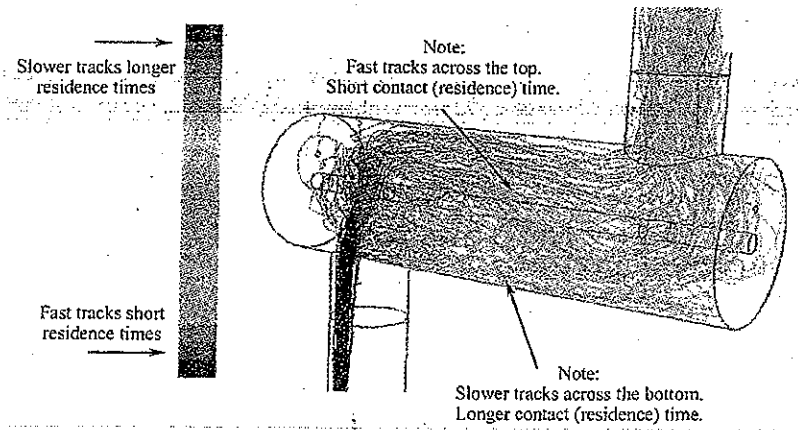


Fig 3.72 Chamber simulation design with CFD software

treatment equipment chamber. It is a very rough UV light dose calculation method. It cannot precisely reflect the actual processing capacity of the UV light water treatment equipment.

3.3.2.1 CFD Average Dose

The Computational Fluid Dynamics (CFD) is a type of modern hydrodynamics. It is the product of the combination of numerical mathematics and computer science. It uses electronic computers as the calculation tool. Various types of discretized mathematical methods are used for the numerical experiment, the computer simulation and the analytical investigation of hydrodynamics, to solve various types of actual problems.

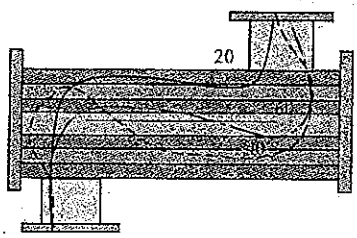
The CFD software can be used for the simulation design of a UV light water treatment equipment chamber. All the microbes that pass through the chamber will be considered to be exposed to different light intensities with retention times. For example, the retention time is shorter for microbes passing through the top of the chamber and longer for microbes passing through the bottom of the chamber (Fig 3.72).

The hydraulic factors within the UV light water treatment equipment chamber will be considered for the CFD average dose. However, the actual dose of microbes passing through different paths will not be considered. As shown in Fig 3.73, assuming that the UV light dose received by the microbes passing through path 1 (solid line) is 20 mJ/cm^2, that received by the microbes passing through path 2 (dotted line) is 40 mJ/cm^2, and that received by the microbes passing through path 3 (discontinuity line) is 60 mJ/cm^2. The calculation of the CFD average dose will sum up all the UV light doses received from all the above paths and then calculate the mathematic average to obtain the final UV dose of 40 mJ/cm^2.

If a type of microbe requires a UV light dose of 40 mJ/cm^2 to obtain a kill rate of 1 lg (90%), a CFD average dose of 40 mJ/cm^2 as calculated in the above example can obtain a kill rate of 1 lg (90%).

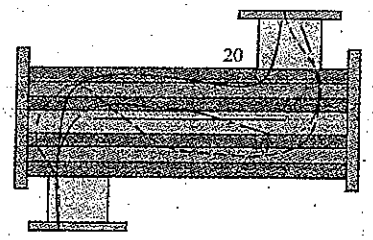
3.3.2.2 CFD RED Dose

The hydraulic factors within the UV light water treatment equipment chamber will be considered for the CFD RED (CFD Reduction Equivalent Dose), and the actual dose for microbes passing through different paths will also be considered.



Microbe flow pattern	Dose	Result
Track 1 (solid line)	20	1 lg reduction
Track 2 (dotted line)	40	1 lg reduction
Track 3 (discontinuity line)	60	1 lg reduction
Total Dose	120	
Average Dose	120/3=40	

Fig 3.73 Calculation of CFD average dose



Microbe flow pattern	Dose	Result
Track 1 (solid line)	20	0.5 lg reduction
Track 2 (dotted line)	40	1 lg reduction
Track 3 (discontinuity line)	60	1.5 lg reduction
RED DOSE	32.8	

Fig 3.74 Calculation of CFD RED dose

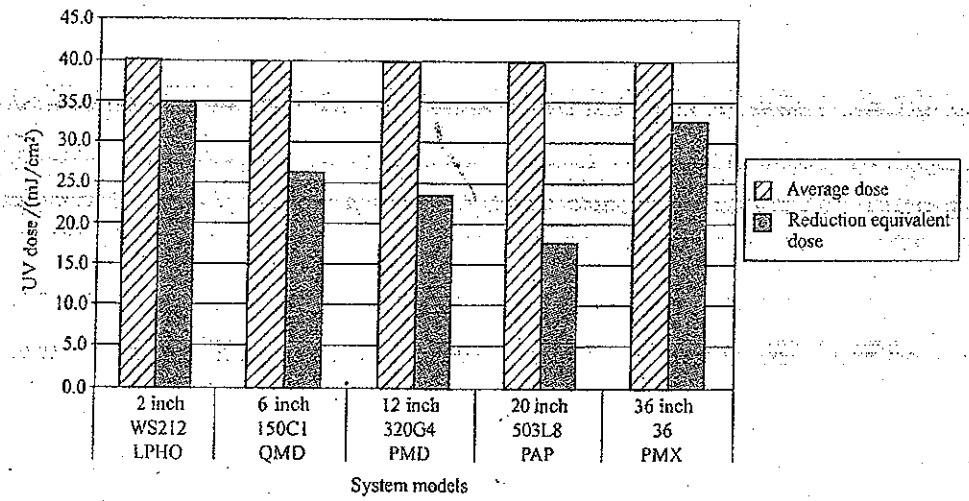


Fig 3.75 Differences in CFD average dose and CFD RED dose

As shown in Fig 3.74, assuming that the UV light dose received by the microbes passing through path 1 (solid line) is 20 mJ/cm², that received by the microbes passing through path 2 (dotted line) is 40 mJ/cm², and that received by the microbes passing through path 3 (discontinuity line) is 60 mJ/cm². If a type of microbe requires a UV light dose of 40 mJ/cm² to obtain a kill rate of 1 lg (90%), the CFD RED dose will be calculated as described below. The UV light dose for the microbes passing path 1 (solid line) is 20 mJ/cm² and it can obtain a kill rate of 0.5 lg (68%). The UV light dose for the microbes passing path 2 (dotted line) is 40 mJ/cm², and it can obtain a kill rate of 1 lg (90%). The UV light dose for the microbes passing path 3 (discontinuity line) is 60 mJ/cm² and it can obtain a kill rate of 1.5 lg (97%). For the calculation of the CFD RED dose the average of all the actual lg kill rate for the microbes of all the paths will be calculated, i.e. (68%+90%+97%)/3=85%. Therefore, a kill rate of 0.82 lg (85%) can be obtained and the corresponding CFD RED dose is 32.8 mJ/cm².

As shown in Fig 3.75, there are certain differences in the corresponding CFD average dose and the CFD RED dose for different UV systems. Generally, for a same UV light water treatment equipment chamber under the same process conditions, the CFD average dose is higher than the CFD RED dose. For example, the system PMD320G4, the CFD average dose under certain

process conditions is 40 mJ/cm² and the CFD RED dose is not even 25 mJ/cm².

3.3.2.3 Bio-validated Dose

For the bio-validated dose, actual microbes will be selected to challenge an UV light water treatment equipment. The specific procedures are as described below: ① Select the representative target microbes, such as MS2 phage and adenovirus. ②Perform the disinfection test on the selected microbes using a standard UV light with known power. ③Count the live cells for the microbes before and after the treatment by the standard UV light source. ④Change the treatment duration to obtain a response curve of the UV light dose to the Log kill rate of the microbe. ⑤Select the same target microbe. ⑥Perform the microbial challenge test on the UV equipment. ⑦Count the live cells for the microbes before and after the treatment by the UV light equipment. ⑧Change the operation conditions of the UV equipment, such as flow, medium UV transmittance, lamp power, etc., to obtain the response curve of the UV equipment to the Log kill rate of the microbe under different operation conditions. ⑨Finally, calculate and analyze the test results of the UV equipment and the test results of the standard UV source to obtain the bio-validated dose of the UV equipment (Fig 3.76).

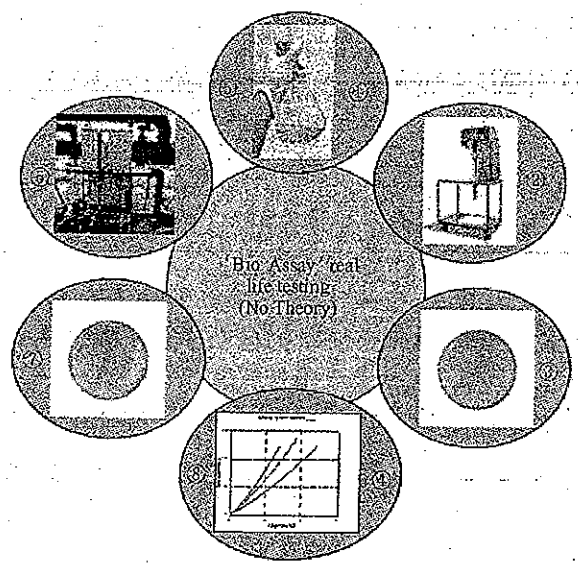


Fig 3.76 Bio-validated dose test procedures

Based on the differences in the water treatment applications, the requirements on the UV light dose calculation can also be different. For disinfection and sanitization, the optimal UV light dose should be the bio-validated dose. As a second choice, the CFD RED dose can be used. For the UV chemical destruction applications, such as dechlorination, the ozone destruction or TOC reduction, the CFD average dose is usually selected.

3.3.3 Laws and Regulations

The UV light water treatment technology can be used in the water generation and distribution systems of the food, beverage and pharmaceutical industries. The major applications include disinfection, dechlorination and ozone destruction. The use of UV light in pharmaceutical water systems has been recognized in various laws and regulations both home and abroad, including those issued by the International Society of Pharmaceutical Engineers (ISPE), the *US Pharmacopoeia*, the US *Milk Pasteurization Regulations*, the Chinese Design Codes for *Pharmaceutical Process Water Systems* (GB 50913—2013), etc.

a. International Society of Pharmaceutical Engineers (ISPE). The Baseline Guide Volume 4 of ISPE, *Water and Steam Systems* has the following specifications for UV light water-treatment systems.

4.9.3 *Removal by UV Irradiation*

Ultraviolet light also can be used in the reduction of chlorine. In this process (UV-photolysis), where 100% photodecomposition of free chlorine is achieved, UV light photolysis decomposes free chlorine to form approximately 80% chloride ions and 20% chlorate ions. The typical UV dose for photodecomposition of free chlorine is about 20 times higher than the standard disinfection UV dose. Generally low pressure 185 nm UV lamps are incorporated as the radiation wavelength. Successful chlorine removal is a function of the UV dosage of average irradiance and contact time in a UV chamber. Consideration of this process is based on the ppm level of chlorine concentration in the feed water. The UV Transmittance (UVT) in a typical municipal feed water source is about 85% to 95%. The UV dose required for dechlorination of a particular water stream also depends on the following factors.

- *the type of residual chlorines present, free chlorine versus chloramines*
- *the background of natural organic concentration in feed water source*
- *turbidity, color, and suspended solids*
- *the ratio of target effluent chlorine concentration to influent chlorine concentration*

Advantages: no harmful chemicals are added to the water stream, low maintenance, and can be hot water sanitized or ozonated. Additionally, it provides significant

TOC reduction.

Disadvantages: systems can be large in size and take up floor space based on inlet flow rates. The initial capital cost can be higher than the other methods.

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13.5.1.1 *Ultraviolet Light Sanitizers*

Light is maximally absorbed by the pyrimidine bases in DNA across the ultraviolet wavelengths of 240 nm *to* 280 nm. *The absorbed energy makes these bases reactive, causing them to covalently bind to neighboring pyrimidine bases in the DNA, which prevents microbial replication and protein synthesis and ultimately kills the cells. The UV light emitted by low pressure mercury vapor fluorescent light bulbs has an intense emission at 254 nm and is the type of bulb used in UV Sanitizers. At the appropriate flow rate, water can flow through a chamber containing such bulbs and be in contact with the UV light long enough to kill 99% or more of the microorganisms in the water. As much as 1% may not be killed and no bacteria are killed outside of the exposure chamber. Those that survive the journey through the exposure chamber may do so because of being attached to an opaque particle (such as rouge) or imbedded in the center of a biofilm bloc, where they are shielded or shadowed from the deadly light rays.*

Many users incorrectly assume that in-line UV sanitizers sanitize the entire water system constituting continuous sanitization. Such in-line UV sanitizer lights can kill only what they shine on. Surviving microorganisms can form downstream biofilms. In-line sanitizers slow the downstream development of biofilm from planktonic cells that pass through the chamber suspended in the water flow. This is most valuable where the downstream biofilm has already been eliminated by a highly effective approach, helping to reduce the frequency of this aggressive sanitization.

The remaining 1% of microorganisms that survive the UV sanitizer light can be captured or significantly delayed from passing further downstream, by placing micro-retentive filters downstream of a UV sanitizer, further extending the period between required between sanitizations.

Another type of UV sanitizer uses medium pressure UV bulbs. These bulbs emit strongly across a broader spectrum including both 254 nm *and* 185 nm. *The se shorter and more energetic wavelengths can create extremely reactive, short-lived hydroxyl free radicals from the water molecules. The hydroxyl free radicals rapidly react, within a split-second, with organic molecules with which they make contact, including those on bacterial cells and some of the dissolved organic molecules that constitute the TOC in the water. When the free radicals react with the organic molecules, they can oxidize C—C covalent bonds creating organic carboxylic acids and increasing the conductivity of the water. If a polishing deionizer is positioned just downstream of an* 185 nm *UV sanitizer or elsewhere within the tank and distribution systems, these ionized organic molecules can be removed from the water, therefore reducing its TOC level. As the water continues to recirculate past the* 185 *nm UV sanitizer and polishing deionizer, the TOC levels continue to drop. Care should be taken when using ultra low TOC values to control biofilm, as deionizer beds and electro-deionizers can provide an ideal environment for biofilm to flourish. For this and other reasons, including flow limitations, a separate polishing loop circulating around a tank, which incorporates microbial control features such as UV sanitizers, may be used. For further information, see the Chapter 8 of this Guide. A separate low pressure* 254 nm *UV sanitizer normally is not required when using a medium pressure UV unit because they also strongly emit the "bactericidal" wavelength of* 254 nm. *If required in a different location for a different purpose, such as for ozone destruction or downstream of a distribution system polishing deionizer, a separate low pressure* 254 nm *UV sanitizer may be justified.*

b. *US Pharmacopoeia.* The *US Pharmacopoeia* (USP) has clear specifications on UV light devices.

3.2.1 *Operation Unit Concerns / UV Light*

The use of 25*Anm low pressure UV light for microbial control will be discussed in the Sanitization chapter below. However, the use of UV light for the purification of chemical substances has also started. The* 254 nm *UV light can be used to decompose ozone. It has been proved that medium pressure UV lamps can be used during the pretreatment phase for PW, to effectively remove the residual chlorine, which is the sanitization reagent used in the raw water. High density UV light in combination with other oxidants (such as hydrogen peroxide) has been proved to have the ability to reduce the TOC level of a recirculated distribution system. The organic substances are usually converted to carbon dioxide. It will be balanced to bicarbonate, or incompletely oxidized to carboxylic acid. They can all be easily removed by polished ion exchange resin. The areas that need to be considered should include the UV light intensity, the retention time, the attenuation of lamp output UV intensity, the gradually formed UV light absorption membrane at a surface in contact with water, unexpected partial photolysis of the residual chlorine in the raw water, the ammonia generated by the photolysis of chloramine, occasional UV lamp failures, and the increase in the conductivity in the distribution system caused by the* 185*nm UV light. The management measures include the periodic inspection, or the monitoring of the UV light intensity and sleeve contamination with alarms, the periodic cleaning of*

the sleeve, installing a downstream residual monitoring instrument and a downstream polishing deionization device, and the periodic (about every year) replacement of the UV tube.

3.2.2 *Sanitization*

A UV lamp with a wavelength of 254 nm *can also be used for the continuous sanitization of the water circulated within the system. However, the UV lamp must be appropriately selected based on the water treatment flow. A UV lamp can inactivate the microbes flowing through the chamber in a highly efficient way (but not* 100%*). But it cannot be used to directly control microbes upstream or downstream itself. However, when a UV lamp is used in combination with the traditional thermal sanitization or chemical sanitization technologies, it is very effective and can prolong the periodic sanitization intervals.*

c. *Pasteurized Milk Ordinance* 2013 *Revision* Appendix H Pasteurization Equipment and Procedures and other Equipment IX. Acceptable Methods for Manufacturing Equivalent Pasteurization Water.

UV Disinfection of Water

As we all know, the UV light with a wavelength of 200 *to* 400 nm *can deactivate pathogenic microbes through several mechanisms, including causing the polymerization reaction between the hydrogen bonds between DNAs (for form dipolymers), to stop its propagation. Different microbes have different responses to UV lights of different wavelengths. This can also explain why there are different requirements on the overall dosage. Some microbes can repair their impaired DNA through their own enzymes and mechanisms, or the enzymes of the host cells. This requires higher UV light dosage to cause irreversible damages to the microbes and obtain the sanitization effect equivalent to pasteurization.*

In any cases, the following three types of critical factors will determine whether the UV equipment can ensure the required dosage: the UV light transmittance in the water, the output efficiency of the lamp, and the hydraulics and flow within the UV chamber. The color, the turbidity, the particles and the organic foreign matters will reduce the UV light transmittance in the water and reduce its sanitization effect against pathogenic microbes. Similarly, there can be uneven attenuation of the UV light tube. Water can contaminate the external surface of the sleeve, making it impossible for the UV light to reach some of the microbes. Different hydraulic design, or a too high or too low flow can all cause the uneven distribution of the dosage and result in insufficient sanitization at some parts of the chamber.

Other important influencing factors include the geometric shape and the power of the UV light reactor, the wavelength (within the chamber) and the spacial distribution of the UV light tube, and the length of the UV light passage. The longer the UV light passage, the more chance of being in contact with the microbe and inactivate it. When the water flows through the chamber, the UV light will sanitize the water instantly. However, it does not have a continuous sanitization function. Using a type of UV light sanitization technology to produce sanitized water equivalent to pasteurization cannot be used to replace the appropriate maintenance and the periodic rinsing and sanitization of the distribution loop of a factory.

Criteria

The following criteria should be met when using a type of UV light sanitization technology to produce sanitized water equivalent to pasteurization:

1. *When producing pasteurized water, the water treated by the UV light equipment for sanitization should at least be treated by the following dosages:*

a. For low pressure UV light (wavelength 254 nm*), the dosage needs to reach* 186 mJ/cm^2 *or ensure a* 4 lg *kill rate for adenovirus.*

b. For medium pressure UV light, the dosage needs to reach 120 mJ/cm^2 *or ensure a* 4 lg *kill rate for adenovirus.*

2. *A flow control or delay device should be provided to ensure that all the water flowing through the delay area or the diverter valve is exposed to the minimum dosage described above.*

3. *When designing the UV light equipment, it should be allowed that it can be frequently cleaned without being disassembled. A UV light equipment should be frequently cleaned to ensure that the required dosage can be provided at any time.*

4. *An automatic flow control valve should be installed, which should be precisely compatible with the expected pressure. This is used to restrict the maximum flow through the UV light equipment and ensure that any microbe can be exposed to the minimum dosage described above.*

5. *A precisely calibrated UV light intensity sensor should be installed to monitor the UV light intensity. The intensity sensor should be restricted to be sensitive only to the UV light with a wavelength ranging from* 250 *to* 280 nm *only, which has the disinfection effect.*

6. *A sensor should be equipped for each tube.*

7. *An on-line UV light transmittance detector should be installed to adjust the UV light intensity output based on the changes in the water quality to ensure the consistent precision and reliability of the UV light dosage.*

8. *A diverter valve or a valve that can be closed automatically should be installed to ensure that only the water exposed to the minimum UV light dosage can be allowed to the subsequent pasteurization phase. When the UV light*

system is closed, the valve should be closed to prevent any water not treated with UV light from entering the pasteurization phase.

9. *The construction material of an UV light equipment should not leach any toxic substances into the water, either from the construction material itself or produced under the UV light treatment.*

10. *The UV light equipment should be able to record the relevant operation parameters (flow, UV light transmittance and dosage) in real time. The se records should be easily accessible for any inspection authorities. If an electronic record is used, requirements in the Appendix H and the Appendix H should be met.*

d. Chinese codes for *Design of Pharmaceutical Process Water Systems* (GB 50913—2013). 4.5 Cleaning, Sanitization and Sterilization of PW and WFI Systems; 4.5.4 the sanitization and sterilization measures should meet the following specifications:

1. *When UV light sanitization is selected, the effective UV light dosage shall be no less than* 40 mJ/cm^2, *and the UV light sanitization equipment shall conform to the requirements of the current national standard UV Light Sanitization Equipment for Municipal Pluming Systems (GB/T 19837). The UV lamp shall be equipped with a timer and an illuminometer.*

2. *When ozone sanitization is used, UV light shall be used to remove the ozone.*

3. *Different sanitization methods can be used in combination according to the seasonal changes.*

3.3.4 UV Light Functions

The UV light water treatment technologies are mainly used for the PW generation, storage and distribution systems of the pharmaceutical industry. The major applications include disinfection, ozone destruction and dechlorination.

UV has been widely used in the purified water systems of the pharmaceutical industry, due to the characteristics and advantages of UV on-line disinfection technology, In some mature markets such as Europe, the US and Japan, on-line UV light disinfection has almost become the standard device for ambient temperature PW systems. In China, the decision is made by the pharmaceutical enterprises according to their specific conditions. The on-line UV light sanitization technology has been widely adopted by the enterprises with higher requirements on microbial control and risk control for their water systems.

Compared with the traditional dechlorination technologies, the medium pressure UV light dechlorination technology has drawn the attention of more and more professional technicians home and abroad because of its numerous process application advantages. Meanwhile, some of the pharmaceutical enterprises in China with leading technologies have also started using medium pressure UV light dechlorination technologies and have achieved satisfactory results.

a. UV disinfection. Typical bacterial structures include the cell wall, the cell membrane, the cytoplasm, the nucleic acid substances, etc. Among them, the deoxyribonucleic acid (DNA) is playing the core genetic role. DNA has a typical helical structure. It is composed of base pairs of the following four types: adenine, guanine, thymine and cytosine. The number of adenines equals to that of thymines, and the number of guanines equals to that of cytosines (Fig 3.77).

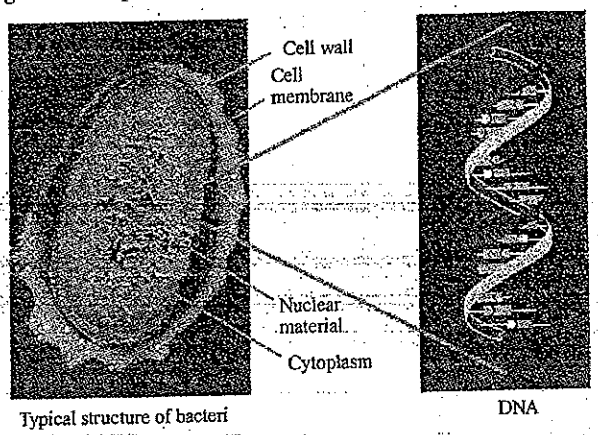


Fig 3.77 Typical bacterial structure

Mechanism of UV Light Disinfection: After exposure to UV light, the polymerization, and the formation of a type of dipolymer, of the hydrogen bonds of the DNA within the cells of the microbes. The original structure is thus damaged, which prevents its normal genetic and copying processes. Please see the chapter *Sanitization and Sterilization Technologies* below in this book.

For the on-line sanitization technologies for PW systems, UV light has the highest comprehensive cost effectiveness. Its initial investment cost is far lower than that of ozone (maintaining a certain concentration within the storage tank) sanitization, and its operation cost is far less than maintaining a low or high temperature for the storage and distribution system.

The commonly seen installation positions of UV light equipment in a PW generation, storage and distribution system are as described below; ①Between

the active carbon filter and RO, to reduce the microbes that easily grow in the active carbon filter output water and the RO return concentrate (if any), to protect the RO and the EDI (if any) units and reduce their sanitization frequency. ②Between the EDI and storage tank, to reduce the number of microbes entering the storage tank, because once any microbes enter the PW storage tank, they will grow faster. ③ Between the transfer pump and points of use of the distribution loop, the most commonly seen installation positions are located here for a pharmaceutical water storage and distribution system. It can directly reduce the number of microbes entering the points of use, ensuring the safety of water used at the points of use, and reduce the periodic sanitization frequency for the storage and distribution system.

b. UV dechlorination. Chlorine sanitization technologies are widely used. About 80% of the countries and regions in the world use chlorine for the sanitization of the municipal tap water. The usual method is to introduce chlorine or sodium hypochlorite into the tap water to obtain hypochlorous acid and hypochlorites with very high oxidizing capacity, which is used to kill many types of bacteria. The reaction used for sanitization by introducing chlorine in the tap water is as shown below: $Cl_2 + H_2O \longrightarrow HCl + HOCl$, $HOCl \rightleftharpoons H^+ + OCl^-$. The reaction used for sanitization by introducing sodium hypochlorite in the tap water is as shown below: $NaOCl + H_2O \longrightarrow NaOH + HOCl$, $HOCl \rightleftharpoons H^+ + OCl^-$.

In a PW generation system, the reverse osmosis (RO) membrane plays a crucial role in ensuring the water quality. Generally speaking, the RO membrane cannot tolerate the oxidation of any residual chlorine. The traditional method uses active carbon at the pretreatment phase to adsorb any residual chlorine, or uses $NaHSO_3$ to remove any residual chlorine.

Studies show that UV light can effectively remove the residual chlorine in water. A medium pressure and high dosage UV light can be used to replace the active carbon filter or sodium bisulfite dosing device. Besides removing any residual chlorine, it can also thoroughly inactivate any microbes, which provides a solution to the microbial growth risk from the source. UV light can achieve the 100% photolysis of the residual chlorine. Its working principle is: $2HOCl + 2h\nu \longrightarrow O_2 + 2HCl$; $2OCl^- + 2h\nu \longrightarrow O_2 + 2Cl^-$. Normally the dosage used for residual chlorine photolysis is more than 20 times the standard dosage for on-line UV light disinfection. Whether the residual chlorine can be successfully removed is related to the UV light exposure dosage. The major compounds of the residual chlorine that have the sanitization function are HOCl and OCl^-. Their UV light absorption wavelength mainly concentrates within the range from 260-330 nm (Fig. 3.78).

Compared with the two traditional residual chlorine removal methods, the active carbon method and the sodium bisulfite method, the UV light dechlorination has the following advantages: high efficiency residual chlorine removal effect, it can also thoroughly deactivate any microbes in the water, thus eliminating any microbial growth risks from the source. It can effectively prevent the microbial contamination at such downstream units as the RO, the EDI and the storage and distribution systems, and greatly reduce their periodic sanitization frequency. Its routine operation and management cost is much lower than that of the active carbon method. The intensity monitoring and dosage

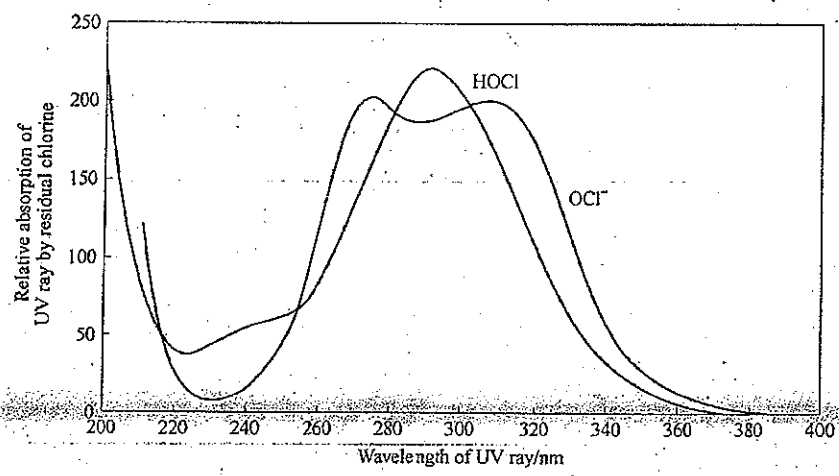


Fig 3.78 UV absorbance spectrogram of residual chlorine

indication are allowed for the UV light, and can accurately predict the chlorine removal effect. It has a very small footprint and the system itself is very clean, without the need for periodic cleaning or sanitization. No chemical dosing is required, which can prevent the scaling of the RO system. And the dechlorination efficiency of a medium pressure multispectral band UV light system is far better than a low pressure single spectrum UV light system. Using a medium pressure multispectral band UV light system for dechlorination can effectively reduce the number of UV light tubes and reduce the initial investment cost and the subsequent maintenance cost. Fig 3.79 shows a PW generation system using the medium pressure multispectral band UV light technology developed by the author.

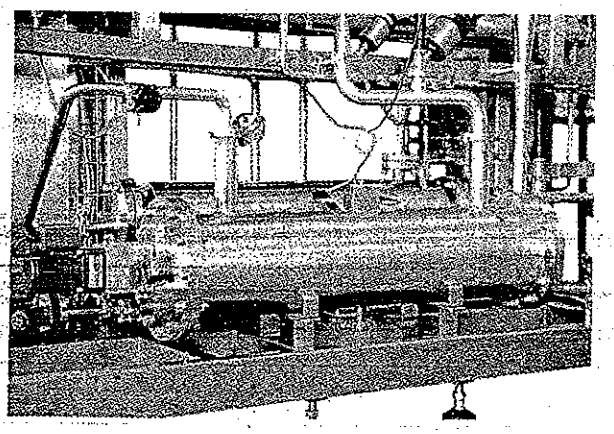


Fig 3.79 PW generation system using medium pressure multispectral band UV light system for dechlorination

The efficiency of UV light dechlorination is related to the quality of the feed water, such as the pH, the TOC, the residual chlorine concentration, the UV light transmittance, etc. For example, if the feed water quality is UV $T_{10}=98\%$, residual chlorine concentration = 2 ppm, pH = 7, TOC concentration less than 0.5ppm, the required dosage will be about 1,000 mJ/cm^2 for a 1 lg residual chlorine reduction by a medium pressure UV light system while maintaining the same water quality, and the required dosage will be about 5,000 mJ/cm^2 if a low pressure UV light system is used. That means the dosage required for a low pressure UV light system is more than 5 times of that of a medium pressure UV light system. Therefore, considering the technical feasibility and the investment cost, the medium pressure UV light technology is the best choice for UV light dechlorination application.

c. Ozone destruction. The UV light can destroy ozone. The ozone molecules mainly absorb UV light between 200 nm and 300 nm with the maximum absorption peak at 253.7 nm (Fig. 3.80). Generally, the UV light dosage required for destroying 90% of the ozone is more than 3 times of that required for normal UV light sanitization. Medium pressure UV light systems are more efficient in ozone destruction compared with low pressure UV light systems. The reaction principle for the destruction of ozone by UV light is as described below. The reaction is very fast and is usually completed in nanoseconds.

$$O_3 + H_2O + h\nu \longrightarrow O_2 + H_2O_2$$

$$H_2O_2 + h\nu \longrightarrow 2 \cdot OH$$

$$H_2O_2 + \cdot OH \longrightarrow H_2O + HO_2 \cdot$$

$$HO_2 \cdot + H_2O_2 \longrightarrow H_2O + O_2$$

The flow, the initial ozone concentration, the required ozone removal rate and the investment and operation cost should be considered when deciding whether a medium pressure system or a low pressure system should be used. Generally, the higher the flow and the

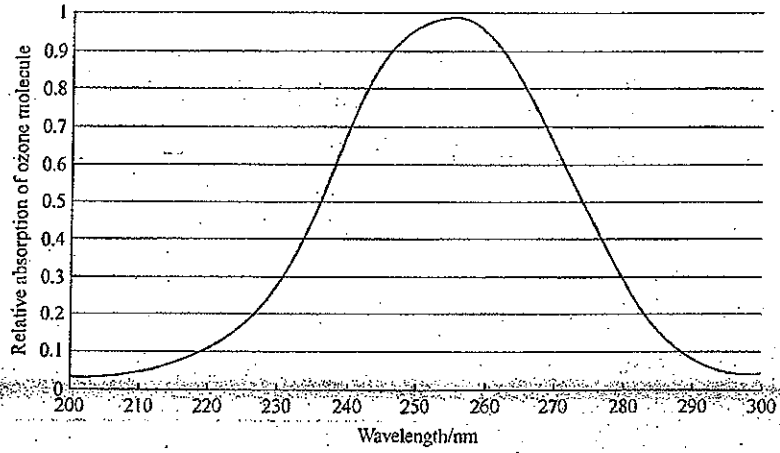


Fig 3.80 UV absorbance spectrogram of ozone

Table 3.4 Comparison on membrane filtration technology parameters

Names	Reverse Osmosis(RO)	Nano-filtration (NF)	Ultra-filtration (UF)	Micro-filtration (MF)
Membrane Type	Symmetric membranes Non-symmetric membranes	Symmetric membranes Non-symmetric membranes	Non-symmetric membranes	Symmetric Non-symmetric membranes
Pore Size	<1 nm	>1 nm	>1 kDa	>0.01 μm
Retained Ingredients	Sodium chloride, inorganic salts	Small molecule substances, antibiotics, polypeptides, amino acids	Large molecule substances, proteins, polysaccharides, viruses	Particles, bacteria
Membrane Material	Cellulose acetate(CA), polyamide	Organic membranes: polyether sulfone(PES), polyvinylidene fluoride(PVDF) Inorganic membranes: aluminum oxide, zirconium oxide	Organic membranes: Cellulose derivatives (cellulose acetate, regenerated cellulose); polyether sulfone (PES), polyvinylidene fluoride (PVDF), polyacrylonitrile Inorganic membranes: aluminum oxide, zirconium oxide	Organic membranes: polypropylene(PP), polyvinylidene fluoride(PVDF), polyether sulfone (PES), Nylon, polytetrafluoroethylene(PTFE) Inorganic membranes: aluminum oxide, zirconium oxide

higher the required ozone removal rate, it will be more appropriate to select a medium pressure UV light system. More detailed information on the application of UV light for ozone destruction can be found in the UV light relevant parts in the *Sanitization and Sterilization Technologies* chapter of this book.

3.4 Filtration Devices

Since the large scale application of the membrane filtration and separation technologies in the industry starting from 1960s, they have been rapidly developing. There are more and more types of filter products and their application scope is continuously expanding. It has become one of the advanced technologies with the most promising prospects in the early 21 century. The filter membrane is the core component of a filter.

The National Standard of the People's Republic of China (GB/T 20103—2006, *Terminology in membrane Separation Technologies*) provides a clear definition on the membrane used in the filtration area, "*A membrane is a type of thin barrier with certain physical or chemical properties at its surface, which providing a non-continuous space between two adjacent flowing fluids and affecting the permeation speed of different ingredients in the fluids*". Filtration is one of the most widely used operation units in pharma-ceutical water preparation systems. Generally speaking, filtration is a process that uses a type of filtration material with certain permeation capabilities to separate such contaminants as particles and microbes from a certain type of liquid or gas (Fig 3.81).

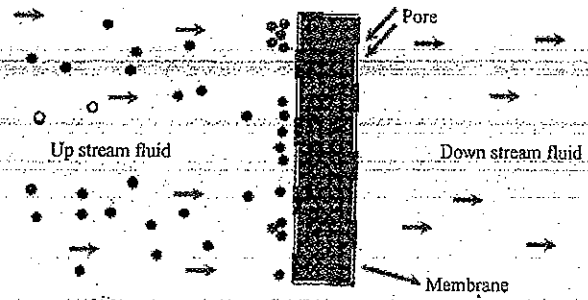


Fig 3.81 Schematic drawing of filtration

Filters can be divided into different types based on different criteria. They can be divided into Micro-filtration membrane filters, Ultra-filtration membrane filters, Nano-filtration membrane filter and Reverse osmosis membrane filters, etc. Table 3.4 shows a comparison of these four types of filters.

A micro-filtration membrane is a separation membrane with an average pore size no less than 0.01 μm. Correspondingly, the filtration process of using a micro-filtration membrane to separate particulates is called micro-filtration (MF). A micro-filtration membrane is generally used for the filtration of particles with μm size such as bacteria and large molecule substances. Up to now micro-filtration membranes are the membrane technologies that were developed the earliest and are most widely used around the world. They are mainly used to remove bacteria in the pharmaceutical industry, to filter the water, gases and reagents used

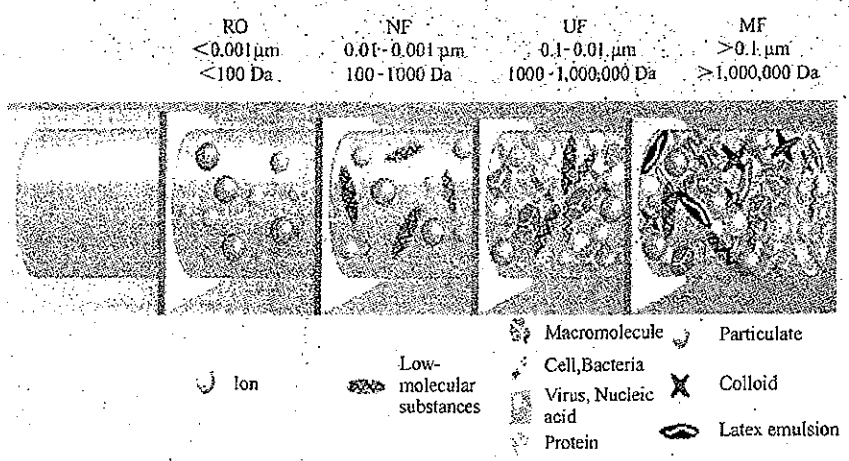


Fig 3.82 Corresponding relationship between membrane types and contaminants

in the micro-electronics industry, and the final filtration for the production of ultra-pure water. And they are also widely used in the food industry, the petroleum industry, and for analyses and environmental protection.

An ultra-filtration membrane is a type of membrane with a molecular weight cut off of several hundred to several million Da (Dalton, abbr. Da) composed of a very thin surface separation layer and a thicker porous supporting layer. The process of separating ingredients using this type of membrane is called ultra-filtration (UF). The retention molecular weight range of a UF membrane is usually 1-1,000 kDa. The typical application is separating large molecular weight substances from a solution. It has been widely used in the food industry, the industry waste water treatment industry, the ultra-pure water generation systems and the bio-pharmaceutical industry.

Nano-filtration (NF) is a type of membrane separation process to remove multivalent ions, some monovalent ions and organic substances with a molecular weight of 200-1,000 Da using pressure as the driving force. Because of the lower molecular weight, the sizes of these small molecules are usually at the nanometer level (usually between 1-2 nm). The molecular weight range of the retained substances is from 150-1,000 Da. The NF membrane is applicable to the purification and softening of water, and the separation of low molecular weight substances (such as antibiotics, polypeptides, amino acids, etc.)

One technology that has a higher retention level than nano-filtration is reverse osmosis (RO). It makes use of the capability of a reverse osmosis membrane in retaining all the ions or small molecular weight substances and only allowing the solvent (usually water) to pass. The membrane pore size is less than 1nm and the molecular weight range of the retained molecules is generally less than 200 Da. The RO technology is mainly used for the desalination of brackish water, the sea water desalination, renal dialysis, the pre-treatment for the pharmaceutical water preparation, and the recovery and the recirculation of small quantities of waste water.

Fig 3.82 shows the corresponding relationship between the types of membranes used for fluid filtration and related contaminants. The combination of a specific type of filtration membrane and the corresponding components forms a filter with a certain function. In this chapter we will focus on introducing the MF and the UF technologies. For the RO and NF technologies, please see the chapter on *Purified Water Preparation*.

3.4.1 Basic Principles

A filtration process mainly uses the direct retention mechanism, the inertial impaction mechanism and the diffusion interception mechanism to retain contaminants. Each mechanism has a different importance and action in different applications.

The direct retention mechanism is applicable to particles that cannot pass through the filtration material because of their large size. The contaminants are screened according to the pore size of the filter membrane and the contaminants that are larger than the pore size can be retained. The direct retention mechanism has the same effects for both liquids and gases (Fig 3.83).

Fig 3.84 shows the schematic drawing for the in-

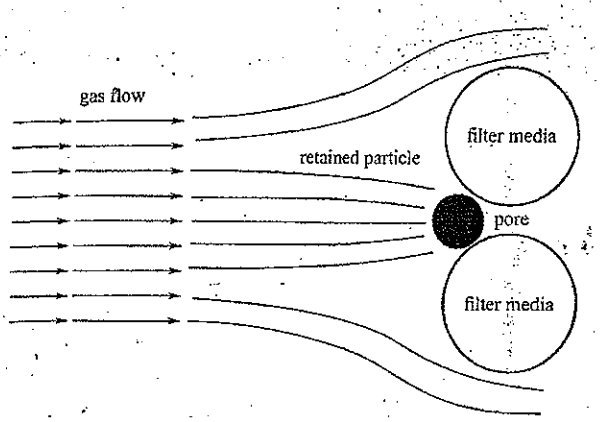


Fig 3. 83 Direct retention mechanism (from PDA TR26)

ertial impaction mechanism. The inertia prevents the contaminants in a fluid from bypassing the filter material along with the fluid. They will directly impact onto the filter material instead. The larger the mass of a particle, the more distinct the inertial impaction will be. So the retention efficiency for inertial impaction will also increase with the increase of the size of the contaminants.

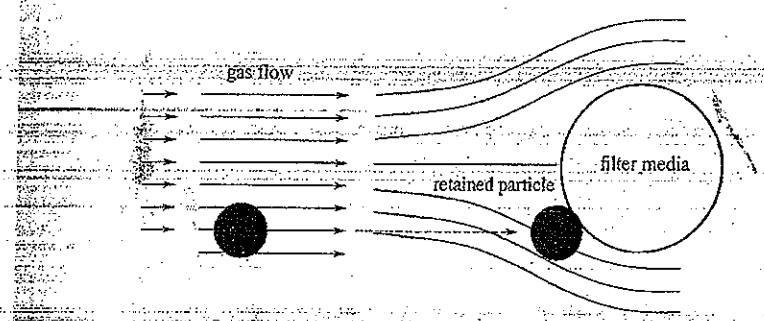


Fig 3. 84 Inertial impaction mechanism (from PDA TR26)

Fig 3. 85 shows the diffusion interception mechanism. Because of the Brownian motion caused by the continuous and random impaction of the molecules of the air, the suspended particles will move randomly around the fluid stream line. The Brownian motion improves the chances of the particles to come in contact with the filtration material, thus improving the chances of retaining the particles. However, the Brownian motion has more influences on small particles. So the retention efficiency by diffusion interception increases with the decrease in the particle size.

Compared with the density of a gas, the density of the particles is closer to that of a liquid. The suspended particles in a liquid have less deviation compared to the suspended particles in a gas. Besides, the Brownian motion of suspended particles in a gas is not as obvious as that in a liquid. The diffusion interception mechanism in a liquid has only a limited range. So both the inertial

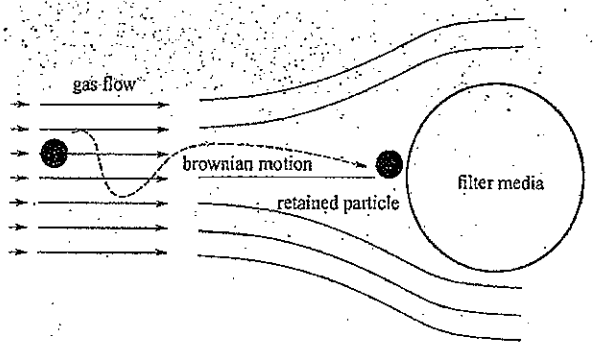


Fig 3. 85 Diffusion interception mechanism (from PDA TR26)

impaction and the diffusion interception in a liquid are not as effective as those in a gas. The same filter has far higher retention capacity in filtering dry gas than liquid. For example, the retention rating of a filter is 0. 2 μm when it is used to filter a type of liquid, and the retention rating can reach 0. 003 μm for gas.

Besides the above three major mechanisms, electrostatic capture can also be used to remove small size contaminants. A static charge can be generated when particles rub against each other. When such particles come in touch with the filtration material, it is very easy for them to hit the internal pores of the filtration material and get absorbed. Most of the contaminants in a pharmaceutical process are negatively charged. If the filtration material is positively charged, it can greatly improve its capability in removing contaminants.

3. 4. 2 Influencing Factors

When selecting filters, the important factors that should be paid more attention to include the fluid properties (such as the fluid type, quantity, and whether it is stable), the operation conditions (such as the temperature, the pressure and the flow), the particle properties (such as the size, the shape, the hardness and the quantity of the particles to be removed), the filtration membrane type, and the required filtration level.

a. Fluid properties. The filtration material, the filter element hardware and the filter house material used must be compatible with the fluid. If the filter element is corroded or damaged by the fluid, it will contaminate the filtrate. So it is essential to verify whether the fluid is acidic, basic, aqueous, oily or a type of solvent first. The other fluid properties include viscosity and the ions. The viscosity of the fluid can directly affect the filtration speed. The higher the viscosi-

ty, the slower the filtration speed will be. This means that the fluid has more time to be in contact with the membrane surface and the internal structures. When the fluid ingredients are kept the same, the actions of the filtration will change if the filtration speed becomes slower. The ions will also affect the filtration effect. The higher the charges of the ions in the fluid, the more distinct the electrostatic capture will be.

b. Operation conditions. The operation conditions are another type of important factors for filtration. The operation conditions mainly include the differential pressure, the flow rate and the temperature. For a fluid with a certain viscosity, the smaller the filter material pore size, the higher the resistance to the fluid will be. This will influence the pressure drop between the upstream pore size and the downstream pore size of the filter. The pressure drop across the filter is called a differential pressure or ΔP. The higher the resistance of the filter material to the fluid, the higher the differential pressure resulted will be. Because a fluid will always flow towards the direction of the lower pressure, a differential pressure will drive the fluid to flow. And when a filter is working, the particles will stop flowing and locally block or retard at the gaps of the filter material, which in turn increases the resistance and the differential pressure of the flow. So, when selecting a filter, a sufficient pressure source must be provided. This is not only to offset the pressure difference caused by the filter resistance, but also to ensure that the fluid can continue flowing at an acceptable flow rate when the filter is blocked. However, the differential pressure cannot be increased infinitely, otherwise the filter structure can be damaged and its retention capacity decreases. The filter users should ensure that the filter is operated under the appropriate differential pressure recommended by the supplier.

The flow is indicated by the volume per unit time (such as ml/min, L/h, etc.). The flow is directly influenced by the differential pressure. For the same fluid, the higher the differential pressure, the higher the flow rate will be. This means that the time required for the fluid of the same volume to pass will be less. Different viscosities of fluids with will also affect the flow rate. If all other conditions are kept the same and the viscosity is doubled, the original resistance of the filter system to the fluid will also be doubled. Therefore, the differential pressure needs to be doubled in order to maintain the same flow.

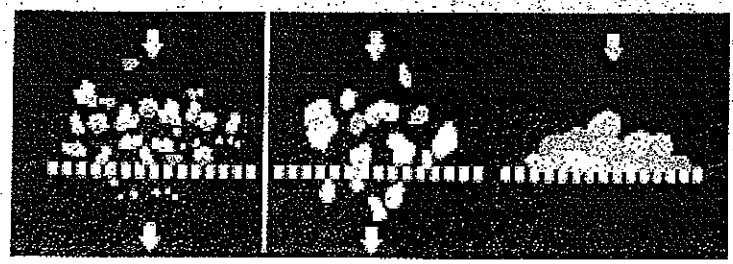
Besides the flow rate and the pressure, the temperature is another type of operation condition. The temperature during filtration can affect the viscosity of the fluid and the compatibility between the fluid and the filter. The viscosity of a fluid often decreases with the increase in the temperature. If the fluid viscosity is too high, it can be recommended to heat the fluid first to reduce the viscosity before filtration. Of course, the compatibility between the fluid and the filter at that temperature should be considered at the same time. A same filter has different differential pressure tolerance at different temperatures. The higher the temperature, the lower the maximum tolerable differential pressure will be. Table 3.5 shows the differential pressure tolerance data of a 0.2 μm hydrophilic PES membrane filter at different temperatures. During the actual production process, the user needs to have a certain understanding of the properties of the filter used and ensure that the operation parameters are controlled within the allowable ranges during the production, cleaning and sterilization processes.

Table 3.5 Influences of temperature on a filter

Temperature/℃	40	80	125(SIP)
Maximum Tolerable Positive Differential Pressure/bar	5.5	3.0	1.0
Maximum Tolerable Negative Differential Pressure/bar	2.0	—	—

c. Particle properties. The particles can be divided into deformable particles and non-deformable particles based on the impacts of the particles on the filtration effect. Deformable particles are soft particles that can deform under a certain pressure, such as colloids, liposomes, and cell debris. Non-deformable particle are hard particles such as sands, dusts, shed fibers, metal powders and active carbon powders.

Fig 3.86(a) is the schematic drawing of the hard particle filtration effect. Particles larger than the pore size are retained at the upstream side of the membrane and a layer of cake structure is formed. However, there are certain gaps in the accumulated structure. The liquid can penetrate through the sands and reach the downstream of the filter paper. For example, the filtering of activated carbon by a depth filter in a parenteral manufacturing process is a typical case of hard particle filtration. Fig 3.86(b) shows the filtration of soft particles. Under different operation condition, there can be many uncertainties because of the deformation of the



(a) Hard particle filtration (b) Soft particle filtration

Fig 3.86 Particle type impact on filtration

soft particles under pressure. It should be noted that soft particles can deform under pressure and penetrate through a pore smaller than its size to reach the downstream side. In this case the expected filtration effect cannot be reached. At the same time, when soft particles are accumulated on the surface of the filter membrane, they can block the pores and make it impossible for the filtration process to continue successfully. The service life of the filter will also be reduced.

d. Filter types. The filter materials can be divided into depth type and surface type. All the pores of a filter are in a single plane. This type of filter retains the contaminants mainly based on the direct retention mechanism. There are only a few types of surface filters in the market, such as metal screen filters (Fig 3.87) and fabric filters. Most of the filter membranes have a certain thickness. This type of filter material is like a sponge of a certain thickness with a three dimensional network structure. The retention of the contaminants happens not only on the surface but also inside the internal bending passages to a larger extent.

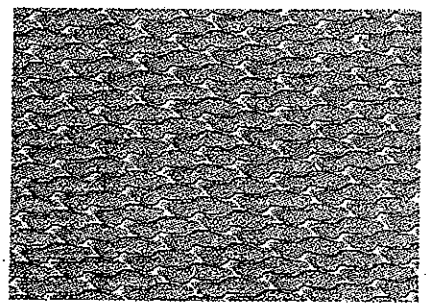
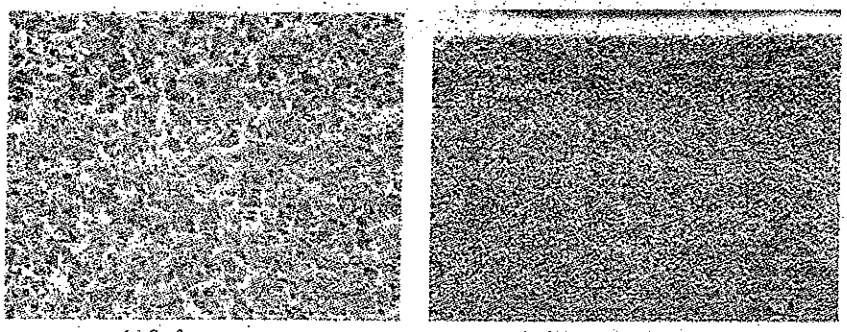


Fig 3.87 Metal screen filters

The retention rating of a membrane filter can reach more than 99.999,99%. All the sterile filters are membrane filters. Fig 3.88(a) shows the surface structure of a filter under a microscope. A filter with evenly distributed pores, a firm structure, and a good high pressure tolerating capacity can make it easier to perform and successfully pass a filter integrity test. Usually, a membrane filter can tolerate a working pressure of more than 5 bar. Fig 3.88(b) shows the sectional structure of a membrane filter under a microscope. The thickness is usually 100 to 260 μm. The complex bending passages within the filter can effectively improve its bacterial retention capability. The commonly seen membrane filter materials include Nylon, polyether sulfone, PVDF, PTFE, PP, fiber glass, regenerated cellulose, etc. The commonly used manufacturing processes include the phase inversion method, the melting and extrusion method, and the tensile method.

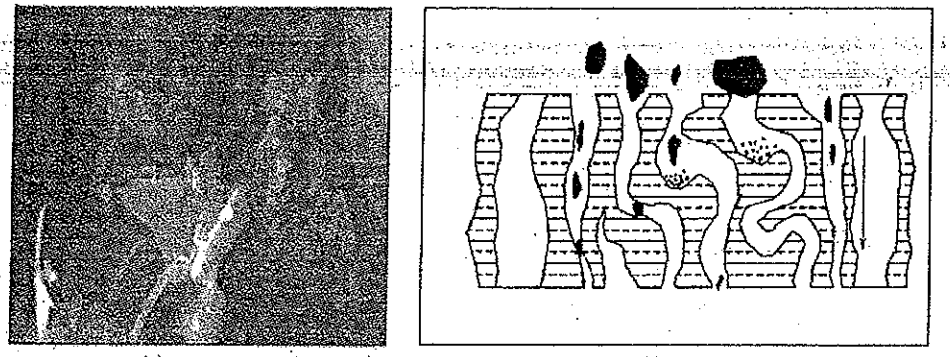
Compared with membrane filters, depth filters have thicker filter materials, with a thickness of 3-5 mm, and larger contaminant containing capacity. The major materials are the fiber base structure, the filter aids and the synthetic resins. The fiber base structure is usually a type of non-homogeneous natural cellulose fiber. It provides a basic structure with good porous water permeability. Perlite, diatomaceous earth and microcrystalline cellulose are commonly used as filter aids. They effectively combine with the porous passages provided by the cellulose base structure, and aid the retention of contaminants through the mechanical retention mechanism and adsorptive properties. The surface of synthetic resin particles is often positively charged and can adsorb negatively charged contaminants such as large biological molecules. At the same time the resin particles can also effectively improve the wetting of the filter membrane. See Fig 3.89(a) for the electron microscopic pictures of the internal structures of a depth filter. See Fig 3.89(b) for the schematic drawing of the internal structures.

The filter manufacturers usually divide the filter materials into non-fixed pore size filter materials and fixed pore size filter materials. Non-fixed pore size filter materials are those whose pore size can be increased with the increase of the differential pressure, such as felts, yarn and asbestos cushions. Because the filter material structure is not an integral entity, if



(a) Surface structure (b) Side sectional structure

Fig 3.88 Membrane structure of a membrane filter



(a) (b)

Fig 3.89 Internal structures of a depth filter

there is an increase in the differential pressure or the flow or there is a pulse, the filter with an enlarged pore size may release contaminants. This can often happen for this type of filter after it has been observed for a certain period of time. At the same time, the problem of filter material migration can also happen. This means that some of the filter material of the filter can drop off and contaminate the filtrate at the downstream side.

The pore size of the fixed pore size materials will not change under a high pressure. This type of material is composed of multiple layer filtration materials or a thick single layer of filtration material. The mechanism of action is mainly the direct retention mechanism for large size contaminants, and the inertial impaction mechanism and the diffusion interception mechanism for small particles. The structure is mainly used to avoid the distortion of the filtration material structures and ensure that the fluid will pass through the filter material through a winding passage. During the manufacturing of this type of filters, the pore size is controlled. And through the use of filter material of sufficient thickness, it is ensured that the amount of the retained small size contaminants that can be released will be greatly reduced even if there is an increase in differential pressure or flow rate or a pulse. Fixed pore size filters have advantages in many applications. They not only have higher membrane area, but also have much higher contaminant retaining capability. And the possibility of releasing of contaminants when the operation conditions changed is also greatly decreased. Most of the membrane filters on the market are using fixed pore size filter materials.

e. Filtration degree. The selected filter should be able to remove the contaminants from the fluid according to the process requirements. Once the size of the contaminant has been determined, the type of filter can be appropriately selected. Usually, selecting a filter with a pore size finer than required will result in a higher cost. Fig 3.90 shows the common particle types and sizes in pharmaceutical processes. The end user can select the appropriate filtration method in combination with the particle size and properties.

Based on the different contaminants to be removed, the filtration can be divided into particle removal filtration, bio burden control filtration, sterile filtration, mycoplasma control filtration, virus removal filtration, etc. The retention rating of a particle removal filter is usually about 0.45 μm. It is mainly used to remove large particles and to protect the downstream filters.

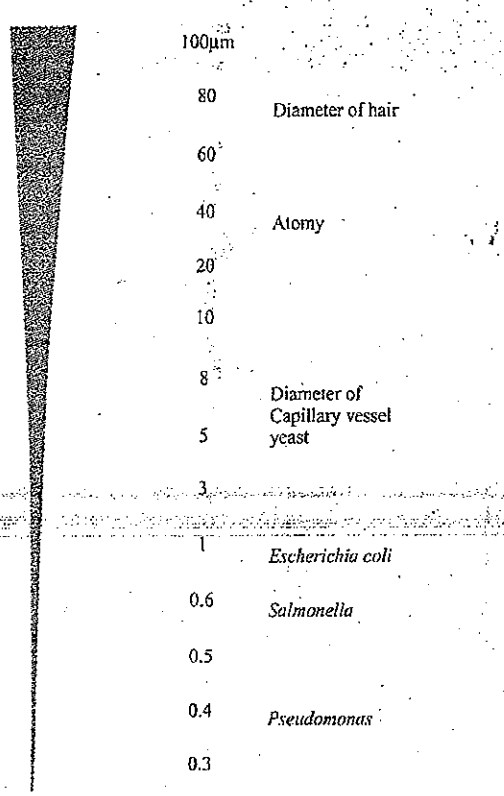


Fig 3. 90 Common particle types and their sizes

The particle removal filters are mainly large flow rate PP or glass fiber depth filters (Fig 3. 91).

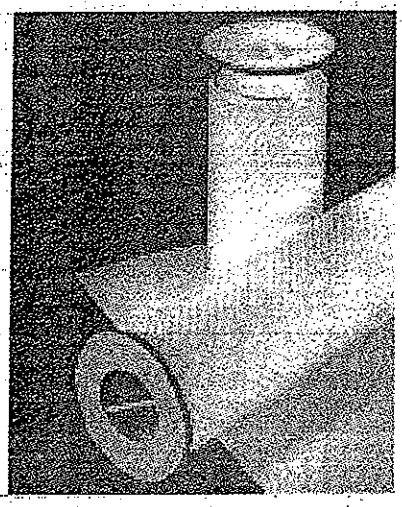


Fig 3. 91 PP filters

The retention rating of a microbial burden control filter is usually 0. 45 μm or 0. 2 μm. Its major purpose is to reduce the bio burden in the fluid. And it is not applicable to absolute removal. For example, although the nominal retention rating of a polyether sulfone filter of a brand is 0. 2 μm, its microbial removal capability can reach more than 10^7 CFU for 10-inch filter (with an effective filtration area of 1. 04 m^2), its microbial removal capability cannot meet the sterile filtration requirements. So it can only be considered a bio burden control filter.

Sterile filtration is the process that can remove all the microbes in a fluid. The retention rating of a sterile filter is generally no more than 0. 22 μm or 0. 2 μm. Because there is not a uniform type of criteria for the measurement of the pore size, the nominal pore size does not make any sense for microbial retention. So the microbial retention capability is required to define a sterile filter. Usually each square centimeter of the effective filtration area of a sterile liquid filter can retain 10^7 CFU *Brerundimonas diminuta* (ATCC 19146) and can obtain a sterile filtrate. Fig 3. 92 shows the picture of a Nylon sterile filter with *Brerundimonas diminuta* retention of more than 10^7 CFU/cm^2. The oval particles shown in the picture are *Brerundimonas diminuta* (ATCC 19146). The materials used for a sterile filter include Nylon (N66), PVDF, PES, cellulose acetate (CA) and PTFE.



Fig 3. 92 Electron microscopic pictures of a sterile filter

The retention rating of a mycoplasma control filter is usually 0. 1 μm. It can completely remove any mycoplasma or reduce it to an acceptable level. The retention rating of a virus removal filter is usually expressed in nanometers, such as 50 nm. It can effectively remove the small non-enveloped viruses and the large viruses (LRV>4-6).

Besides the liquid filters described above, air and other gas filters are also widely used in the pharmaceutical and biotechnological area. In the applications of gas filtration, in order to reduce the risk of filter element blockage by the accumulated water vapor within the filter, especially the accumulation within the pores of the filter membrane, the material should be hydro-

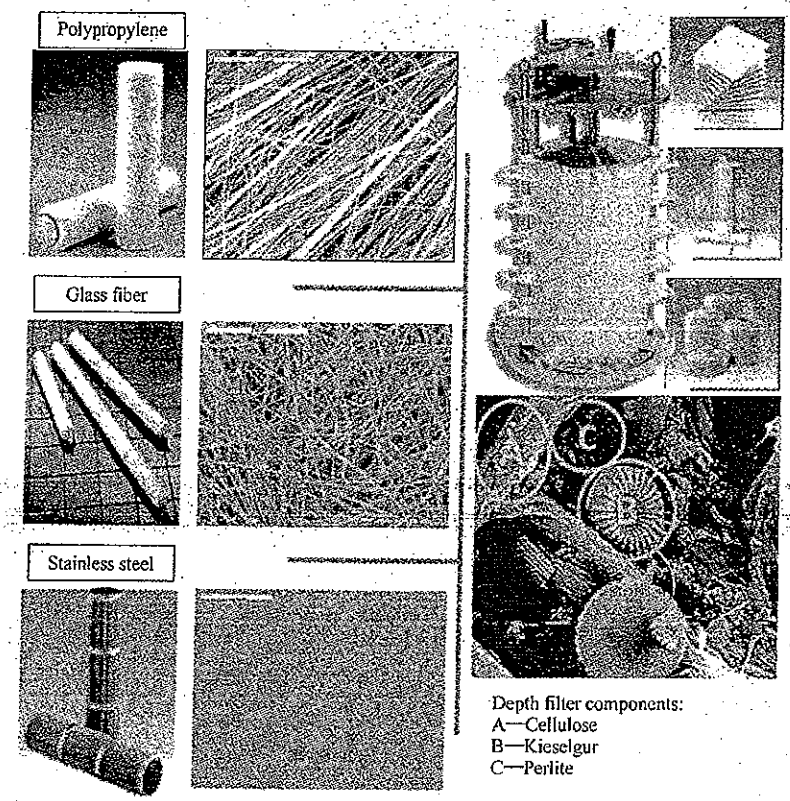


Fig 3.93 Schematic drawings for pre-filters and membrane structures

phobic. The commonly used hydrophobic filtration materials include PTFE, PVDF, PP and PE. In most of the applications that require the use of a hydrophobic filter, the filter should have the following ideal properties as much as possible: A high gas flow rate can be ensured when the filter differential pressure is low. The filter membrane should be hydrophobic to resist any water blockage. The filter must have high thermal and mechanical tolerance and tolerate multiple cycles of steam sterilization and should have a sufficiently long service life under the required conditions. The filter should be able to retain microbes even in unfavorable conditions (such as high humidity). The filter should not shed any fibers. It should be easy to install and maintain.

3.4.3 Filtration Types

In the fluid processing industry, filter products have been widely used. Because there are many types of fluids and the types and the physical and chemical properties of the contaminants and foreign matters they may contain are highly diversified, it is very difficult to have one type of filter that can process all types of fluids or perform the simultaneous processing of many types of foreign matters. So the selection and the application of filter products should be treated differently based on the actual conditions. Taking the functions of the bio-pharmaceutical and water treatment industries as the criteria, the filters can be divided into pre-filters, microbial control filters, sterile filters, mycoplasma removal filters and virus removal filters.

The retention rating of a pre-filter is less than 0.45 μm in most cases and this type of filter is used to remove any particulate matter in the fluid to protect the early blockage of the downstream filters. At present, the materials (membranes) used for the pre-filters used in the above industries include PP, glass fibers, stainless steel, synthetic fabrics, etc. The corresponding filter retention rating range is rather wide. It is mainly within the range of micro-filtration. The relevant filter appearance and the filter membrane microstructures are as shown in the electron microscopic images in Fig 3.93. The materials for a sterile filter include PES, PVDF, Nylon (N66) and PTFE. Its absolute retention rating is 0.2 μm. It is relatively open compared with the retention rating of 0.1 μm for mycoplasma removal filters and the retention rating of tens of nanometers for virus removal filters.

Because the materials themselves have different properties, the sterile filters made of the above materials have different advantages in chemical compati-

bility in the field of fluid filtration. They are roughly described qualitatively in Table 3.6.

Table 3.6 Chemical compatibility of commonly used materials for sterile filters

	High pH Value	Low pH Value	Solvent
PES	Good	Good	Good (except for acetones and aldehydes)
PVDF	Poor	Good	Good (except for acetones and aldehydes)
N66	Good	Poor	Good
PTFE	Excellent	Excellent	Excellent (except for methylbenzene)

Taking a sterile filter as an example, this type of filters can be divided into cartridge filters (AB type), bag filters, and special filters based on the structure and appearance.

Cartridge filters (AB type) are the most widely used filters in the pharmaceutical industry (Fig 3.94) and their heights include 5 inches, 10 inches, 20 inches, 30 inches and 40 inches. There is a strong cylindrical support inside and another one outside a cartridge filter. The supports are usually in PP material. This type of material has a high melting point, which is generally more than 160 ℃. So it can usually tolerate high temperature humid sterilization at a temperature of 100 ℃. A cartridge filter can be steamed on line during a pharmaceutical process. However, the filter element manufacturer's recommendations on the sterilization temperature and pressure and other technical operation parameters should be strictly followed.

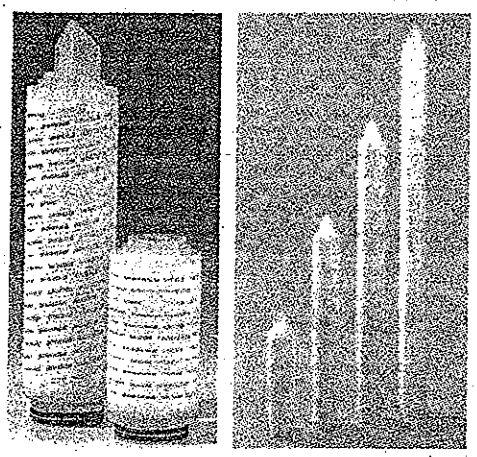


Fig 3.94 Cartridge filter elements

A pre-filter (including depth filter elements) or sterile filtration membranes can be installed within a cartridge filter element as required. The depth filtration membranes should be installed in multiple layers folded together. And all the other pre-filter membranes and sterile filter membranes should be installed in different pleating modes (Fig 3.95). After the filter membrane has been pleated as designed and loaded into the filter element supports, the effective filtration area (i.e. the membrane area) of each filter can be improved to the maximum. Generally speaking, the larger the filter membrane area, the higher filtration speed [expressed in $L/(m^2 \cdot h)$, LMH] and the maximum filtration throughput (expressed in liter/square meter, L/m^2).

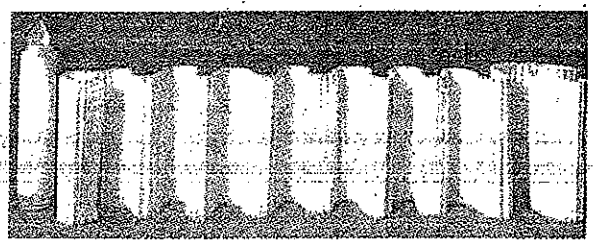


Fig 3.95 Pleated structure membrane within a cartridge filter

A bag filter is composed of the core component (filter membrane) and the shell in a type of organic material. The materials that can be used for the manufacturing of bag filter shells include PP, polyesters, etc. Some of the shell materials high strength and good thermal resistance and can tolerate high temperature processing conditions such as on-line steam sterilization. In order to meet the different pipeline connection requirements from the users, the bag filters have multiple types of interfaces. At the same time, 20 inches bag filters and 30 inches bag filters are developed based on the 10 inch bag filters in order to meet the requirements for using filters with different filter membrane areas at different points of a same process (Fig 3.96).

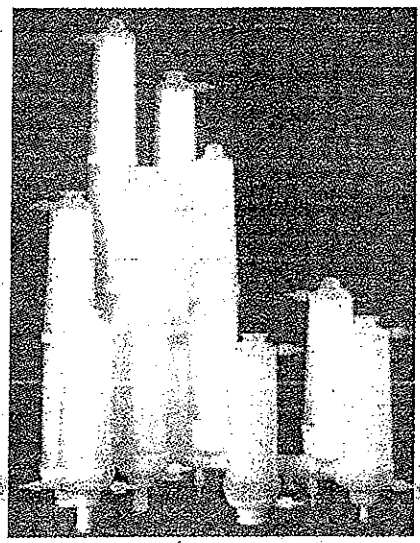


Fig 3.96 Bag filters

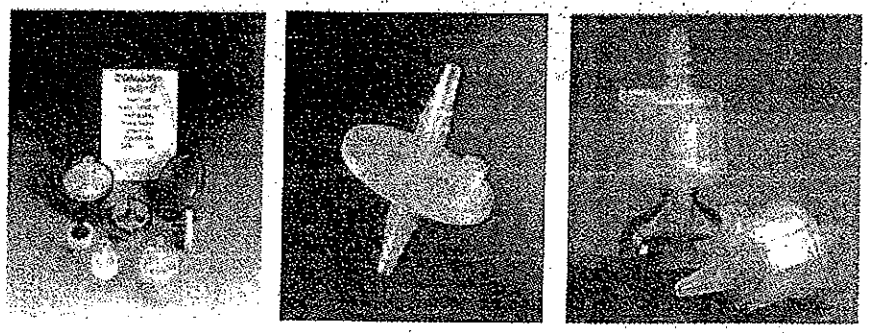


Fig 3.97 Small bag filters

In the bag filter family, besides the large area filters that are suitable for pilot scale and large scale production, there are also small bag filters used to facilitate the quality control and lab tests (Fig 3.97). These small bag filters have the same advantages as the cartridge filter element based large area bag filters. At the same time, the small bag filters have simpler installation steps compared with the routinely used cartridge filters. The disassembling and the re-assembling of stainless steel shells are not necessary, which reduces the validation activities on production, cleaning and sanitization, reduces the cost for procuring the shells. In addition, because small bag filters have the same core structural components (filter membrane), as those of large area bag filters and cartridge filters, they are usually used for small scale lab tests with good process scaling up results.

In the area of fluid filtration, there are extremely diversified user process conditions and requirements. Thus, other special filters are developed based on the structure of cartridge filters for the pharmaceutical industry because the filtration speed is not required to be too high, the total filtration throughput is small and the required volume is small. Different types of filters as shown in Fig 3.98 have been used with different levels of acceptance. The sealing elements of these filters include internal O rings and external O rings, corresponding to steel shells of different structures. The optimal products can be selected based on such specific requirements as the target fluid treatment parameters and the spatial arrangement at the specific locations of the process pipeline. At the same time, at some locations the small flow rate and small volume treatment requirements as well as some specific regulatory requirements (such as the GMP requirements for pharmaceutical water systems) are to be met at some locations during the entire fluid filtration process. Thus, manufacturing small scale filters with a complete set of documentation support can very well meet the regulatory requirements and the user requirements.

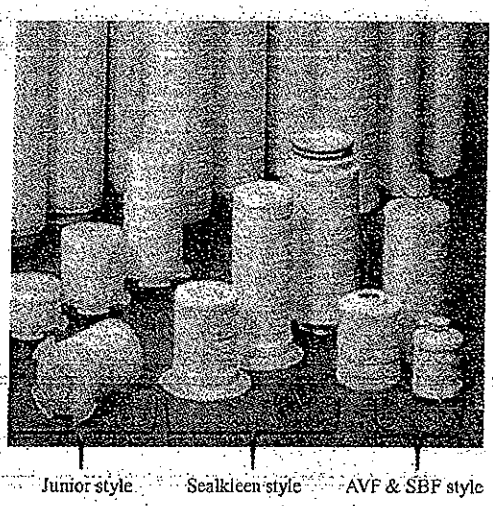


Fig 3.98 Special format filters

A complete filter is composed of the filter elements and the stainless steel shell. The stainless steel shell is installed outside the filter element. The material should be 316L stainless steel. The stainless steel shells can be divided into I shells and T shells based on the appearance (Fig 3.99). Each shell includes an inlet port, an outlet port, a vent port and a drain port. A pressure gauge port is also provided for a T shell.

When selecting a filter for the filtration of pharmaceutical water, the calculation and the assessment can be performed based on the flow rate and pressure curve provided by the filter manufacturer. The AB1 shown in Fig 3.100 (representing a 10 inch cartridge filter) is taken as an example. Identify the crossing point of the dotted line representing 3 psi on the y-axis, which represents the differential pressure, and the red curve. The n the actual flow rate value can be identified on the x-axis representing the flow in L/min (that is 25 L/min). This indicates that at a temperature of 20 ℃, a filtration flow rate of 25 L/

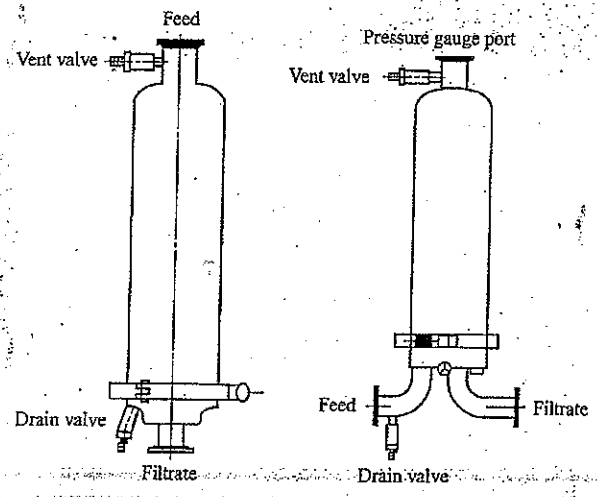


Fig 3.99 Shell models

min can be achieved with this filter at a differential pressure of 3 psi.

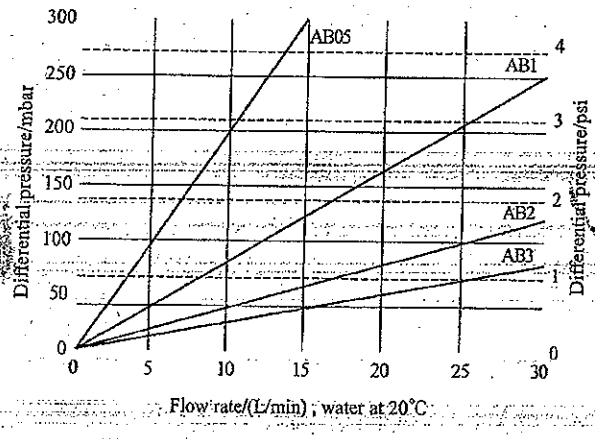


Fig 3.100 Schematic drawing for filter flow rate/differential pressure curve

If the viscosity of the fluid is high, the flow rate/differential pressure curve of water cannot be referenced directly. The filter manufacturer should provide tests for providing more accurate data for filter selection, such as the test for P_{max} and T_{max} of the filter, and the test for the V_{max} of a membrane filter. A 47 mm small filter can be used to perform the test based on the specific process requirements to obtain the maximum volume of a type of fluid the filter can process. A reasonable safety margin should be considered for the calculation. And then the data of the 47 mm membrane will be linearly scaled up to the actual process. The maximum effective linear scaling up rate of the small scale test is 500. Fig 3.101 shows the filter linear scaling up parameters provided by a filter manufacturer. The test results of the 47 mm filter can

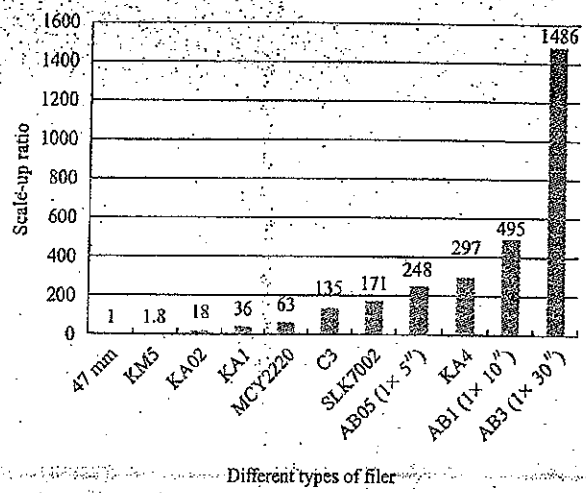


Fig 3.101 Filter linear scaling up parameters

be linearly scaled up to a 10 inch filter element. If it is required to filter a type of liquid with a larger volume, a pilot scale test should be performed to ensure the effectiveness of the process scaling up.

3.4.4 Tangential Flow Ultra-filtration

In the field of fluid treatment, the filtration processes are often divided into direct flow filtration (DFF) and tangential flow filtration (TFF) based on the filtration mode.

DFF means that the liquid directly penetrates through the filter membrane to the downstream side, under pressure, and large particles or molecules are retained at the upstream side of the membrane or within the membrane, small particles or molecules penetrate through the membrane and go to the downstream side (Fig 3.102). In this type of operation mode, the flowing direction of the liquid is vertical to the membrane to the downstream side. This type of filtration mode is also called the dead end filtration. The advantages of DFF are that the pipelines and operations are simpler. However, the filtration speed decaying is rather rapid because of the rather significant filter membrane blockage. The applications of DFF include the clarifying filtration, sterile filtration and virus removal filtration mentioned above.

Tangential flow filtration (TFF) means the direction of the liquid flow is in parallel to the membrane surface. Under pressure, only a part of the liquid penetrates through the membrane and reaches the downstream side of the membrane. This type of operation mode is also called cross flow filtration (Fig 3.103). Because of the continuous scouring of the membrane

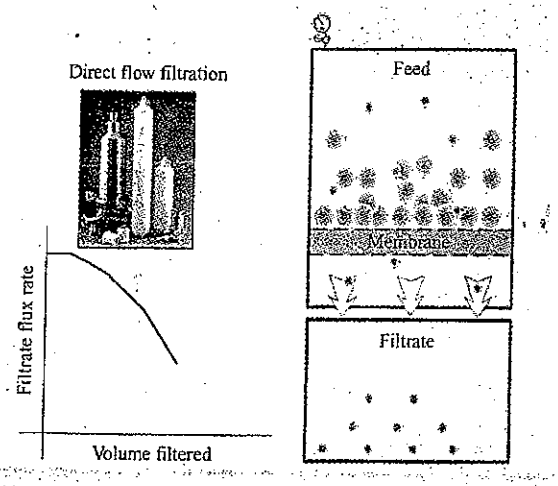


Fig 3. 102 Schematic drawing of direct flow filtration

surface by the tangential flow during the filtration process, the accumulation of particles and molecules on the membrane surface is effectively removed, which is a unique advantage of this type of operation mode in many applications. For example, it is more difficult for the membrane to be blocked and the filtration speed can be maintained stable within a certain range.

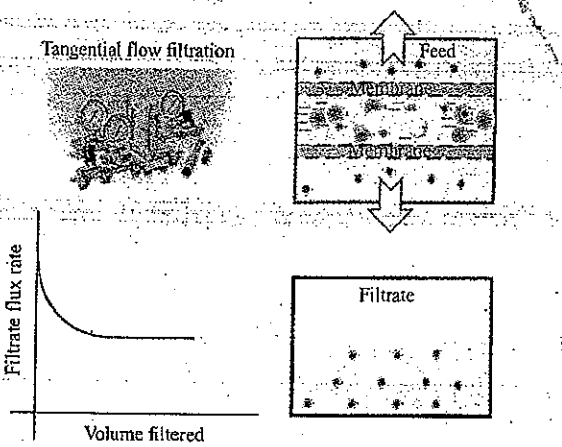


Fig 3. 103 Schematic drawing of tangential flow filtration

As described above, an ultra-filtration (UF) membrane is a type of membrane with a molecular weight cut off at several hundred to several millionDa composed of a very thin surface separation layer and a thicker sponge like or finger like porous supporting layer. During an UF process, the solvents and the small solute particles in the feed solution penetrate through the filter membrane from the high pressure side to the low pressure side under the static differential pressure. The low pressure side is generally called the filtrate side or the permeate side. The large particles are retained by the membrane, making their concentration in the upstream return flow side to become higher and higher. Compared with MF membranes, UF membranes are with finer porous structures, so the filtration speed is lower, the required differential pressure is higher, and they are easier to be blocked compared to MF membranes. The TFF technology can use the cross flow to sufficiently scour the membrane surface, to significantly relieve the blockage of the UF membranes. The two types of technology are often combined; this is called tangential flow ultra-filtration (TFF-UF).

The molecular weight cut off (MWCO) of the pores is often used to indicate the retention rating of a TFF-UF membrane. Particles and molecules larger than the specified retention rating will be retained at the upstream side of the membrane (the return flow side/feeding side). Different criteria are followed by different UF membrane manufacturers for the specified retention rating. So different retention efficiency can be obtained. The solid line curve (Ideal Selectivity) shown in Fig 3. 104 indicates the retention performances of a UF membrane should achieve at a specific retention rating under the ideal conditions. That is to say, a retention rate of nearly 100% around its retention rating (the Rejection in the drawing) to realize the instant switch of the permeability of molecules of specific sizes. Because of the restrictions in the engineering technology, such a high retention rate cannot be achieved by the UF membranes presently available in this industry. Usually, the steeper the slope of the retention property curve at a point near the specified retention rating molecular weight, the higher the efficiency will be.

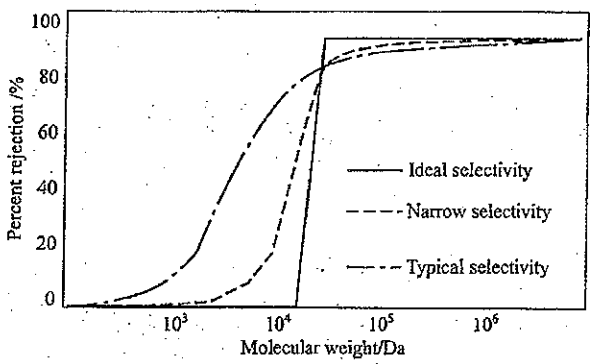


Fig 3. 104 Schematic drawing for tangential flow ultra-filtration retention efficiency

Fig 3. 105 shows the membrane separation test

performed using glucosan model molecules of different molecular weights as the subjects using a type of TFF-UF and the retention efficiency of the UF membrane of the corresponding retention rating. Taking the 10K UF membrane (OMEGA 10 K) as an example, by looking at the corresponding dark blue curve in the drawing it can be seen that its retention efficiency for 10 kDa glucosan molecules is nearly 70%. There are a few TFF-UF membranes used in this industry can have a retention efficiency of as high as nearly 90%. It needs to be specially pointed out that the retention by a membrane can be affected by such factors as the solute shape and compressibility, and their interactions with other substances in the solution. So when the solutes larger than the specified retention rating of a membrane are retained, some solutes with smaller molecules will also be retained.

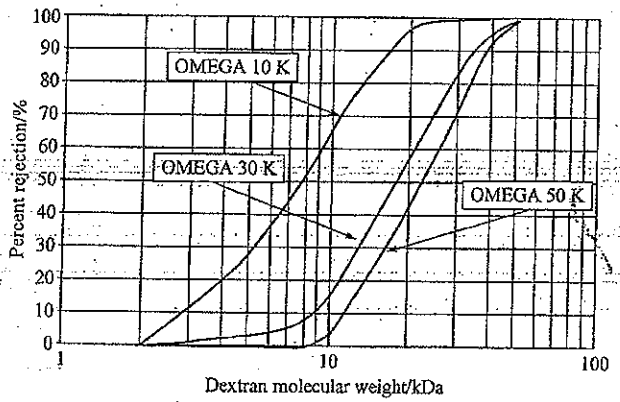


Fig 3.105 Schematic drawing for tangential flow ultra-filtration retention efficiency

TFF-UF has such characteristics as no requirement for heating, lower power consumption, and can be used repeatedly. It is a common type of filtration used in the pharmaceutical industry and is widely used for clarifying filtration, product concentration, depyrogenation, small molecular foreign matter removal, desalination and buffer solution displacement. Taking plate membrane products as an example, Fig 3.106 shows the appearance (upper left), the membrane slice scanning electron microscopic image (lower left) and the profile of the structure.

A typical TFF-UF system includes a material solution storage tank (may including the cleaning filtrate supplementation pipelines), a pump, a membrane and the clamps, the connecting pipes and fittings, valves, pressure gauges. Please see Fig 3.107(a). A TFF-UF system can be run in different modes based on different requirements. The right picture of Fig 3.107(b) shows three example modes, A, B and C.

In order to better understand the tangential flow filtration technology, the terms commonly used in this process and their meanings should be understood. The commonly used terms in the tangential flow filtration technologies include cross flow rate (CFF), transmembrane pressure (TMP), differential pressure (ΔP), filtration speed (Flux), retention rate, concentration (the volume concentration factor, VCF), and the product recovery. Fig 3.108 shows the flow channels of a TFF-UF device. The pressure at the feeding side is P_F. The pressure at the return end is P_R. And the pressure at the permeate end is P_P.

The CFF is to a great extent dependent on the selected membrane and the flow channel type. The red arrow from the left to the right along the horizontal direction in the drawing above is the flow direction of CFF. Generally speaking, when the transmembrane pressure is kept the same, improving the tangential flow can increase the scouring effect of the tangential flow on the filtration membrane, alleviate the concen-

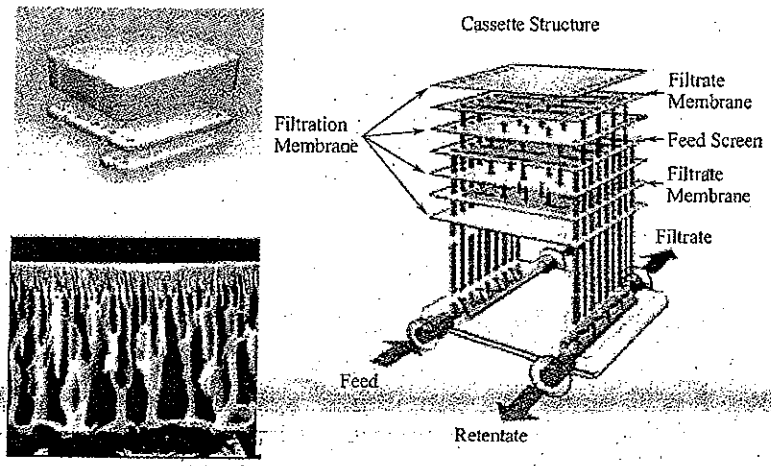


Fig 3.106 Schematic drawing of tangential flow ultra-filtration plate membrane structure

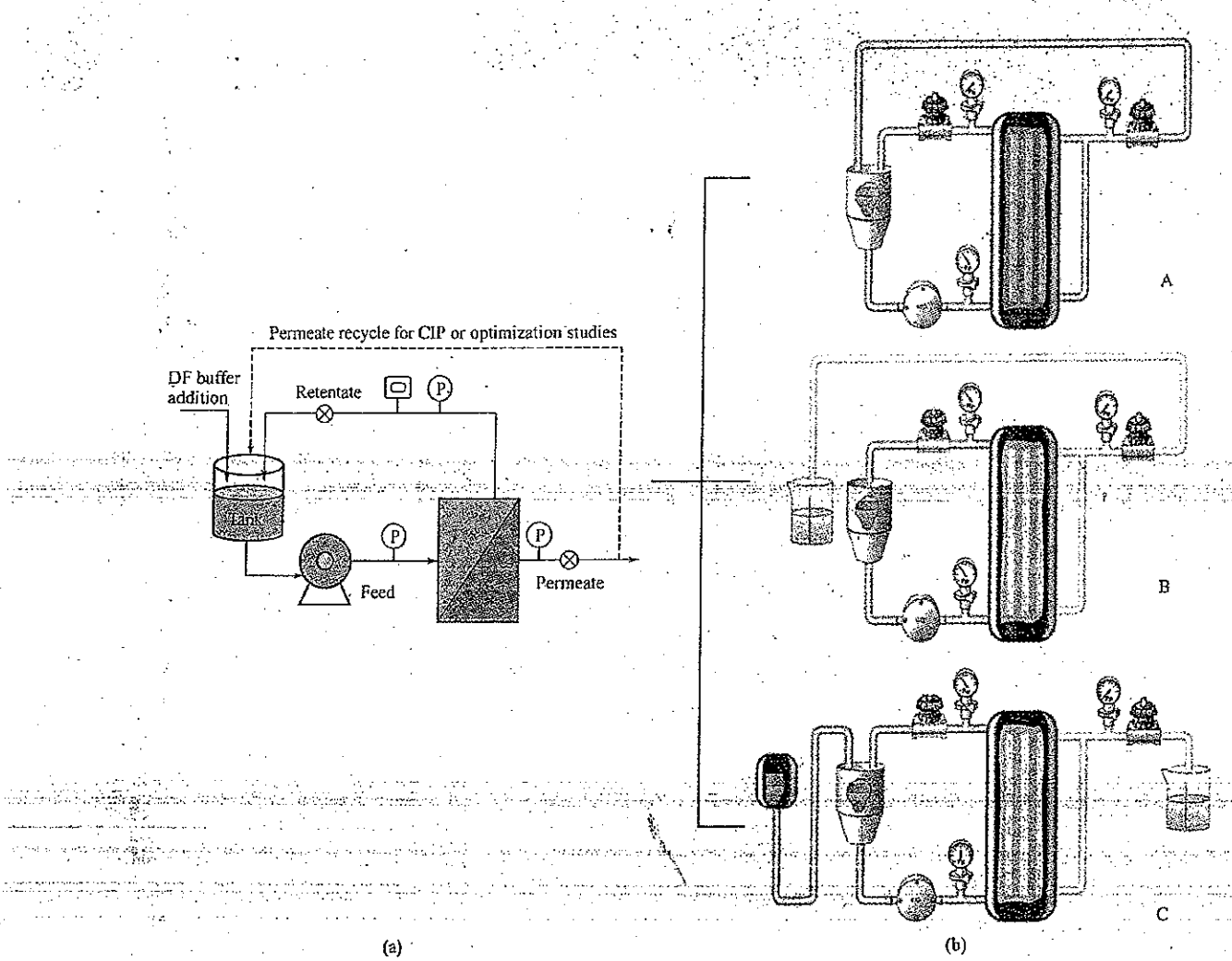


Fig 3. 107 Schematic drawing for structure and operation of TFF-UF

Mode A is the operation parameter optimization (such as the transmembrane pressure, TMP, which is explained later) test process. The filtrate pipeline returns to the feeding solution storage tank.

Mode B is the routine UF separation process. The filtrate is directly transferred to another storage tank. During this operation process at this state, if the materials to be filtrated are those at the upstream side of the UF membrane, this process is mainly used to remove the small molecular foreign matters. With the operation of the UF process, the volume at the upstream side will be gradually reduced. So this process can also be called concentration. If the products to be filtrated are at the permeate side, this process is used to remove the large molecular foreign matters.

Mode C is continuousdiafiltration (DF). Another type of wash fluid is to be supplemented to the feeding solution storage tank. This process is mainly for the products at the upstream side. The added wash fluid will go along the UF process and gradually come out from the permeate side. And it can carry some of the small molecule foreign matters with it. So this process is often used for physical desalination. It needs to be noted that if the products to be recollected are at the permeate side, the volume of the wash fluid added should be able to recover any residual products at the upstream side as much as possible.

tration polarization and improve the flow of the permeate. However, a too high tangential flow can also cause the increase in the shear force on the product, causing the possible decrease in the product activity. So the relevant parameters should be optimized based on the specific applications. The transmembrane pressure (TMP) provides the driving force for the trans-membrane filtration activity. For its calculation, the pressure at the permeate side is subtracted from the average of the inlet pressure and the return end pressure.

$$TMP = (P_F + P_R)/2 - P_p \qquad (3.9)$$

Generally speaking, the higher the TMP, the higher the filtration speed will be. However, during the actual filtration process, there will be a limit level for the filtration speed. At this speed the filtration

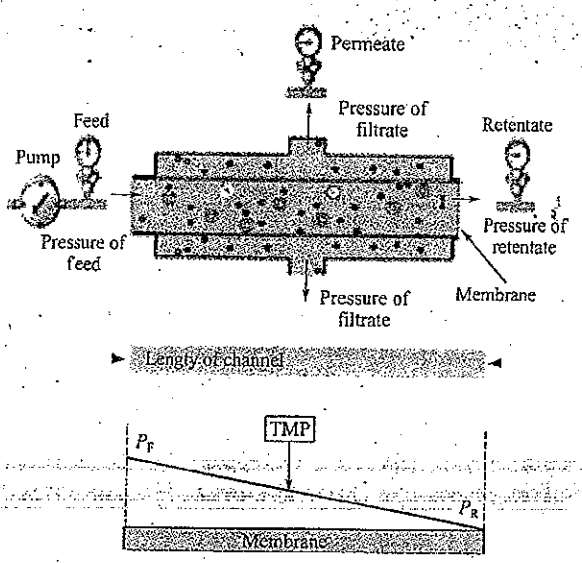


Fig 3. 108 Schematic drawing of flow channels of a tangential flow ultra-filtration device

speed will not be increased further because of the concentration polarization. The extreme concentration means that during a tangential flow process, the concentration of the solutes (large molecule substances retained) at the membrane surface will increase continuously because of the gradual permeation of the solvent and the low molecular substances from the high pressure side (return end), and a concentration polarization will be generated between the membrane surface and the main fluid (Fig 3. 109).

In a tangential flow filtration test under a constant flow, the relationship between the throughput and the transmembrane pressure can be divided into two phases, the membrane control area and the gel control area (Fig 3. 110). In the beginning, the factor that affects the filtration speed is only the resistance of the filter membrane. So when the TMP is increased, the filtration speed will increase linearly. This process is at the membrane control area. With the increase of the TMP, the concentration at the filter membrane surface increases gradually (concentration polarization). Some of the increased TMP is balanced by the resistance of the gel layer. So the filtration speed increase trend will slow down gradually, until the filtration increase stops when the TMP is completely balanced by the resistance. This is characteristic of the gel layer controlled region.

The methods for regulating TMP includes changing the cross flow rate (CFF) through a regulation pump, changing the return flow pressure through opening/closing the return flow valve, etc. At the same time, for different tangential flows, the TMP optimization curve can still maintain roughly the same trend. However, the actual filtration speed will be significantly affected. As shown in Fig 3. 111, increasing the CFF appropriately within an appropriate scope with the TMP kept the same can get a relatively higher filtration speed, thus shortening the UF process and improve the efficiency.

The differential pressure (ΔP) represents the driving force provided to the tangential flow. The differential pressure is proportional to the feeding flow. It can be adjusted by the flow and its value can be calculated by the following formula:

$$\Delta P = P_F - P_R \qquad (3.10)$$

The filtration speed (Flux, expressed as J in the formula) means the filtration speed of a unit membrane area. It represents the working efficiency of a tangential flow filtration process and is usually expressed in LMH, L/(m² · h).

The retention rate is used to indicate the ratio of

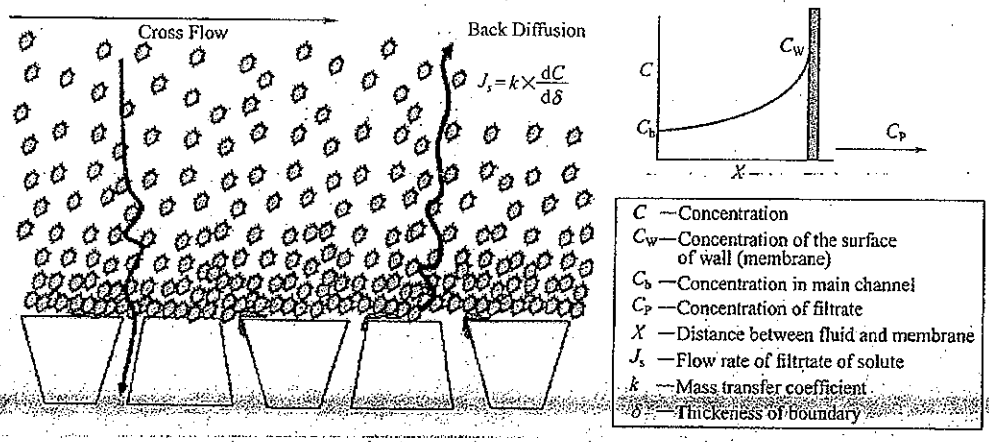


Fig 3. 109 Relationship between material concentration distribution within the flow channel and the filtration speed

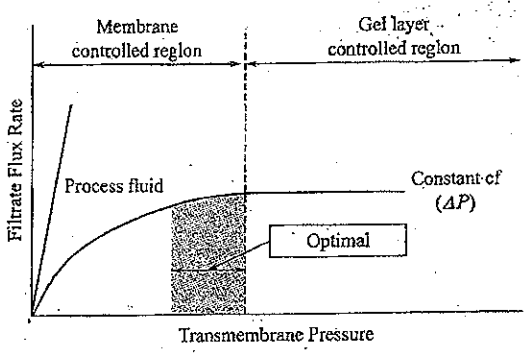


Fig 3.110 Formation, distribution and optimization of TMP

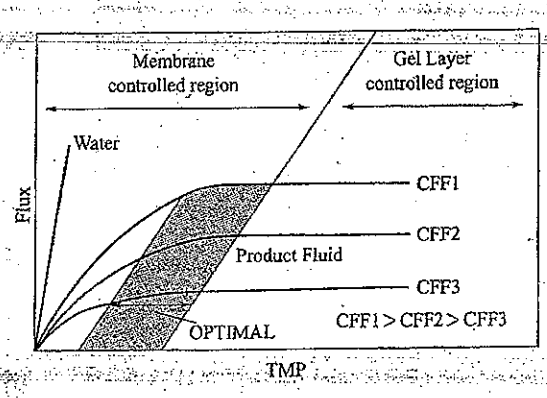


Fig 3.111 Relationship between CFF and filtration speed

retention of a type of substance by a membrane. It can be expressed by the following equation, in which % Retention is the retention rate, Passage is the permeation rate, $[\%]_{permeate}$ is the concentration of a type of substance in the permeate, $[\%]_{retenate}$ is the concentration of a type of substance in the return solution.

$$\%\text{Passage}=\frac{[\%]_{permeate}}{[\%]_{retentate}}\times 100\% \qquad (3.11)$$

$$\%\text{Retention}=100\%-\%\text{Passage} \qquad (3.12)$$

The volume concentration Factor (VCF) is the ratio of the initial volume to the final volume in the concentration process. The concentration factor is the actual concentration factor during the concentration of a type of substance, which is usually lower than the volume concentration factor. The se two can be expressed by the following equations:

$$\text{VCF}=\text{initial volume / final volume}=V_{initial}/V_{final} \qquad (3.13)$$

$$\text{CF}=\text{final concentration / initial concentration}=C_{initial}/C_{final} \qquad (3.14)$$

The product recovery is the ratio of the total amount of products that can be obtained after the tangential flow process is completed to the total amount of the initial products. For a tangential flow filtration process, it is very difficult for the recovery to reach 100%. The major losses result from the following areas: ①Losses at permeate side and return flow side; if the retention rate is not 100% during the concentration process, some large molecular substances will be leaked to the permeate side, and the small molecular products will be retained at the return end during a clarification filtration. ②Membrane adsorption means the adsorption of the products by the filter membrane. ③Any products that cannot be recovered because of the hardware restrictions, such as a dead volume.

The above professional terms have already covered all the concepts and the operation parameters of a TFF-UF device. During the actual use of the equipment, besides the above operational factors, it is very important to clarify the target of the ultra-filtration process to establish reasonable and effective operation strategies. We will take the operation of a TFF-UF device for diafiltration as an example to describe this in detail.

Diafiltration is the process of reducing the concentration of or completely removing the ingredients of a material or replacing the low molecular ingredients of a sample. This process can be achieved through two types of modes, a continuous one and a dis-continuous one. Fig 3.112 shows the schematic drawing of the dis-continuous diafiltration mode taking a 2-fold gradient diluting level as an example. In the drawing the horizontal black belt is the cross section of the TFF-UF membrane. Above it is the upstream concentrate side and below it is the downstream permeate side. The larger red dots represent ingredients having a molecular weight or particle size larger than the MWCO of the UF membrane, and blue small dots represent small molecular substances that can permeate through the UF membrane.

By repeatedly diluting and concentrating back to the initial volume of the material (fluid), the small molecular weight substances can gradually pass through the UF membrane, and finally achieve the separation of the substances (also called molecular weight cut off). The principle of continuous diafiltration is similar. The only difference is that in the continuous diafiltration mode, the filtrate and the diafiltration solution supplementation are operating at almost the same speed, keeping the upstream material volume constant. The differences in the small molecule dis-

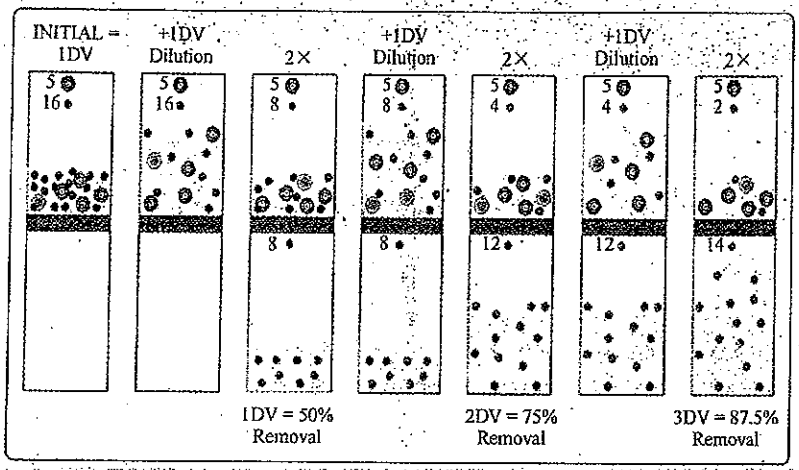
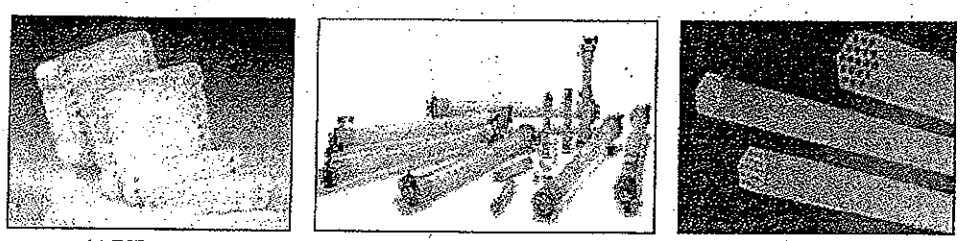


Fig 3.112 Schematic drawing of discontinuous diafiltration mode



(a) TFF-cassette (b) TFF-HF Column (c) Ceramic Membrane

Fig 3.113 Common tangential flow ultra-filtration devices

placement efficiency of the above two diafiltration modes obtained through theoretical study and calculation are shown in Table 3.7.

Table 3.7 Displacement efficiencies of different diafiltration modes

Diafiltration Volumes	Continuous Percent removal (100% Permeable)	Discontinuous 2× Percent removal (100% Permeable)
1	63	50
2	86	75
3	95	88
4	98.2	94
5	99.3	96.9
6	99.7	98.4
7	99.9	99.2

The commonly used tangential flow filtration membrane materials include PVDF, PES microfiltration membrane, cellulose and other molecular material high filtration membranes, etc. The tangential flow filter devices mainly include TFF-cassette, hollow fiber column UF devices (TFF-HF, Hollow Fiber) and ceramic membrane UF devices (Fig 3.113).

A TFF-cassette is composed of membrane sheets and turbulence nets alternately piled and sealed together. The fluid is pumped into the alternating liquid feeding channels and the filtrate goes to the filtrate channels after passing the membrane. The advantages of the TFF-cassette design include high retention efficiency, a high mechanical stability and a broad scope of working pressure. There are many types of channel screens that can be used for a TFF-cassette UF device. They are easy to install and disassemble, easy to clean, with a small footprint, and can be easily scaled up. The disadvantages mainly include higher requirements on membrane strength, a supporting layer required, and relatively limited concentration limit [i.e. material (fluid) concentration limit].

A TFF-HF UF device is composed of many bundles of very small hollow membrane tubes. The internal diameters of such membrane tubes are usually 0.8 to 1.4 mm. The materials are pumped into the membrane tubes and the filtrate passes the filter membrane into the space between the membrane and the shell. The advantages of TFF-HF include a relatively higher concentration limit. Some TFF-HF devices adopt the design of double membrane fibers and the materials can be fed and out fed in two directions. So such measures as backwashing can be used for filtration

or equipment cleaning. The TFF-HF has a high effective membrane area within a unit volume, a high working efficiency, a small floor area, and no support requirements for the hollow fiber. Because of the open channels, the shear force due to the ordinary tangential flow is also relatively low. This is especially useful for products sensitive to the shear force. The major disadvantage of TFF-HF is low retention efficiency, low pressure tolerance, and it can be easily damaged when operating at a high pressure.

The basic structure of a ceramic membrane UF device is similar to that of TFF-HF. The only difference is that there are several channels within the membrane column; this is determined by the membrane column manufacturing process. The surfaces of the hollow channels are the filtration membranes formed by special coatings. The operation principles are almost the same as those of TFF-HF. The only difference is that most ceramic membrane columns do not have the double-membrane design. So they cannot be back washed. The advantages of ceramic membrane column UF devices include a lower concentration limit (compared with that of TFF-cassette and TFF-HF), and they can tolerate higher material concentration or wet solid content. The disadvantages include the equipment is usually large in size, the power requirement is high (pump flow or head should be compatible) and the overall cost of the equipment is higher.

Because different degrees of concentration polarization can occur during a UF process, it is very easy for a gel layer to form at the membrane surface, and thereafter the membrane throughput will not increase with the increased differential pressure. For a solution with a certain concentration, the filtration speed will come to a critical value after the TMP reaches a certain value. So a TMP value should be selected (generally 1 to 5 bar, depending on the specific UF device), that will not cause the filtration speed to reach the limit. A too high pressure (including the inlet valve and the TMP) will not be beneficial to the filtration speed and the relevant concentration or diafiltration functions. On the contrary, it will bring certain hazards and risks to the safety of the equipment and the operators.

The early tangential flow filtration technologies are mainly used for waste water treatment. After the development of the tangential flow filtration technologies, they have been widely used in the food industry, the beverage industry, the dairy industry, the biopharmaceutical industry, the chemical industry, the traditional Chinese medicine industry, the clinical medicine, the printing industry, the treatment of food industry waste water, resource recovery, environmental engineering, etc. The applications of tangential flow filtration technologies in the bio-pharmaceutical industry mainly include: ①Clarification, such as cell and cell debris separation (cell collection and cell removal); ②Concentration, such as product concentration, water removal or buffer solution removal; ③Desalting; ④Buffer solution displacement, such as the change of the buffer solution system before and after chromatography; ⑤Depyrogenation, such as the depyrogenation for pharmaceutical water; ⑥Separation and purification, such as the separation of proteins, polypeptides, polysaccharides, viruses, endotoxin particles, nucleic acids and antibodies.

3.4.5 Integrity Test

For sterile filtration, the integrity test of the filtration system is an essential to ensure the safety of the filtration process. The integrity test can be used to determine the integrity of the filter, the sealing performance of the filtration system, and ensure that a correct filter is installed in the system. At the same time, the integrity test is also compulsory by regulation in various countries.

The Article 75 of Annex Ⅰ *Sterile Products* of the *Chinese GMP* 2010 specifies that, *the sterile filtration of non-terminally sterilized products shall conform to the following requirements*:

(Ⅲ) *After a sterile filter is used, an appropriate method must be used to perform an integrity test immediately and this shall be documented. The commonly used methods include bubble point test, diffusive flow test and pressure hold test.*

(Ⅳ) *A sterile filtration process shall be validated. The time taken to filter a known volume of bulk solution and the pressures at the two sides of the filter shall be determined. Any significant deviations from the normal duration or pressure shall be recorded and investigated. The investigation results shall be included in the batch record.*

The Annex 1 *Manufacturing of Sterile Medicinal Products* of EU GMP has the following specifications in its Article 113: *The integrity of the sterilized filter shall be verified before use and shall be confirmed immediately after use by an appropriate method such as*

a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter shall be determined during validation and any significant differences from this during routine manufacturing shall be noted and investigated. Results of these checks shall be included in the batch record. The integrity of critical gas and air vent filters shall be confirmed after use. The integrity of other filters shall be tested periodically.

The FAD specifies in its guideline *Sterile Drug Products Produced* by Aseptic Processing that whatever filter or combination of filters is used, validation shall include microbiological challenges to simulate worst-case production conditions. A filter integrity test can be performed before use and it shall be performed routinely after use. It is very important to perform a filter integrity test after use. It can determine whether there is any leakage or perforation of the filter during use. When properly used, the forward flow and the bubble point are two acceptable methods to be used for a filter integrity test. The finished product filter integrity test specifications shall be consistent with the data of the bacterial retention verification study.

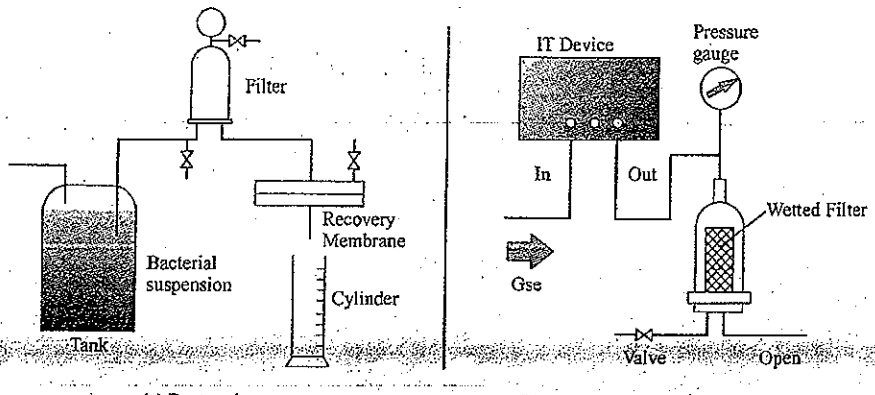
The PDA Technical Report No. 26 has the following specifications on when an integrity test should be performed.

Where the claimed purpose of the filter is to sterilize, pre- and post-filtration integrity tests shall be performed. Whether to test filters online or externally will depend upon actual process requirements.

The filter testing methods are divided into destructive methods and non-destructive methods (Fig 3.114). The destructive tests include bacterial challenge tests (for filters with bacterial retention capabilities), particle challenge tests (for some prefilters with particle retention capacities). And non-destructive tests are the integrity tests often used by the filters. For a filter supplier, the results of a destructive test are used by the supplier as one of the criteria for the release of each batch of filters. For a filter user, a bacterial challenge test is required during the validation of the sterile filtration process. The actual process fluid is used and the study is performed under the worst case conditions.

The main purpose of a non-destructive test is to determine whether there is a defect that can affect the retention capacity of a filter without damaging the filter. It shall be performed by the manufacturer before delivery and by the user at the user site. The non-destructive integrity tests mainly include bubble point, forward flow, pressure hold/decay, and water intrusion test. If a failure is detected through an integrity test, the measures shown in Fig 3.115 can be used (please refer to PDA TR26 7.7 *Failure Analysis/Troubleshooting* and 10.6.1 of *Sterile Products of GMP Guideline*).

a. Destructive tests. For a sterile filter, a destructive test usually means the bacterial challenge test. A sterile filter means a filter that can retain 10^7 colony forming units (CFU) of *Brerundimonas diminuta* (ATCC 19146) for each unit square centimeter of effective filtration area under the process conditions. According to the ASTM F-838, this challenge level is the standard method to be used for the validation of a liquid sterile filter. The bacterial challenge test is a destructive test. It cannot be used to prove the integrity of a filter to be used for production. So for a filter user, a non-destructive test is required. The destructive test and the non-destructive test must be correlated, so that the non-destructive test data can be used indirectly to prove the bacterial retention per-



(a) Destructive test (b) Non-destructive test

Fig 3.114 Schematic drawing of filter integrity tests

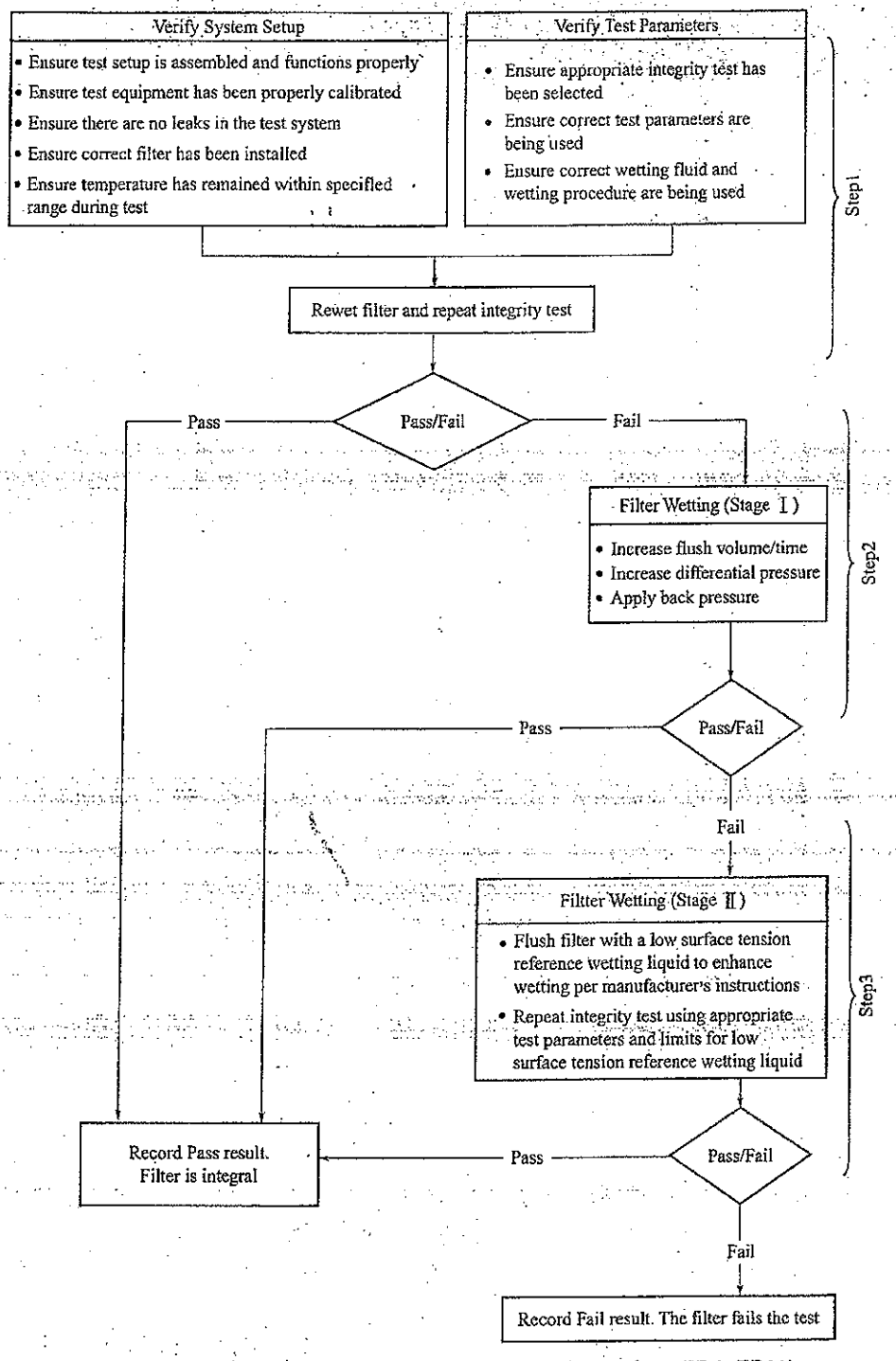


Fig 3.115 Decision tree for integrity test failure analysis (from PDA TR26)

formances of the filter. Taking the forward flow test as an example (Fig 3.116), the user integrity test limit is lower than the limit of the destructive test of the supplier, and it is within the acceptable range. The bacteria challenge tests for the filter have all been passed. The correlation of the water intrusion test and bubble point test values and the filter bacteria retention performances are the same as that of the forward flow test.

b. Bubble point test. The bubble point test is a non-destructive filter integrity test. If the internal structures of the membrane pores are filled with the wetting fluid, the liquid is retained within the filter membrane because of the surface tension. When the pressure applied at the up steam side of the membrane is low, a large amount of bubbles cannot be seen at the downstream side of the filter because of the blockage of the liquid. When the pressure at the upstream side is

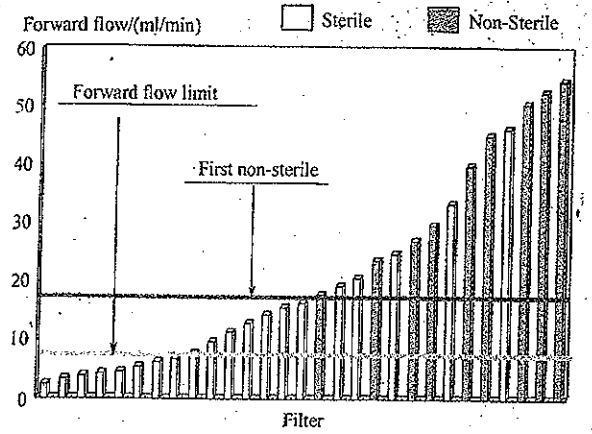


Fig 3. 116 Correlation between filter integrity tests limit and bacteria challenge tests

increased to a level that is sufficient to expel the liquid in the large pores, a large amount of bubbles will occur at the downstream side of the membrane. The pressure at this point is the bubble point value (Fig 3. 117).

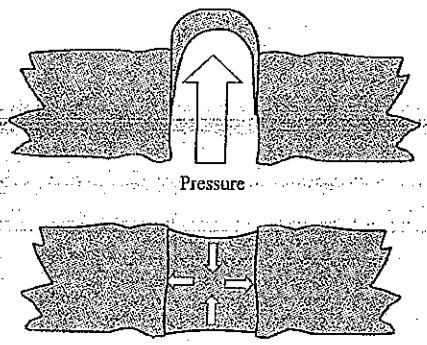


Fig 3. 117 Bubble point test principles

The principles of the bubble point test are based on the capillary model theory. In PDA Technical Report 26 the formula for the calculation of the Bubble Point is specified as below.

$$P = \frac{4k\gamma\cos\theta}{d} \qquad (3.15)$$

Where: P = the differential pressure at which a guver pore will open; k = correction factor for the shape of the largest pores; γ = the surface tension of the wetting liquid; $\cos\theta$ = the contact ("wetting") angle between the liquid and the membrane; d = the diameter of the largest pores.

When the surface chemical properties of the wetting fluid and those of the membrane are same, the bubble point value is inversely proportional to the maximum pore diameter of the filter membrane. The measurement of the bubble point can reflect the maximum pore diameter of the filter membrane. For a filter membrane, there are many micro-pores. And the membrane pores are not standard capillary tubes. It is not possible to use the bubble point value to directly calculate the membrane pore diameter. The bubble point test cannot reflect the number of pores with the maximum diameters. And this number can affect the bacterial retention capacity of the membrane. For a filter element with a small area, the bubble point test is relatively simple. For a filter element with a large area, the forward flow will be already very high when it gets near the bubble point Value, so the sensitivity of the bubble point test will be greatly reduced. So for a filtration system with a large area, the bubble point test is not recommended.

The bubble point test methods are divided into manual and automatic. Manual tests are applicable to filters with a very small filter membrane or area. The testing pressure at the upstream side is manually adjusted. When the pressure is sufficiently high to expel the liquid in the large pores, an increase amount of air flow will result. When a sufficiently amount of air flows through the large pores of the filter, a "steady bubble flow" will result at the downstream side of the filter (Fig 3. 118). For a filter with a large area, the bubble point value determination can be affected during a manual integrity test because of the large diffusive flow. So the forward flow test is recommended for a filter with a large area.

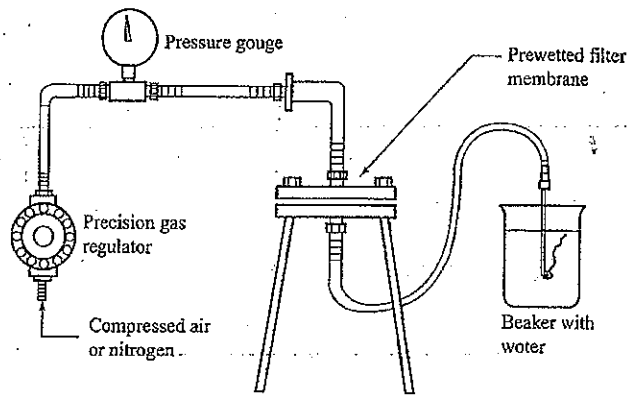


Fig 3. 118 Manual bubble point test (from PDA TR40)

c. Water intrusion test. The principle of a water intrusion test is that under a low pressure, a dry hydrophobic filter membrane will not allow water to pass. Below the water breakage pressure (the pressure at which the water is forced through the pores), it is similar to the diffusive flow for the traditional integrity

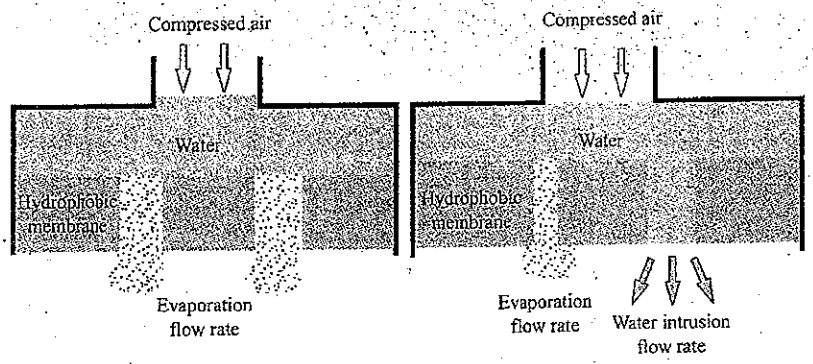


Fig 3. 119 Principle of water intrusion test

test for wet membrane filters, a small but detectable water flow will occur. The flow speed is also proportional to the surface area and the porosity of the membrane. The limit of this water flow is correlated to the bacterial retention capacity of the filter membrane. If the measured water flow equals to or is lower than the specified lower limit, it can be considered that the filter is integrate and can be put into use, the retention capacity of the filter is not damaged. When the water flow exceeds the limit, it may indicate that the filter is defective and further investigation is required.

For a water intrusion test, water is introduced at the upstream side of a hydrophobic filter and the water flow is observed under the specified pressure. For an integral filter, no water will go through the membrane and actually reach the downstream side of the filter membrane. The value obtained through a water intrusion test is the evaporation flow of water towards the downstream side of the filter membrane under a high pressure. As shown in Fig 3. 119, if there are any large pores in the filter membrane, a water breakage flow will result and the detected water intrusion value will also exceed the limit.

Because the water intrusion value is very low and needs to be measured at the downstream side, the manual method is not practical for this test. The test is usually performed automatically by a piece of equipment as shown in Fig 3. 120. After the test is completed, the water will be drained from the filter shell. If water affects the subsequent process, the filter can be blown dry.

The automatic tester measures the water flow by monitoring the volume of air that displaces the water under the set test pressure. The analysis of the test results is similar to that for the forward flow

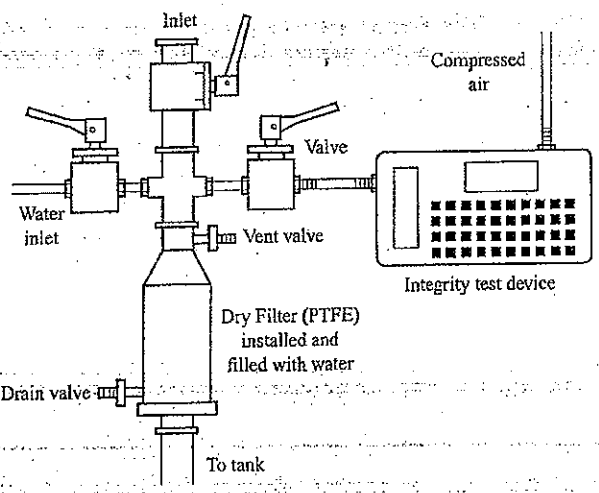


Fig 3. 120 Water intrusion tester (from PDA TR40)

test. However, it should be noted that the reported (gas) flow of some instruments is converted to the volume under the standard or atmospheric pressure. Because it is nearly impossible to compress water, under the test pressure (such as 3 bar), the 1 ml of water equals to the 1 ml gas in the test. And at the atmospheric pressure it is equivalent to 4 ml of gas.

The water intrusion test has distinctive advantages when compared with the traditional solvent wetting filter integrity tests. It is not necessary to introduce any combustible solvents with contamination potentials and no downstream operations are required In many applications, the filter membrane is not wetted during a water intrusion test. It is kept almost dry, which reduces the subsequent drying efforts after the integrity test.

d. Forward flow test. The forward flow test is based on a pressure lower than the bubble point of the filter membrane. Gas molecules pass through the liquid that wets the filter pores following Fick's Law. The gas dissolves in the wetting fluid at the upstream higher pressure side and diffuses to the downstream low

pressure side. The gas flow at the lower pressure side is the forward flow or the diffusive flow (Fig 3. 121).

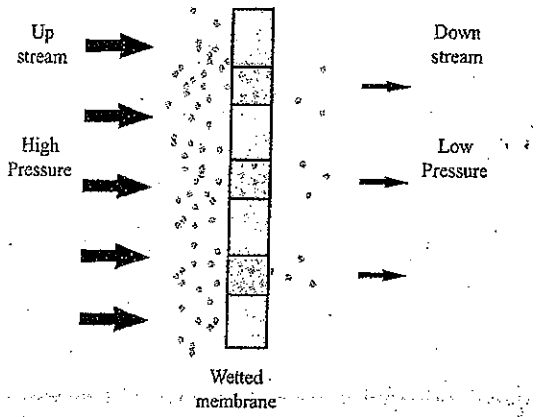


Fig 3. 121 Principles of forward flow test

The diffusion speed of the gas through the filter membrane depends on the solubility coefficient and the diffusion rate of the gas in the filter wetting fluid. It is proportional to the applied differential pressure, the effective surface area of the filter membrane, the total porosity of the filter membrane and is inversely proportional to the liquid viscosity and thickness. The formula is as shown below.

$$N=\frac{DHP}{L}\varphi \qquad (3.16)$$

Where: N = the diffusive flux of the test gas; D = the diffusivity of the test gas through the wetting liquid; H = the solubility coefficient of the test gas in the wetting liquid; P = the applied differential pressure (or gauge pressure if collected at atmospheric conditions); φ = the overall porosity of the structure; L = the thickness of the wet layer (thickness of the membrane corrected by a "tortuosity" factor).

During a forward flow test, if the test gas, the wetting fluid and the testing differential pressure are kept the same, the forward flow value is related to the filter membrane area, the porosity and the membrane thickness. And the porosity and the thickness of the filter membrane are closely related to its bacterial retention performances. Based on the above theory, the forward flow result can be affected by changing the test gas or the wetting fluid for the integrity test. For example, when Nitrogen and compressed air at 2. 76 bar are used respectively to perform the forward flow test for the same 10 inch filter element, the diffusion flow value of Nitrogen is no more than 14. 3 ml/min, and that of compressed air is no more than 17ml/min (Table 3. 8).

Table 3. 8 Integrity test parameter examples

Filter	Wetting fluid	Test pressure /mbar	Test gas	Max acceptable flow/(ml/min)
10" Cartridge	Water	2760	Air	17
10" Cartridge	Water	2760	Nitrogen	14. 3
10" Cartridge	70/30 IPA/H_2O	930	Air	10

The forward flow test increases the testing sensitivity for large area systems. So for the test of a large area system, the test results will not be affected by the filter membrane area. And the forward flow test is recommended in such cases. In addition, because the forward flow test measures the speed of the gas diffusion flow, it is highly influenced by the temperature as compared with the bubble point test. It is more sensitive to the test temperature and the temperature fluctuations during the test.

The forward flow test can be performed both manually and automatically. For the manual method, a scaled device placed in a water channel is used to collect the gas at the downstream side at an appropriate time under the test pressure (Fig 3. 122). However, the manual method involves some downstream operations, which can affect the sterility at the downstream side.

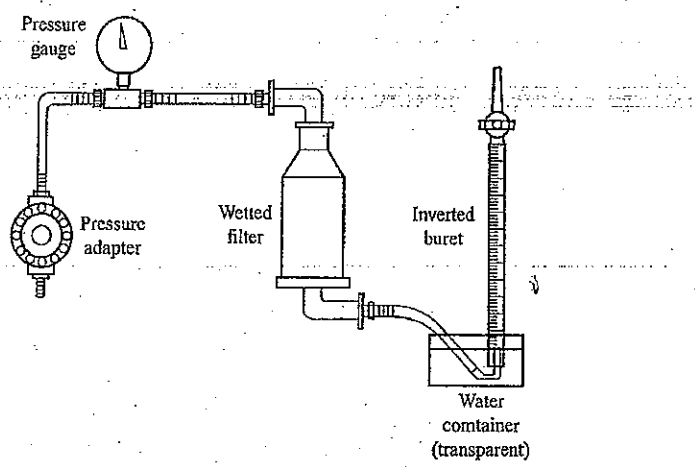
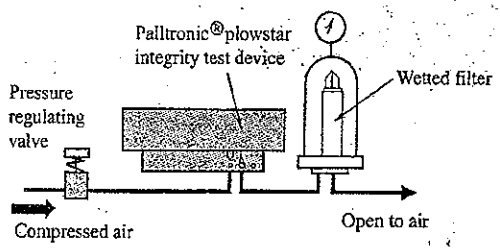
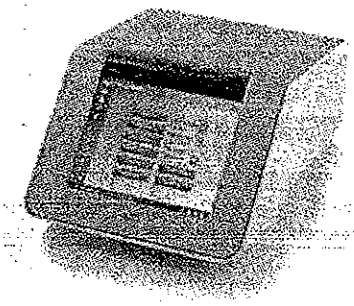


Fig 3. 122 Schematic drawing of manual forward flow test (from PDA TR40)

For the automatic test, integrity test equipment is used to apply a certain pressure at the upstream side of the filter element to measure the gas flow required to maintain the pressure at the upstream side. All the operations are performed at the upstream non-sterile side, which eliminates the risks of contaminations to the downstream sterile side (Fig 3. 123).



(a)



(b)

Fig 3. 123 Schematic drawing of an automatic forward flow test and device

3. 5 Valves

In modern plant and mechanical engineering, valve designs are playing an important and increasingly significant role. A valve can be used to control and regulate flow capable media, the pressure, and the flow. It is also a device that can allow the media (liquids or gases) within a transferring pipe or equipment to flow or stop and control the flow. By changing the section of the channel and the medium flowing directions, valves can be used for flow diverting, cutoff, throttling, checking, splitting and overflow pressure releasing. Valves can be combined with other equipment or devices to achieve certain functions. Fig 3. 124 shows the design for the combination of a diaphragm valve and a sterile sampling bottle. It is used for the sterile sampling in the biological product industry.

During recent years, more and more types of valves have been designed and promoted to meet the continuously changing requirements in the engineering applications. Stainless steel valves are often used in the biotechnology field and the pharmaceutical water systems. Sterile design concepts are adopted for these valves and the surface roughness can reach 0. 4 μm. In addition, the actuator is separated from the medium, making these valves indispensable for sterile applications. These valves are divided into two main groups,

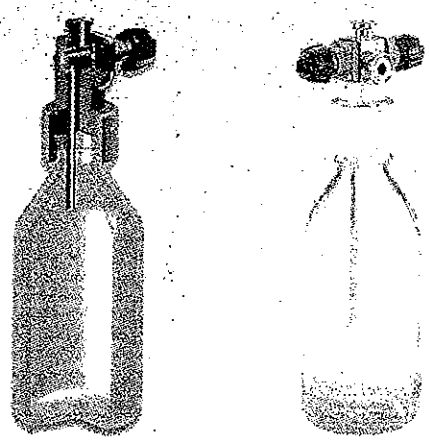


Fig 3. 124 Sterile sampling bottle with diaphragm valve

linear and quarter turn valves, based on the direction of movement. The feature of a quarter turn valve is that it can rotate 90° (Table 3. 9).

Table 3. 9 Valve types

Linear valves	Quarter turn valves
Check valves (short-stroke and long-stroke)	Butterfly valves (various design functions)
Diaphragm valves (full bore and weir type)	Plug valves
Gate valves (various design functions)	Ball valves

Different types of valves have different functions and features. Specific valves are to be selected depending on the type of application and area of use. When making the selection, the features that need to be taken into account include the switching frequency, pressure loss, control characteristic and suitability with regard to the specified process conditions, for example temperature, pressure and media purity. In Table 3. 10, the most common types of valves and their advantages and disadvantages are listed.

Table 3. 10 Advantages and disadvantages of the different valve types

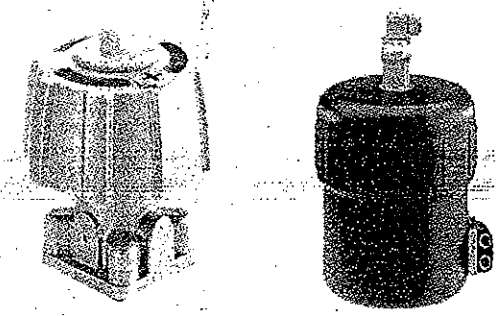
Valve type	Advantages	Disadvantages
Globe valve (long-stroke)	— For high frequency of use — For high temperatures and pressures — Good control characteristics (in particular straight seat design)	— Medium to high pressure loss — Specified flow direction — Only for clean and non-particulate media

cont

Valve type	Advantages	Disadvantages
Diaphragm valve (weir type)	— For high frequency of use — For clean to contaminated media — Good clean ability — Good control characteristic(for liquids) — Optional flow direction	— Medium to high pressure loss — Operating pressures and temperatures limited
Butterfly valve (concentric)	— Low pressure loss — Optional flow direction — Compact and lightweight construction — Relatively low cost	— Low working frequency — Relatively poor control characteristic — High level of wear (particulate media) — For relatively low operating pressures
Ball valves	— Full bore, hardly any pressure loss — Optional flow direction — For high temperatures and pressures	— Low working frequency — Relatively poor control characteristic(standard version) — Large dead space, closed ball

In various regulatory codes and directives which stipulate industry-specific requirements, there is often an indirect limitation of the valve types that can be selected. For example, the *EU-GMP Guidelines* put emphasis on the avoidance of cross contamination and the need for equipment which is easy to clean. Accordingly, valves that are used for this type of applications are easily cleaned and sterilized, self-draining and cavity filled. In practice, FDA compliant diaphragm valves have become the established valves for sterile applications, and FDA compliant globe valves for hygienic applications. In the case of sterile applications, the FDA has even explicitly specified the use of diaphragm valves, as these have better clean ability. For cooling water or non-clean media for heating steam, mainly butterfly valves, ball valves, as well as globe valves, are used. At the same time, valves in areas that do not come in direct contact with the product are mostly selected based on financial considerations, as these are not primarily relevant to the quality of the product.

Multiple driving modes can be used for valve control. The company used driving modes in the pharmaceutical industry include manual and pneumatic (Fig 3. 125), such as manual ball valves and pneumatic diaphragm valves. Valves can perform actions in a pre-defined mode under the pressure, temperature or other transmitted signals, or perform such simple actions as open and close without depending on the transmitted signals. The driving or auto-mechanisms of the valves are used to make the opening and closing elements to rise, slide, sway or rotate, thus changing the section area of the flow channel.



(a) Manual (b) Pneumatic

Fig 3. 125 Valve actuations

The dimensions of the valves used in a process system are determined based on the required flow. Under different working conditions, the K_v value is a technical parameter used to define the flow of a valve. It can be used as the basis for the calculation of the flux of a valve. This value describes the flow of water at 5 to 30 ℃ passing through the valve at a pressure loss of 1 bar. The K_v s value is the K_v value of the valve when it is opened 100%.

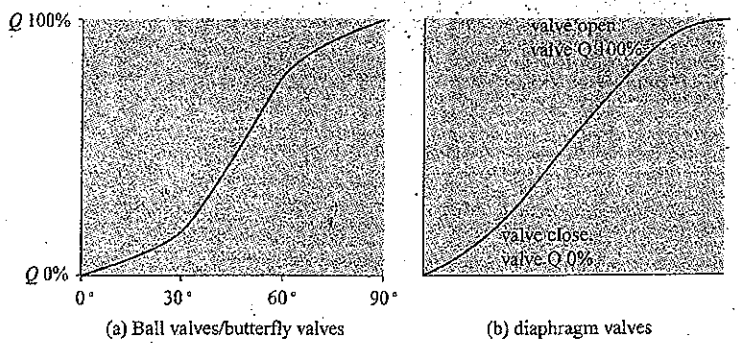
$$K_v = \frac{Q}{\sqrt{\Delta P}} \tag{3.17}$$

In the formula, K_v is the flow parameter in m^3/h. Q is the volume flow rate in m^3/h. ΔP is the pressure drop after passing through the valve, in bar.

There are many types of valves that are used in pharmaceutical water systems, from the simplest ball valves, and globe valves to very complicated counterbalance valves and proportional regulation valves. Different valves should be selected based on the actual working condition requirements to control the process. Fig 3. 126 shows that the regulation curves of ball valves, butterfly valves and diaphragm valves are basically the same. However, the regulation curve of diaphragm valves has a gentler slope. So, it is more suitable for the working conditions of such sanitary fluids as PW and WFI.

3. 5. 1 Diaphragm Valves

A diaphragm valve is a special type of globe



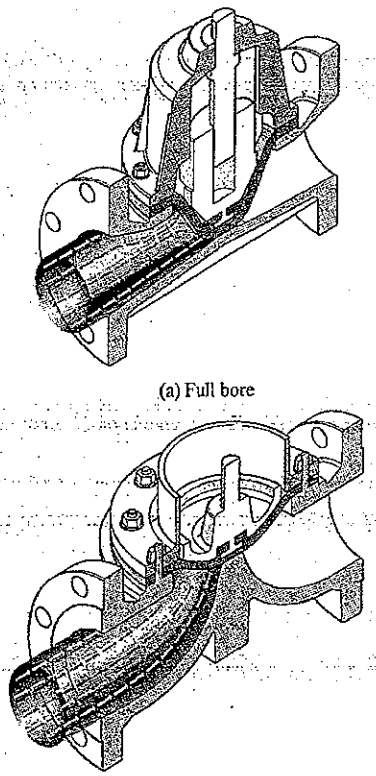
(a) Ball valves/butterfly valves (b) diaphragm valves

Fig 3.126 Valve regulation curves

valve. Its open and close piece is a diaphragm made of a type of soft material, which separates the valve internal chamber, the valve cover internal chamber and the driving parts. Its outstanding feature is that the upper valve chamber and the lower valve chamber are separated by the diaphragm, so that such components as the valve rod, and valve flaps will not be corroded by the medium. In this way the sealer packing structures exist and there will be no leakage of media. During the working process, the diaphragm is deformed by a press block, and is pressed against the seal weir of the valve. The press block is driven by the main shaft and moves up and down together with the actuator, and the medium flow within the channel will be restricted or completely closed. At the same time, the flow direction of the medium can also be selected.

Based on the different seal weirs, the diaphragm valves in general can also be divided into full bore diaphragm valves and weir type diaphragm valves. The full bore design has only one indicated sealing weir [Fig 3.127(a)]. As a result, the fully opened valve has a free cross-section, through which the medium can flow unbindered, however the very high mechanical stresses on the diaphragm considerably limit the cycle duties. The weir type design greatly increases the service life of the diaphragm. So the diaphragm valves on the market are usually the weir type diaphragm valves [Fig 3.127(b)].

The commonly used diaphragm valves include rubber lined diaphragm valves, fluorine lined diaphragm valves, no-lining diaphragm valves and plastic diaphragm valves. A diaphragm valve is composed of the actuator, diaphragm and valve body connected together through bolts and nuts (Fig 3.128). And an actuator is often composed of the position sight glass indicator, cylinder, guide gas connection port, piston seal, main shaft guide and cylinder. Diaphragm valves have



(a) Full bore

(b) Weir type

Fig 3.127 Diaphragm valve types

become the optimal valves for the applications where contact with PW or WFI occurs because of their smooth and gentle flow regulation curves and deadleg free design.

The interactions of different components are very important, because they can directly impact the maintenance frequency, the process reliability and the product quality. Setting the spring set to the actual working pressure is a very important factor, which can directly affect the maintenance frequency. If the current spring set pressure is always lower than the maximum working pressure, a weaker spring set than the standard spring set can be selected. This reduces the force applied onto the diaphragm and increases its serv-

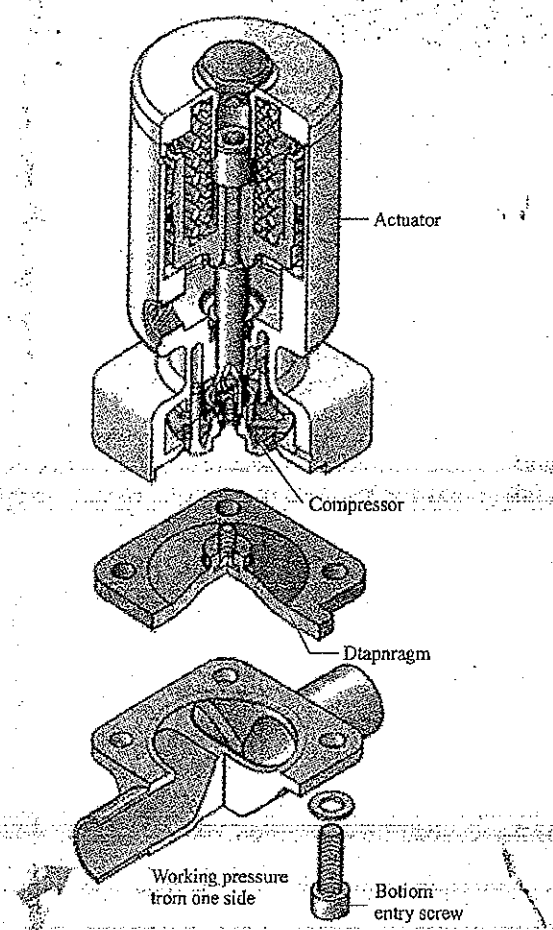
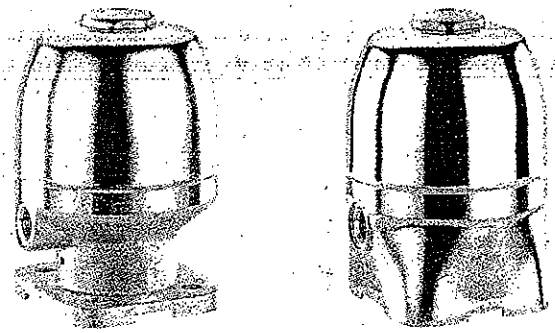


Fig 3. 128 Diaphragm valve structure

ice life. Alignment of the diaphragm and valve body contour plays an important role in the process reliability and product quality. Ensuring that the two contours are aligned results in not only in better external sealing, but also in improved clean ability. It is therefore not advisable to combine components from different manufacturers. This should only be done in exceptional cases, where thorough testing has been carried out in advance.

a. Actuators. Different types of actuators can be used for the control of a diaphragm valve. The commonly used actuators in the pharmaceutical industry include manual ones and pneumatic ones. Depending on the material, manual and pneumatic actuators can be divided into plastic ones, stainless steel ones and the combinations of plastic and stainless steel If more stringent requirements are demanded in terms of autoclave capability and external cleaning, stainless steel actuators, as shown in Fig 3. 129 (a), can be used. The sealed and electro polished actuator provides a closed, smooth outer surface which, in comparison with plastic actuators, ensures easier cleaning and better temperature resistance. An additional advantage is the more compact design of the actuator, resulting from it being heat sealed, and meaning that there is no need for bolting. The version shown in the Fig 3. 129 (b) is a sterile pneumatic actuator developed in accordance with the hygienic design requirements. The actuator is bolted together from below, thus enabling the side surface areas of the actuator to remain closed, and omitting the need for fixing nuts. This reduces horizontal areas on which the medium, dust or cleaning agent can accumulate.



(a) Stainless steel (b) Sterile

Fig 3. 129 Metal actuators

According to the actual operation requirements, manual or pneumatic actuators can also be installed with mechanical position limits, signal feedback devices, open controls, PID controls, dual-cylinders, safety brake and other controls. Fig 3. 130 shows a user point manual diaphragm valve with an automatic closing function. It is mainly used in aseptic applications in the pharmaceutical industry. This diaphragm valve is driven by a piston and the closed status of the valve is not maintained through manual operations. When air is introduced to the valve head, the valve can only be opened or closed. When air is withdrawn at the valve head, the open and the close of the valve can no longer be controlled through the hand wheel. At the same time, this valve also has a visible position feedback function. The feedback on the closed position of the valve is achieved through a proximity switch. For example, when too many user point valves have been opened within a plant, the circulation speed at the end of a WFI system loop will be decreased to a critical level. This type of specially designed user point valve can reduce the number of user points through the central control system and close some of the user points to increase the circulation speed within the loop.

A throttle orifice or a diaphragm valve needs to be

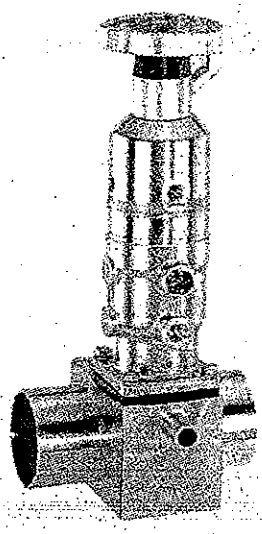


Fig 3. 130 User point valve with automatic closing function

installed at the cooling system of the WFI sub-loops and a back pressure needs to be created to ensure the sufficient turbulence within the loop. Fig 3. 131 shows a manual 2/2-way diaphragm valve that is very suitable for the sub loop cooling modules. It can maintain a stable pressure turbulent flow within the main loop for this type of cooling module. This valve has a limit switch and is equipped with a stainless steel cover and a stainless steel hand wheel. The hand wheel also has standard visual position feedback. Additionally, this valve can also have a locking function to prevent any mis-operations.

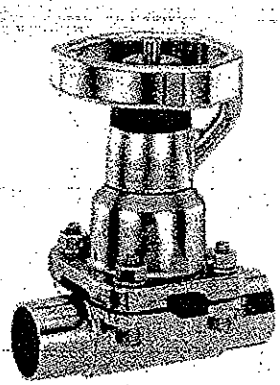


Fig 3. 131 A manual limiting diaphragm valve with a locking function

Fig 3. 132 shows a diaphragm valve with a 2-section cylinder on the actuator. The cylinder has a stainless steel shell. Two independent pistons are used to control the cylinder and effectively regulate the throughput of the valve. The regulating bolts on the cylinder can be used to set the open and close of the valve and limit the opening degree. When compressed air is introduced in the valve, the piston of the lower cylinder can limit the position 100% . The upper cylinder can regulate the opening degree through the limiting bolts and the lock nuts. When using the limiting bolts, the piston can precisely regulate the flow going through the valve with the help of the limiting bolts. When air is introduced in the lower cylinder, the valve will be fully opened and push the shaft level towards the upper cylinder.

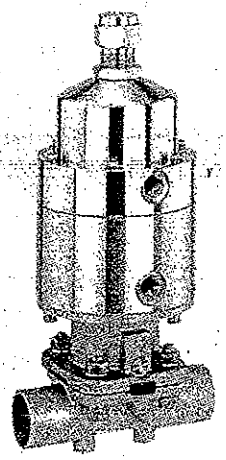


Fig 3. 132 Dual cylinder pneumatic diaphragm valve

The position indicator design can vary significantly based on the different operations. For example, the position indicators of pneumatic actuators are mostly integrated as standard. This can either be a mechanical indicator, which indicates the linear movement of the actuator spindle, or an electrical position indicator. If the valve is intended for control tasks, positioners or remote process controllers are adopted. Depending on the manufacturer, the controllers can be directly or externally connected to the actuator (Fig 3. 133).

b. Diaphragm. The diaphragm is the most important component of a diaphragm valve. The diaphragm is the only component in direct contact with the working medium except for the valve body. A diaphragm valve uses the diaphragm to segregate the working medium and the actuators from the external air. The materials of diaphragm valve diaphragms used in pharmaceutical water systems should meet the relevant FDA requirements. The diaphragm is a moving part. A diaphragm valve relies on the up and down movement of the diaphragm to control and cut off the flow of the working medium. So the diaphragm is the major wear part of a diaphragm valve. Depending on the different working conditions, the diaphragms used for diaphragm valves include EPDM diaphragms, PKM diaphragms, EP-

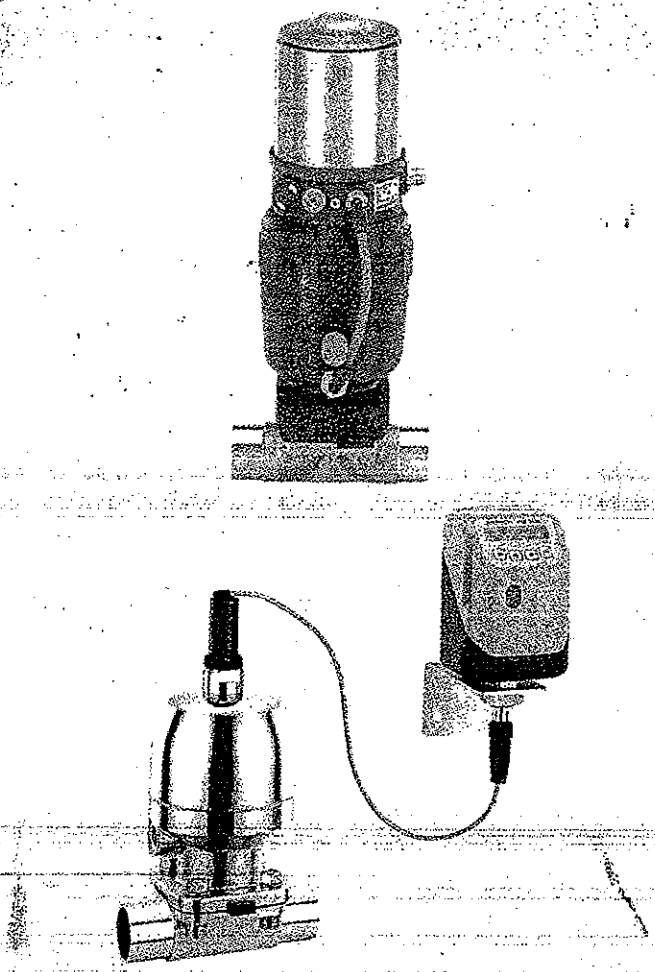


Fig 3. 133 Connections of process controllers

DM. PTFE dual diaphragms and reinforced EPDM/PTFE dual diaphragms.

Ethylene-Propylene-Diene (EPDM) Monomer has such advantageous properties as excellent elasticity, resistance to oxidation, resistance to ozone, and resistance to corrosion. This type of diaphragm is applicable not only to polar materials and steam, but also to hot water, cold water, basic media and non-concentrated acids. The temperature range of EPDM is not as good as that of PTFE. It is applicable to sanitary applications with a working temperature of no more than 100 ℃ (Fig 3. 134), such as a PW system. It should be noted that because EPDM can swell when it comes in contact with organic substances, it is not recommended to use EPDM membranes in working conditions with mineral oils, vegetable oils, vegetable and animal liquids, aliphatic or aromatic hydrocarbons, halogenated solvents or concentrated acids.

Fluororubber (FKM) is a type of synthetic high molecular elastomer with fluorine atoms on the carbon atoms on the main chain or the side chain. In addition to the high elastic properties of rubber, FKM also has excellent thermal resistance, oxidation resistance, oil resistance and atmospheric aging resistance because of the introduction of the fluorine atom.

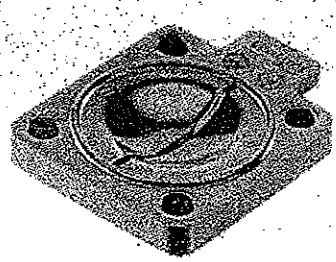


Fig 3. 134 EPDM diaphragms

Poly Tetra Fluoro Ethylene (PTFE) is a type of fluorine containing polymer synthesized with vinyl fluoride. It is a type of fluoroplastic. The chemical inertness of PTFE can prevent any cross links. So it does not have a "memory", i. e. it will not return to its original shape like elastomers. Creep deformation can result for this type of material under tension, which is the so-called "cold flow" phenomenon. PTFE has a wide range of applicable temperatures (−200 to 260 ℃). At the same time, it also has excellent thermal resistance, corrosion resistance, aging resistance, vapor and UV resistance, and it is non-toxic. A severe deformation can result when a pure PTFE diaphragm is under a temperature of more than 130 ℃ or a major temperature change, causing the diaphragm to be deformed or damaged. The EPDM/PTFE combination diaphragms (Fig 3. 135) effectively solved the issues of thermal resistance and high tenacity requirements. It has both the high elasticity of EPDM and the high thermal resistance and corrosion resistance of PTFE. This type of diaphragms has been widely used in such high temperature sanitary working conditions as those of a WFI or pure steam system.

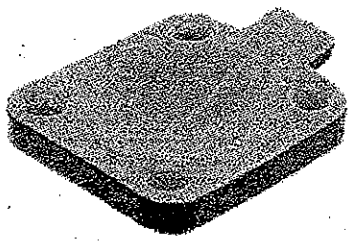


Fig 3. 135 EPDM/PTFE combinational diaphragms

Additional to the properties of ordinary EPDM/PTFE diaphragms, the reinforced EPDM/PTFE diaphragms also have many other advantages. Even under a large load, the deformation of a reinforced EPDM/

PTFE diaphragm is much smaller. Compared with ordinary EPDM/PTFE diaphragms, reinforced EPDM/PTFE diaphragms are much less affected by high temperatures and temperature variations. The ir compact structure reduces the permeability of the diaphragms and improves the process quality. At the same time, the deformation of reinforced EPDM/PTFE diaphragms is much lower compared to ordinary EPDM/PTFE diaphragms. This advantage is more outstanding under repeated loads and high temperatures.

The sealing system of a diaphragm valve can directly impact the quality of PW and WFI. The sealing system of a traditional valve uses the sealing contour on the diaphragm to achieve the required sealing. Usually there is no additional sealing contour on the valve body. Because the diaphragm and the actuators are connected through bolts, a circular notch will result at the sealing surface [Fig 3. 136(b)] . And the medium will penetrate through it during each closing action and then will be expelled out each time the valve is opened. Although any deadleg has been reduced to the minimum through the design of a diaphragm valve, this small amount of fluid is sufficient to contaminate the contacted PW or WFI. Fig 3. 136(a) shows a newly developed deadleg free sealing design which has been fully tested and validated by the European Hygienic Engineering and Design Group (EHEDG). There is a sealing contour between the valve body and the diaphragm. This type of design greatly reduces the circular gap between the diaphragm and the valve body when it is extruded, thus preventing the intrusion of the medium.

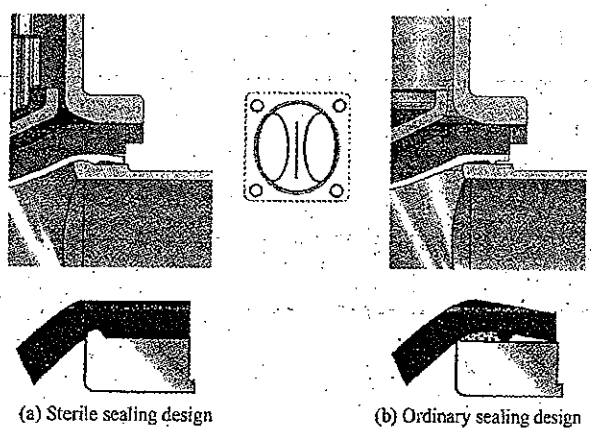
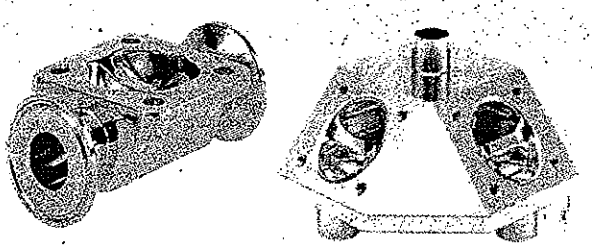


Fig 3. 136 Comparison of sealing systems

In order to ensure the purity of the medium, not only the formation of bio-film and microbial growth should be prevented; any release of extractable into the medium from the diaphragms should also be prevented. The FDA cGMP and USP both specify that the relevant limit extraction tests should be performed for the non-metal materials. Only materials conforming to CFR 21 Part 177 or section 5 of USP should be certified.

All the material certificates and certification reports should be integrated. CFR 21 Part 820 clearly specifies that each batch of materials or components must be traceable and appropriately identified. If any problem occurs during this process, the relevant documents can help determining the appropriate measures to be taken (such as recall any components with problems) to prevent any hazards to personnel and the environment. For a diaphragm, the purpose of traceability is mainly to ensure that such information related to the diaphragm as the manufacturing date is provide on the diaphragm. And the manufacturing date of the diaphragms can also help determining the maximum shelf life of the diaphragm according to DIN 7716. If a diaphragm is appropriately stored (in a cool, dry, and well ventilated place without any heavy loads), the shelf life of an EPDM diaphragm is 5 years and that of a PTFE diaphragm is 10 years. Of course, the maximum shelf life of a diaphragm is not necessarily its service life. A diaphragm is a wear part when experiencing the open and close actions. It must be replaced periodically. The service life of a diaphragm depends to a large extent on the working conditions. So its maintenance cycle cannot be predicted precisely. Generally speaking, the maintenance cycle should be based on the relevant data and experience.

c. Valve bodies. The valve body is a core component that comes in contact with the medium. The design structure of a valve body determines the type of the valve. In order to suit the needs of different applications, different valve bodies can be used for the diaphragm valves, such as 2/2-way diaphragm valves, welded valves, I-valves, T valves, tank bottom valves, multi-channel valves and Robolux valves. The 2/2-way valves and the deadleg free multi-channel valves are the mostly used valves in pharmaceutical water systems (Fig 3. 137). As the medium contacting part, the valve body should also have its corresponding component No. to ensure its traceability. In addition, the corresponding test reports, such as the quality certificates (2. 1 certificates), material certificates (3. 1 material certificates) or special certificates (such as 3. 2 testing certificates) should be provided.



(a) 2/2-way valves (b) Multi-channel valves

Fig 3. 137 Different valve bodies

In order to be applicable to different media, different materials should be selected for the valve body of a diaphragm valve, such as cast stainless steel, forged stainless steel, block stainless steel, as well such special materials as 904L and plastic. Fig 3. 138 shows a disposable diaphragm valve manufactured with special materials. This type of valves is specially designed for the rapid production of small batches. And they have such characteristics as no cleaning required and flexible operations. They are the necessary components of single use systems of the bio-pharmaceutical industry and are widely used in biological product manufacturers.

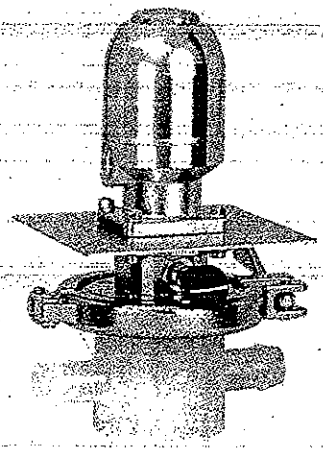
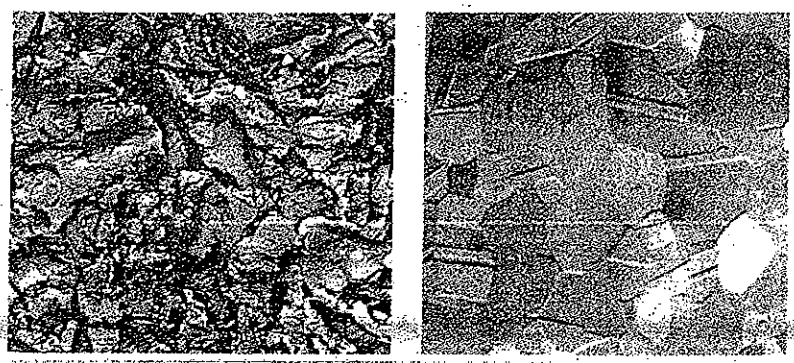


Fig 3. 138 Single use diaphragm valves

According to the manufacturing process, the diaphragm valves can be divided into those with cast valve bodies and those with forged valve bodies. Fig. 3. 139 shows the electron microscope scan images of cast and forged valve bodies. Casting means the process of melting the metal material into liquid conforming to certain requirements and filling it into the casting moulds, to obtain casted pieces of predefined shape, dimensions and properties after cooling and trimming. Casting is a basic process of the modern mechanical manufacturing industry. The work blanks obtained through casting have relatively low costs. The advantage of low cost is especially prominent for components with complex shapes and components with particularly complicated internal chambers. And they are widely applicable and have rather good comprehensive mechanical properties. Forging is the process of producing forged pieces having certain mechanical properties, shapes and dimensions from a metal blank by applying certain pressing forces onto the metal blank through a type of forging press. Any loose structures and welding pores can be removed through forging. Generally speaking the mechanical properties of a forged diaphragm valve are superior to those of a cast diaphragm valve of the same material. At the same time, the price is higher for forced valves compared to cast valves because of the higher processing precision and raw material requirements.

According to the specifications of the main pipeline, the valve connecting pipes can be processed for different interface sizes (Fig 3. 140). At the same time, diaphragm valves can also be processed for different connections such as welding connections, clamp connections and flange connections according to the different applications.

The valve body requires a certain installation angle to ensure that the axial rotation (emptying angle) to the farthest point of the sealing ridge from the center



(a) Casting (b) Forging

Fig 3. 139 Casting and forging

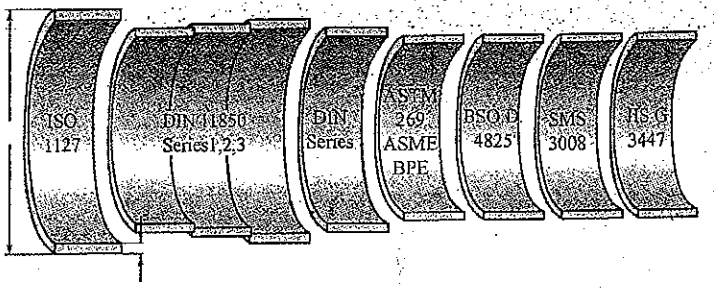


Fig 3. 140 Valve pipe interface sizes

and the lowest point of pipe connection are on a same direct line. In this way, the medium can pass through the valve without any obstacles under a low pressure drop when the valve is opened. There can be residual medium only if the medium is sticky or under the influence of gravity. The emptying angle is different for diaphragm valves with different specifications. If the installation angle is not sufficient, residual liquid can be accumulated at the valve weir, causing contamination or cross contamination. A correctly installed diaphragm valve should be emptied under gravity only. Fig 3. 141 shows the installation angle of a 2/2-way diaphragm valve. The angle gauge installed on the valve seat can be used to adjust the emptying angle for the diaphragm valve.

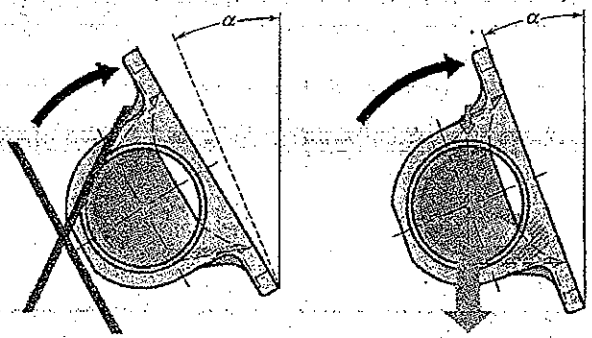
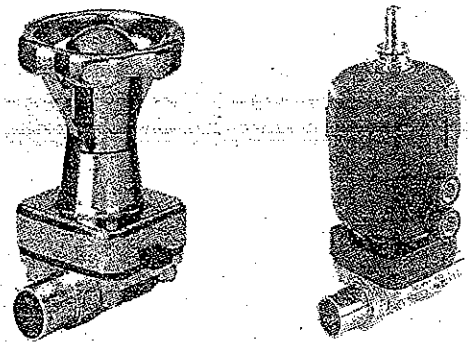


Fig 3. 141 Diaphragm valve installation angle

The 2/2-way diaphragm valves are the most widely used type of diaphragm valves in pharmaceutical systems. Fig 3. 142 shows the manual and pneumatic 2/2-way diaphragm valves commonly used in pharmaceutical water systems. These types of valves are widely used in the manufacturing of water generation systems, the assembling of water distribution modules, and in water distribution loops.

GMP/SAP valves are typical welded combination diaphragm valves composed of two 2/2-way valves. The Good Manufacturing Practice (GMP) valves are mainly used on the vertical pipes at the points of use of PW or other distribution systems. They can effectively

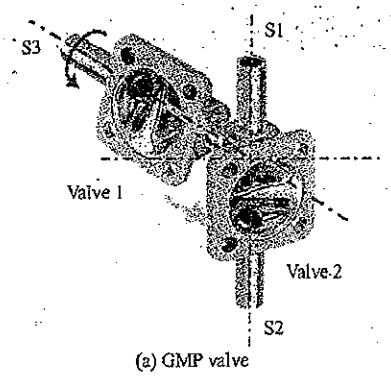


(a) Manual (b) Pneumatic

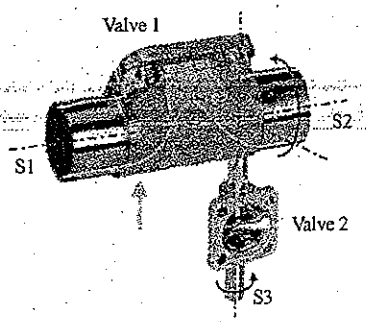
Fig 3. 142 2/2-way diaphragm valves

reduce the number of deadleg. There are two types of design for GMP valves. The first type is a combination valve with a 90° right angle bend. The other type of valve is composed of two valves placed together, one is horizontally placed with a certain emptying angle and the other is placed vertically as the main valve. When the valve is opened, the outlet will be a sampling port without any microbial growth. Sterile Access Port (SAP) valves are mainly used on horizontal pipelines. The main valve needs to be placed horizontally with a certain emptying angle. The branch port is placed at the lowest drainage point of the horizontal pipe of the main valve. The SAP structure can be a combination of the main valve and the branch, or a combination of the main valve and a vertically or horizontally placed branch valve. SAP valves are especially suitable for the sampling of medium, the drainage of cleaning solution or the drainage of sterilization condensate (Fig 3. 143).

The I-body valve is a specially structured diaphragm valve provided for the pharmaceutical industry based on GMP/SAP valves (Fig 3. 144). It is a transition from two valves welded together to block multiple channel valves and can ideally meet the customer requirements for cost reduction and deadleg free. Different from the design of a GMP/SAP valve, the I-body valve added a

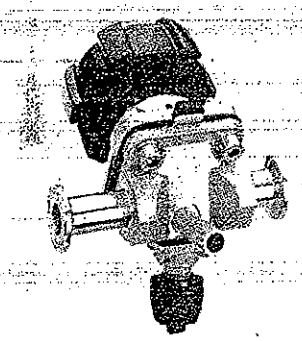


(a) GMP valve



(b) SAP valve

Fig 3. 143 GMP/SAP valve design



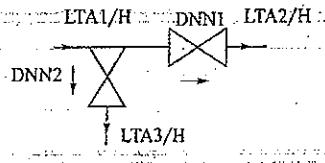


Fig 3. 144 I-body valve design principle

deadleg free DN8 or DN15 small valve on the valve body of the two channel user point diaphragm valve. An I-body valve integrates the sampling, steam sterilization and condensing functions. There are two valve bodies and three ports on the valve bodies. The main valve is forged. The branch valve can be forged or cast. This type of valve is compact in structure and has a light weight. The valve can be emptied when it is installed vertically. The emptying effect is better than that of a GMP/SAP valve. Manual or pneumatic actuation mechanisms can be used for both valve seats. At the same time, an I-body valve has the basic properties of a multi-channel valve such as the maximal reduction of deadleg area and no welding seam at flow contact parts. It has much less deadleg compared to that of a traditional GMP/SAP valve and greatly reduces the risk of microbial growth.

In order to ensure better clean ability, higher product reliability, more compact spacial arrangement and simpler validation, multiple channel valves are often used. A multi-channel valve is a type of valve that is forged from a whole piece of stainless steel blank. It is further optimized in structure based on the design of the combination of multiple 2/2-way valves (Fig 3. 145). The multi-channel valves are also called valve blocks. The one-piece steel manufacturing process ensures that there are no welding seams inside the multi-channel valves. It can ensure a compact design and greatly reduce the amount of residual liquid. The unique customized design can allow the integration of various types of functions such as mixing, distribution, open and close, material feeding or drainage.

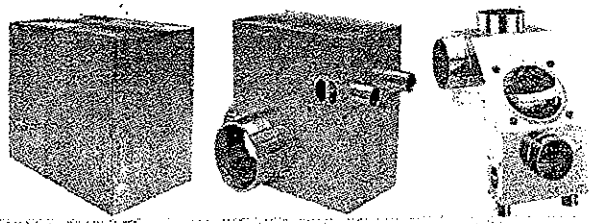


Fig 3. 145 Processing of multi-channel valves

A minimum of three channels can be processed for a multi-channel valve and 40 channels can be processed maximally. And 20 actuators can be installed. Fig 3. 146 shows a valve block with four channels.

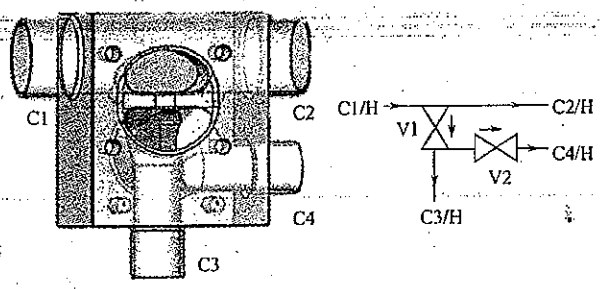


Fig 3. 146 Design example of a four-channel valve

Different multi-channel valves can be used based on different applications. Fig 3. 147 shows a complex design for a WFI point of use valve. This valve integrates such functions as WFI user point, sampling, condensate drainage, tank feeding, drainage and pure steam supply. Fig 3. 147 (a) shows a traditional design, including four T-valves and at least 6 welding seams. The use of a block design [Fig 3. 147 (b)] can avoid three internal welds. And for the installation it is possible to use no Ts, connectors or bends, which makes the valve block design more compact and deadleg free. And the

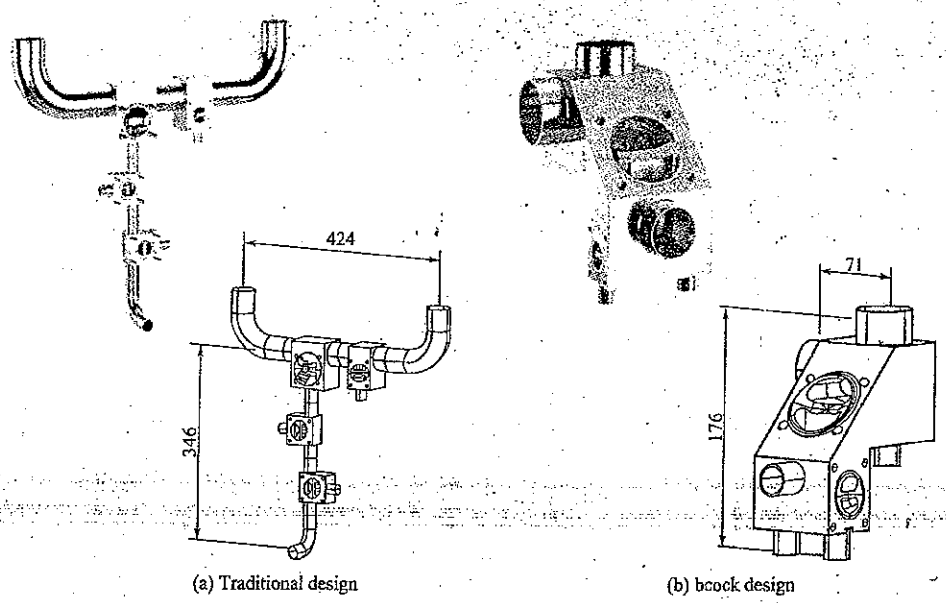


Fig 3. 147 Design advantages of multi-channel valves

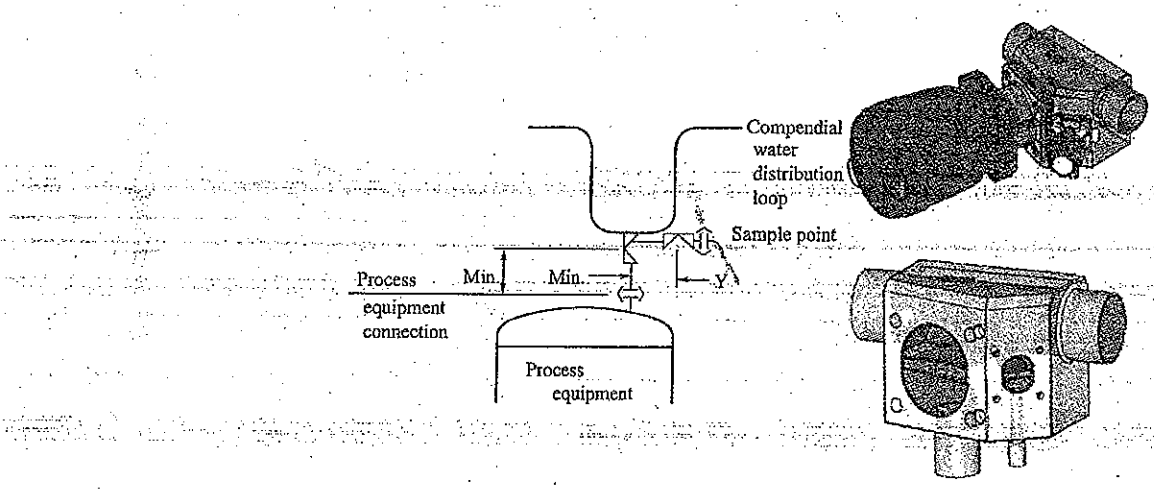


Fig 3. 148 Deadleg free T-valve with a sampling port

eccentric design of the pipe can ensure that it is easier to empty the multi-channel valve.

The deadleg free T-valves are the multi-channel valves with the simplest design and most widely used. The ASME BPE recommends that deadleg free T-valves should be used for the point of use pharmaceutical water (such as WFI) valves with direct product contact. Fig 3. 148 shows a deadleg free T diaphragm valve with a sampling function.

The Robolux valve is a type of multi-channel diaphragm valve specially designed for ultra-pure water, sanitization, sterile steam and CIP. Its patented Robolux technology places two valve seats on one diaphragm (Fig 3. 149). This design eliminates any deadleg on the valve and maximally reduces the valve chamber volume. The entire valve is processed from a stainless steel bar and helps to ensure the compact and modular design of pharmaceutical water systems and aseptic processes.

In a sanitary fluid process system, a multi-channel valve can maximally reduce the residual drug solutions, the installation space, any deadleg, the numerous connections, pipe fittings and welding seams. Because of its outstanding performances in the optimization of the sanitary process and the improvement of the production efficiency, multi-channel diaphragm valves have been widely promoted and used in pharmaceutical water systems and the bio-pharmaceutical industry.

3.5.2 Ball Valves

A ball valve is a type of valve that is driven by a valve rod for its open and close and rotates along the

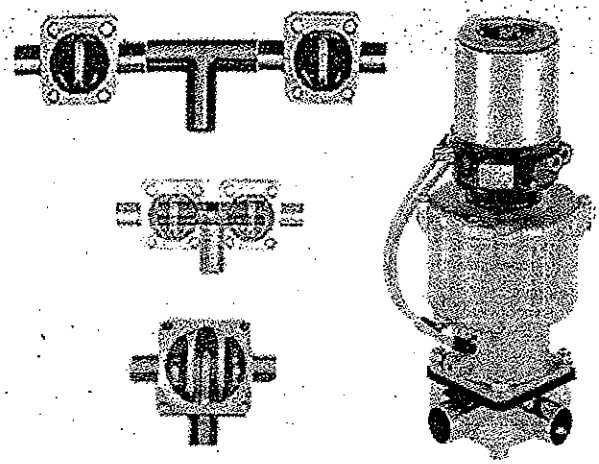


Fig 3. 149 Schematic drawing of robolux valves

axis of the ball valve. Ball valves were developed in the 1950s. With the rapid development of science and technology, the manufacturing processes and the structures of this type of product have been continuously improved. During the last several decades, ball valves have rapidly developed into a major type of valve. Ball valves have such advantages as simple operation, rapid open and close with only 90° from fully open to fully closed, and can easily be remote controlled. Similarly to diaphragm valves, different types of actuators can be used for the control of a ball valve. The commonly used actuators in the pharmaceutical industry include manual ones and pneumatic ones. According to the requirements of actual use, other actuators such as those for proportional regulation, position feedback and dual cylinder can be installed additionally on the manual or pneumatic actuators. Fig 3. 150 shows a pneumatic ball valve with an operation unit.

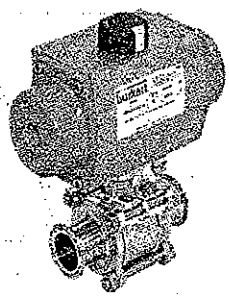


Fig 3. 150 Pneumatic ball valve

Ball valves are widely used in the petroleum refining, long distance transportation pipelines, chemical, paper making, water conservancy, power, municipal, and steel industries. In process pipelines they are mainly used for flow cutting off, flow distribution, and medium flow direction changing. The valve can be tightly closed with a small moment, rotating by 90°. A ball valve has a simple and compact structure and a reliable seal. It can be easily maintained. The sealing surface and the ball surface are usually closed and not easy to be scoured. It is easy to operate and maintain. It is applicable to all the common working media such as water, solvents, acids and natural gas. It is mainly used to cut off or connect through the medium in the pipeline and can also be used to regulate and control the fluid.

In order to meet the cleaning and installation and maintenance requirements, all the ball valves used in sanitary industries are made of 304, 316 or 316L stainless steel and have a three-piece structure. The three-piece ball valves are easier to maintain and disassemble. It is a rather novel type of ball valve. Such connections as welding, clamp or flange connections can be designed. It has a simple structure, a small volume, a light weight, and a small flow resistance (the resistance coefficient is equivalent to that of a long pipe). At the same time, a three-piece ball valve also has very good sealing performances. It has been widely used in transferring vacuum and media. Fig 3. 151 shows the structure of a typical three-piece ball valve. The valve is composed of a handle, the filling material, the valve sealing elements, the valve seat sealing elements, the terminal and the valve body active flange.

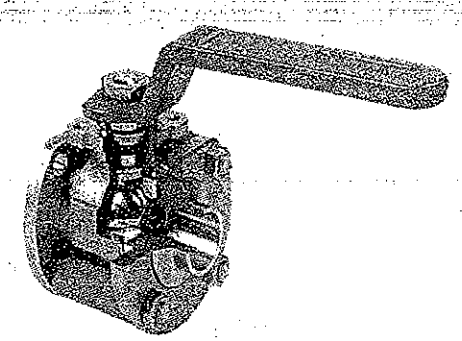


Fig 3. 151 Three-piece ball valves

According to the different degree of enclosure, sanitary ball valves can be divided into the partially enclosed type and the fully enclosed type. Because of the structure of a ball valve, there will be some deadleg within the valve element. When it is closed there will be some accumulated water within the valve element; it will provide an easy harbor for microbial growth and microbial contamination is very likely (Fig 3. 152). So ball valves are not allowed in liquid fluid process

systems such as PW systems, WFI systems and biological process systems. However, sanitary ball valves are widely used in clean gas systems as pure steam systems, clean nitrogen systems, clean compressed air systems, etc.

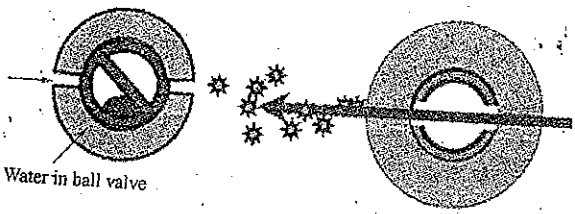
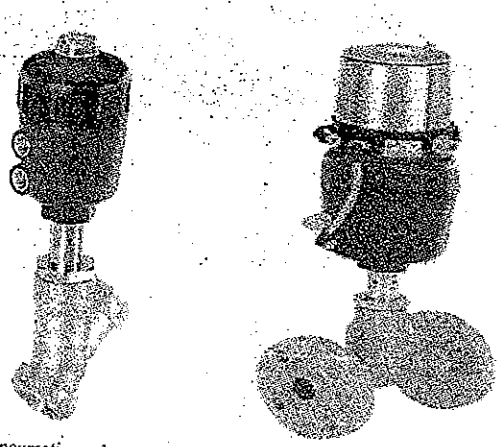


Fig 3.152 Ball valve deadleg



(a) Pneumatic angle seat switch valve

(b) Pneumatic proportional regulation valve

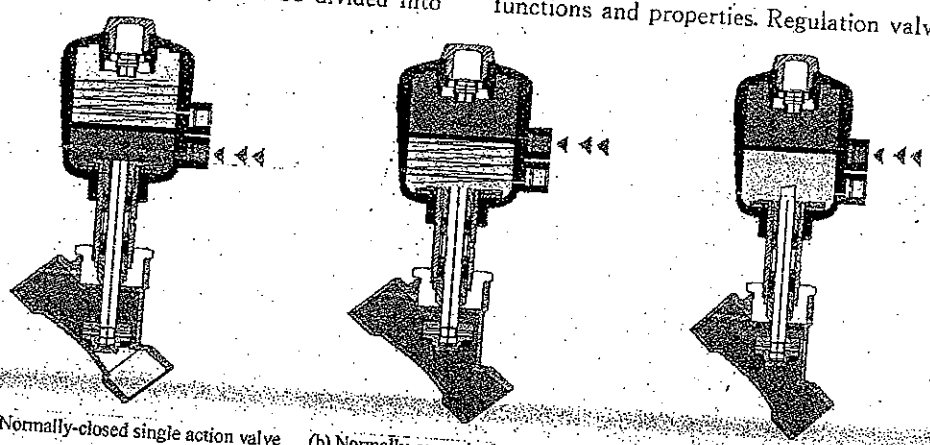
Fig 3.153 Temperature control valves

3.5.3 Other Valves

Pneumatic angle seat switch valves or pneumatic proportional valves are often used in the PW or WFI distribution SKID to control the water temperature (Fig 3.153). A pneumatic angle seat switch valve is a type of shut-off valve with a certain angle between the valve rod and the valve body. This type of valves have such advantages as a high flow, fast responding, long service life and space saving. A new designed valve seat and the reliable automatic adjustment filling materials ensure the high sealing performance of the valve. In contrast with pneumatic angle seat switch valves, pneumatic proportional regulation valves are pneumatic valves with two types of calculations based on proportion and volume during the actuation process. The temperature control precision is relatively higher.

Pneumatic angle seat switch valves are divided into single action ones and dual action ones (Fig 3.154). The working principle of a single action angle seat switch valve is that the restoration of a spring is used to open and close the valve. They can be divided into normally-open valves and normally-closed valves. Normally-closed pneumatic angle seat switch valves are closed when the valve is not working. When compressed air with a certain pressure enters from below the pneumatic actuator, the valve rod of the valve is pulled up and the valve is opened. On the contrary, the normally-open pneumatic angle seat valves are open when not working. Different from a single action angle seat switch valve, a dual action angle seat switch valve is opened and closed using compressed air.

In the industry automation process control area, a regulation valve is also called a control valve. It receives the control signal sent by the regulation and control unit, and changes such process parameters as the flow, pressure, temperature and level of the medium through power operations. A regulation valve is composed of an actuator and a valve. These valves are divided into the two main groups, linear and quarter turn valves, based on the direction of movement. They are divided into linear, equal percent and parabola based on the functions and properties. Regulation valves can be reg-



(a) Normally-closed single action valve (b) Normally-open single action valve (c) dual action valve

Fig 3.154 Pneumatic angle seat switch valves

ulated pneumatically, electrically, hydraulically, etc. In a pneumatically regulated system, the pneumatic signal output from the regula-tor can be used to directly drive such actuators as the springs/thin film actuators or piston actuators, to allow the movements of the valves. In order to prevent any damages to a proportional regulation valve because of the long term scouring by plant steam, it is recommended to install a manual maintenance globe valve, a Y strainer and a pneumatic angle seat switch valve before the proportional regulation valve.

Chapter 4

Generation of Purified Water

Drinking water should be used as raw water for generating purified water; and an appropriate unit operation or combined methods should be used. Common methods for generating purified water include membrane filtration, ion exchange, EDI, distillation, etc. Membrane filtration can be further classified into micro-filtration, ultrafiltration, nanofiltration, reverse osmosis (RO), etc. The technology for purified water machines went through three important development stages; the first generation purified water machines used the " pretreatment → anion bed/cation bed → mixed bed" process; large amounts of acidic and alkaline chemicals were required for the regeneration of cation and anion resins; the second generation purified water machines used "pretreatment → RO → mixed bed" process; the application of RO technology greatly reduced the consumption of chemicals in the generation process, but some chemicals were still necessary for the treatment of the mixed bed; the third generation purified water machine uses the process of "pretreatment → RO → EDI", which effectively avoids the usage of regeneration chemicals; now it has become the prevailing technology for producing purified water in various countries.

The drinking water can be treated by the following physical, chemical, or physicochemical methods to reduce specific organic and inorganic matters in the water: coagulation, sedimentation, clarification, filtration; disinfection, deionization, etc. The conventional treatment process for the drinking water is mainly used for removing suspensions, colloidal substances, pathogenic microorganisms, etc. from the raw water. At present, over 95% of the water plants in China use the conventional water treatment technology; therefore, it is the main technology of the drinking water treatment systems. Generally, the drinking water for pharmaceutical production comes from city water; and normally the supply water quality can meet the standards for *Drinking Water Quality* (GB 5749—2006) (please refer to Appendix I of this Chapter for the details); but for a plant with a small scale or non-central central water supply, in case of abrupt public events which affect water quality, some water indexes may exceed the normal range. At the same time, the drinking water may come from well water, river water, or reservoir water, so the water quality may differ from the China National Standards for *Drinking Water Quality* (GB 5749—2006) greatly; therefore, necessary measures should be taken during the treatment of drinking water.

The requirement for purified water quality indexes depends on the usage of the water; different industries have different requirements for the purified water quality indexes, so different purified water generation processes may be developed. As an example, a large amount of ultrapure water is required for rinsing the chips in semi-conductor and electronic industries; the requirement for granularity and conductivity of ultrapure water is very strict; water resistivity is required to be over 15 MΩ · cm, which means that the water conductivity should not be higher than 0.067 μS/cm.

The requirement for purified water conductivity in the pharmaceutical industry is not as strict as that in semi-conductor and electronic industries, but there are strict requirements for purified water TOC, microorganisms and endotoxin indexes; each country or region has different requirements for purified water quality indexes; please refer to Table 4.1 below for major purified water quality indexes of each country or region's pharmacopeia, including the *US Pharmacopeia* (USP), *European Pharmacopeia* (EP), *Chinese Pharmacopeia* (ChP), *Indian Pharmacopeia* (IP), and *Japanese Pharmacopeia* (JP). Appropriate technology should

be selected to control purified water indexes and to guarantee that the pharmacopeia requirements can be met. For example, filters in the main pipeline of the water systems may become the ideal places for microbial growth due to improper management; therefore, it is not recommended to install the main pipeline filter at the outlet of the purified water tank. Due to the peculiarities of pharmaceutical products, sufficient measures should be taken in designing purified water generation machines for controlling inorganic matters, organic matters, microorganisms, and endotoxins in the water; at the same time, reasonable and effective risk prevention and corrective actions should be implemented.

The following factors should be taken into consideration for the selection of a purified water generation process: raw water quality, output water quality, reliability of the machine process operation, system microbial contamination prevention and disinfection measures, professional qualifications of the machine operators, reliability and adaptability to variations of raw water quality, convenience for routine equipment maintenance, output water recovery rate and blowdown treatment, daily operation and maintenance costs, and system monitoring ability. A purified water machine is mostly used for transforming raw water into purified water through various "purification" processes. A comparison is made in Fig 4.1 for different filtration methods. Because the purified water storage and distribution unit has no purification function, the output water quality of a purified water generation system should be higher than pharmacopeia requirements. For example, the limit value for endotoxin content in purified water is 1.3 μS/cm (25 ℃) according to USP, so it is required that the output water quality of a purified water machine should be generally better than 0.5 μS/cm (25 ℃).

The distillation method is also accepted for producing purified water, but the output water temperature and energy consumption of a multi-effect water still (MWS) are relatively high; and a thermocompression water distiller has higher requirements for maintenance; please refer to the technical sections of thermocompression water distillers for the relevant process characteristics. Therefore, the distillation method is not widely used in purified water generation processes. Filtration is the most-widely used method for generating purified water. In the pharmaceutical industry, a purified water generation system generally consists of a pretreatment system and a purification system. Please refer to Fig 4.2 for a typical process flow diagram of purified water machines in the pharmaceutical industry.

Table 4.1 Pharmacopeia standards for purified water

Parameters①	USP	EP	ChP	IP	JP
Conductivity(at 25℃)②/(μS/cm)	1.3(3- step method)	5.1	Same with EP	Same with USP	Same with USP
TOC/(mg/L)	0.5③	Same with USP	Same with USP	Same with USP	Same with USP
Total number of colonies④/(CFU /ml)	100	100	100	100	100
Nitrate/ppm	—	0.2	0.06	0.2	—
Heavy metal/ppm	—	0.1⑤	0.1	0.1	—
Acidity	—	—	Indicator	Indicator	—
Nitrite/ppm	—	—	0.02	—	—
Ammonium/ppm	—	—	0.3	0.2	—
Readily oxidizable substance/(/100 ml)	—	Alternatively TOC	Alternatively TOC	Alternatively TOC	—
Nonvolatile matters/(mg/ml)	—	—	1/100		

Note:

① Unless otherwise stated, all data are the maximum values.

② Conductivity limit values have a relationship with temperature. For the three-step test method in USP, it is allowed to use a laboratory test method if the online conductivity test value exceeds the limit. Please refer to <645> *Conductivity* for the details.

③ Real response value of limit value is obtained after the standard solution parameter value is subtracted by that of blank water. Please refer to <643> *TOC* for the details.

④ The requirements for microbial testing are the same for all pharmacopeias except that the EP has included test requirements in the Production section; please refer to <1231> for the details.

⑤ The test is not necessary if the conductivity is adequate.

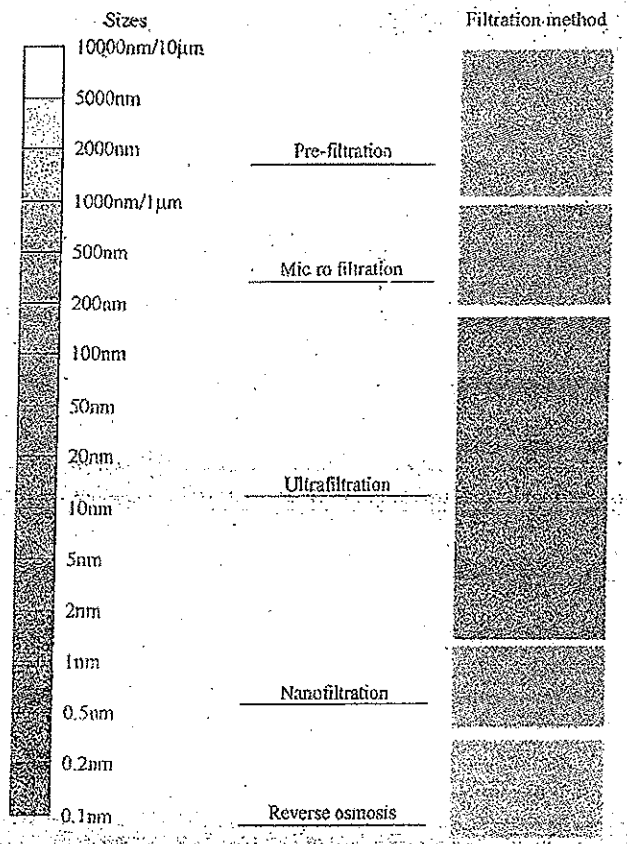


Fig 4.1 Comparison table for different filtration methods

The pretreatment system is mainly used for removing insoluble foreign matters, soluble foreign matters, organic substances, and microorganisms in the raw water, so that the main water quality parameters can meet the requirements for feed water of the subsequent purification system; and the foreign matters load of the subsequent purification system can be effectively reduced to prevent any contamination or irreparable damage to the purification system. A stable and reliable operation of the pretreatment system is the key factor for ensuring the operation stability of the purification system. The pretreatment system generally consists of a raw water tank, multi-media filter, microfilter, ultrafilter, nanofilter, activated carbon filter, softener, etc. The output water quality of the pretreatment system mainly depends on the process selection and raw water quality and should satisfy the requirement for feed water of the subsequent purification system.

The purification system is mainly used for the purification of the pretreated water, so that the purified water can meet pharmacopeia requirements and the internal control requirements of pharmaceutical factories. Purification is a key process of deionization and reducing organic substances, microorganisms, and endotoxins. Purification processes for pharmaceutical purified water include RO/EDI, RO/RO/EDI, RO/RO, etc. At the same time, membrane degassing or terminal ultrafiltration can be considered as an option depending on the actual raw water quality and output water quality requirement.

4.1 Raw Water Quality Indexes

Water quality is comprehensive feature of the water and the foreign matters in it. The criteria for evaluating the water quality are known as water quality indexes. Water quality indexes are specific evaluation criteria for determining if the water quality can satisfy specific requirements and show the variety and quantity of foreign matters in the water. Water quality standards stipulate some restrictions and requirements for the minimum quantity or concentration of specific foreign matters and contaminants in the water. Common water quality indexes include physical indexes, chemical indexes, and biological indexes.

a. Physical indexes mainly consist of solids, turbidity, silting density index, temperature, odor and taste, chroma and tincture, and conductivity.

* Solids. The solids in water include suspended solids and dissolved solids. Suspended solids and dissolved solids are collectively called total solids. Suspended solids are also called suspended matter, abbreviated SS, which refers to the solids suspended in the water. Suspended matter cannot pass through the filter and is a common and important water quality index reflecting the solids content in water, measured in mg/L; dissolved solids are also called dissolved matter, representing the total of inorganic matters and organic matters dissolved in the water. The content can be measured by filtering the water sample and boiling dry

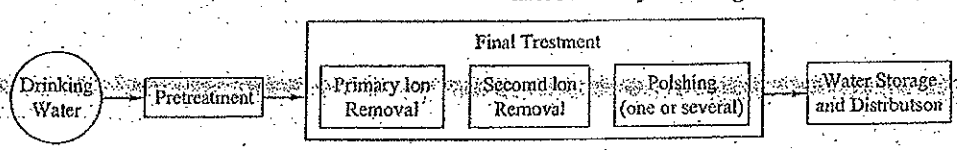


Fig 4.2 Typical process flow diagram of purified water machines

the filtrate.

• Turbidity. The term "turbidity" refers to the resistance of suspended matters in the water to light transmittance. Suspended matters in the water mainly include dirt, sand grains, fine organic matters and inorganic matters, planktonic organisms, microorganisms, and gels. Water turbidity is not only related to the content of suspended matter inside the water but also related to its particle size, shape, and refractive index.

• Silting Density Index. It is one of the important water quality indexes, commonly abbreviated as SDI or FI. SDI represents the content of such matters as particles, gels, and other matters inside the water that can block various water purifying equipment. The SDI measurement principle (Fig 4.3) is based on the measurement of the Penetration Index (PI, %); the method is as follows: continuously pass the water to be measured with a 30 psi, equivalent to 2.1 kg/cm, pressure through a 0.45 μm microporous filtration membrane with a diameter of φ47 mm and record the time t_i (s.) required for obtaining 500 ml of filtered water; after 15 minutes, record again the time t_f (s.) required for obtaining another 500 ml of filtered water. The n calculate the SDI of the RO membrane according to the following formula:

$$SDI=[(1-t_i/t_f)\times 100]/15 \qquad (4.1)$$

In which, 15 represents 15 minutes. When the level of contaminants inside the water is slightly higher, the amount of filtered water to be used can be 100 ml, 200 ml, 300 ml, etc. The interval can be changed to 10 or 5 minutes, so the 15 in the formula should be adjusted to 10 or 5 accordingly.

• Temperature. It is one of the most commonly used physical indexes of water quality. As the temperature is related to many physical characteristics of the water, chemical and microbial processes taking place in the water, it must be measured frequently.

• Odor and taste. It is referring to one of the sensory indexes for determining the water quality. The odor and taste of the water mainly come from the contaminants in the domestic and industrial waste water, decomposition of natural substances or microbial activities in connection with it. Odor determination methods include qualitative descriptions and approximate quantitative methods for odor strength (odor threshold).

• Chroma and tincture. The color is commonly characterized by brightness and chroma. Chroma is a

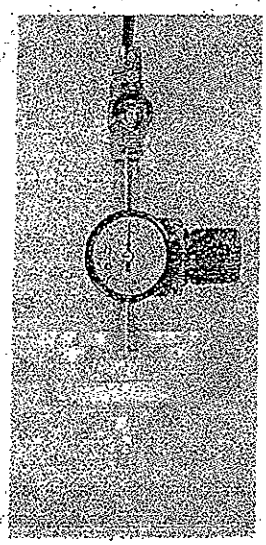


Fig 4.3 SDI measuring meter

type of color characteristic not involving brightness and it reflects the hue and saturation of the color; tincture refers to color and luster. Water color can be described as surface color and true color. Generally, the true color of the drinking water will be quantitatively determined for water quality analysis.

• Conductivity. For a medium, the product of this quantity and the electric field intensity is conduction current density. Conductivity represents the ability of the water solution to conduct electric current and can indirectly reflect the content of dissolved salts in the water. It is one of the key indexes for testing pharmaceutical water quality.

b. Chemical indexes mainly include pH, acidity, hardness, total salt content, total oxygen demand (TOD), biological oxygen demand (BOD), chemical oxygen demand (COD), total nitrogen and organic nitrogen, and toxic substances.

• pH. It is a method for representing the acidity and alkalinity of a water solution. Different waters have different requirements for the pH value, e.g. a pH value of 6.5 to 8.5 for drinking water, 5.0 to 7.0 for purified water, and 7.0 to 8.5 for boiler water.

• Acidity. It can reflect changes in the water quality of the water source. Water acidity represents the capacity of the water to be neutralized by a certain concentration of strong alkali (reported as mg/L of $CaCO_3$) to a certain pH value. Water acidity is related to the proton concentration in the water; and water alkalinity represents the capacity of the water to be neutralized by a certain quantity of strong acid to a certain pH, expressed as mg/L of $CaCO_3$. Water alkalinity is

the total quantity of protons being accepted by the water.

• Hardness. It reflects the content of calcium and magnesium ions in the water, referring to the total amount of CaO and MgO being converted from calcium salt and magnesium salt in 1L water (MgO is also being converted into CaO). Water hardness is an important water quality index. Water with high hardness is prone to scaling.

• Total salt content. The term "total salt content" refers to the total salts in a unit volume of water, i. e. the sum of total cations and total anions in a unit volume of water. The eight major ions in the water include the potassium ion, sodium ion, calcium ion, magnesium ion, bicarbonate ion, nitrate ion, chloride ion, and sulfate ion, which cover 95% to 99% of the total ions in the water. Therefore, the total amount of major ions can be a rough approximation of the total salt contents in the water.

• Total oxygen demand. It is abbreviated as TOD and refers to the oxygen demand when the oxidizable matters in the water, mainly organic matters, are turned into stable oxides by combustion; the result will be reported in mg/L of oxygen. It can be measured by a TOD meter. The working principle of a TOD meter is as follows: a certain amount water from a sample is dosed into a quartz combustion tube containing a platinum catalyst; a carrier gas (nitrogen) containing some oxygen (the concentration is known) will be led into the tube as raw gas. The reducing matters in the water sample will be instantly oxidized by combusting at a temperature of 900 ℃. The TOD of the water sample can be calculated by measuring the oxygen content difference before and after the combustion. TOD can reflect the oxygen demand of almost all organic matters when being turned into CO_2, H_2O, NO, and SO_2 by combustion. Its value is closer to the theoretical oxygen demand compared to BOD, COD, and permanganate index, but there is no fixed proportional relationship between them.

• Biological oxygen demand. It is reported as BOD and refers to the amount of dissolved oxygen required for the organic matters in the water to be decomposed into inorganic matters by aerobic microorganisms in the water body at a certain temperature and during a specific period of time. BOD is not an accurate and quantitative detection, but it can indirectly reflect the relative content of organic matters in the water; therefore, BOD has been a widely used index for long term environmental monitoring.

• Chemical oxygen demand. It is reported as COD and refers to measuring the amount of reducing matters in water sample to be oxidized by a chemical method. It is based on the amount of oxidizing agent consumed for oxidizing the reducing matters in each liter of water sample under certain conditions; the amount will be converted into milligrams of oxygen required for each liter of water being totally oxidized, reported as mg/L. It reflects the level of water contamination by reducing matters. It is also taken as one of the comprehensive indexes showing the relative content of organic matters. COD can be compared with BOD. The ratio of BOD/COD can reflect the biodegradation ability of the water.

• Total nitrogen and organic nitrogen. The total nitrogen content in the water is one of the important indexes for evaluating water quality. Its measurement facilitates evaluating the contamination and self-purification situation of the water body. When nitrogen and phosphorus substances in the surface water are out of standards, a large quantity of microorganisms will breed and planktonic organisms will have an accelerated growth; water eutrophication will occur. The organic nitrogen is a water quality index representing the total quantity of nitrogenous organic matters in water including proteins, amino acids, and urea.

• Toxic substance indexes. Toxic substances are those in the water that can affect human health and the growth of water creatures in the water body. Toxic matters can be classified into inorganic toxic matters and organic toxic matters. Toxic matters that do great harm to human health include cyanide, mercuride, methyl mercury, arsenide, copper, lead, and hexavalent chromium. Phenol is also a common organic toxic matter.

c. Biological indexes mainly include the total bacteria and *E. coli* quantity.

• Total bacteria count. It is one of the indexes for evaluating the water contamination level. The test method is as follows: inoculate one milliliter of water sample in a glass plate or diluting water sample in a heated and liquefied culture media. After cooling and concreting, culture it for a period of time at 37°C. Multiply colony counts on the culture media by the dilution factor to obtain the total bacteria count.

• Total coliforms. Coliform is not a name from

the bacterial taxonomy but a term in the hygiene and health fields. It doesn't represent a certain bacteria or a certain bacteria genus but a group of bacteria with specific characteristics and related to fecal contamination. The se bacteria are not completely identical in biochemical and serology aspects. The definition is gram-negative spore-free aerobic or facultative anaerobic bacilli, which can decompose lactose and produce acid and gas at 37 ℃. It is generally thought that the bacterial flora includes *Escherichia coli*, *Citrobacter freudii*, gas producing *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Total coliforms refer to a group of gram-negative spore-free aerobic or facultative anaerobic bacilli, which can lead to lactic acid fermentation and produce acid and gas after being cultured for 24 hours at 37 ℃. The determination methods include the multi-tube fermentation method and the membrane filtration method.

The recovery rate of the purified water machine, output water quality, routine equipment operation and maintenance requirements depend on the raw water quality to a large degree. The raw water quality report is the basis for the design of a purified water machine. A detailed raw water quality report is helpful in determining the best design idea for a purified water system. The quality of drinking water varies with the season, which must be taken into consideration during the design of the production procedure for pharmaceutical water. In order to determine the stability of the pharmaceutical water quality, the enterprise should spend one year on the third phase of the performance qualification.

Drinking water is purified natural water and its quality must comply with the China National Sanitary Standards for *Drinking Water* (GB 5749—2006). However, with environmental deterioration, it is difficult to guarantee that the city water and deep well water provided by pharmaceutical enterprises can meet the national requirements for drinking water. Equipment manufacturers should make comprehensive analyses of the raw water quality reports provided by enterprises and make reasonable process selections, e. g. the addition of mechanical filters, activated carbon filters or softeners in the pretreatment system. At the same time, it will have a direct influence on the choice of the final purification technology.

4. 2 Raw Water Tanks

The raw water tank is the first treatment unit of the pretreatment process. Generally, a buffer water tank with a certain volume will be provided. It volume should match the system output. There must be enough buffer time to guarantee the stable operation of the complete system. The raw water tank can be made of FRP, PE, or stainless steel. A proper selection can be made according to the disinfection method of the pretreatment process. The water flow rate will be low due to the buffer time of the tank and there will be a risk of microbial growth; therefore, some measures should be taken to avoid the risk of microbial growth arising from the inflow of city water or other raw water into the water generation system. It is generally suggested that a certain amount of sodium hypochlorite solution should be added before the inflow into the buffer tank. The concentration of the added solution should match with the buffer time of the tank. The general advice is that the contact time should be over 30 minutes after the addition of sodium hypochlorite solution and the residual chlorine inside the water should be kept over 0. 3 ppm. The concentration of sodium hypochlorite solution in pretreatment unit should not be too high or too low and is generally controlled in the range of 0. 3 to 0. 5 ppm. An automatic detection can be made by a residual chlorine analyzer; chlorine should be removed before entering the RO membrane.

4. 3 Multi-media Filters

If the turbidity and SDI of the raw water cannot satisfy the standard for the feed water of subsequent treatment equipment, mechanical filters or other appropriate processes can be selected for the pretreatment system; otherwise, the normal operation of subsequent treatment equipment will be affected. In most cases, the multi-media filter is filled with quartz sand, anthracite, etc. Its main purpose is to remove large foreign matter particles, suspended matters, and gels from the water (Fig 4. 4).

The routine maintenance of multi-media filter is relatively simple. This treatment process is widely used in China and the operation cost is relatively low. The treatment function of a multi-media filter can be recovered by an automatic program setup of regular backwashing to remove the foreign matters entrapped in the filtration materials pores. The startup of the backwashing procedure depends on the SDI detection, inlet/outlet pressure difference, or the set interval for

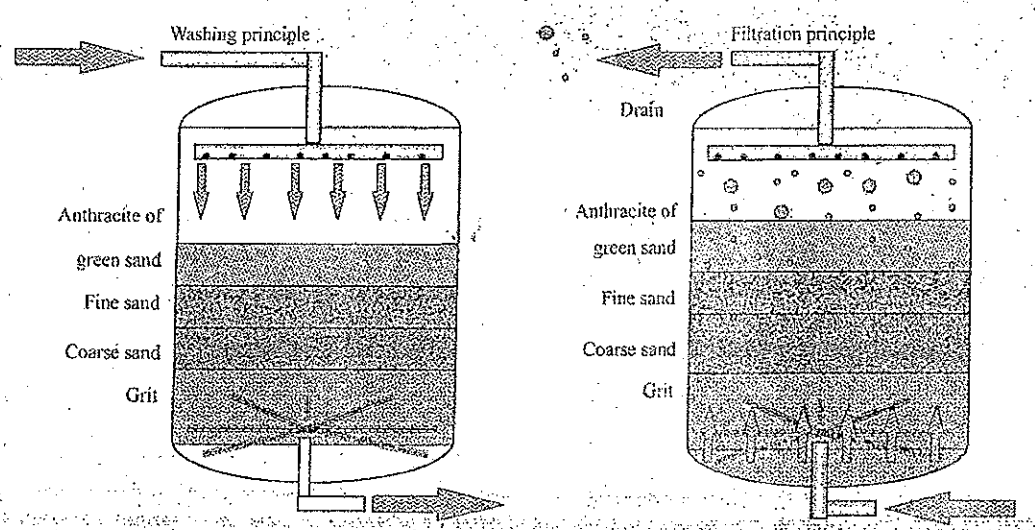


Fig 4.4 Working principle of a multi-media filter

backwashing. As the fluctuation of feed water quality has a relatively large influence on the operation conditions of the multi-media filter, a manual backwashing function will usually be set up. Generally, clean raw water can be used as back washing liquid. It usually takes about 15 minutes to wash at a speed of over two times of the design flowrate. After backwashing, forward washing will be carried out to reset the media bed. When the design diameter of the filter is relatively large or the raw water quality is poor, an air cleaning function can be added in the design; it will greatly improve the back washing effect. Generally, a vertical multi-stage pump is used as the back-washing pump. In order to guarantee a good operation effect of the system, the media of the mechanical filter should be replaced regularly; the replacement cycle is generally two or three years.

When a multi-media filter is selected and designed, a key analysis should be made with respect to the turbidity and silicide contents in the raw water. If the raw water has relatively high turbidity or high concentration of silicide, some flocculants of a certain concentration should be added before the multi-media filter or raw water tank, so that the turbidity and silicide load in the water can be reduced by flocculation and coagulation desilicication respectively. Desilicication by coagulation is a physicochemical method using the silicone adsorption and agglomeration capability of some metal oxides and hydroxides. The addition of such substances can enhance the treatment effect of a multi-media filter, but some of the coagulation matters may leak to downstream treatment unit and cause extra quality risks for the purified water. If a flocculant is used, residue detection and validation must be carried out very strictly. Enterprises should provide good quality raw water, taking into account their own situation to reduce the quality risks and operation costs of the whole system.

4.4 Activated Carbon Filters

Activated carbon filters are mainly used for removing free chlorine, colority, organic matters, some heavy metals and other harmful substances from the water using the adsorption capacity of the capillary pores in carbon surfaces and activated free radicals to prevent any detrimental effect on the RO membrane and EDI of the purification system. The filtering media is generally a fixed layer composed of activated carbon particles (coconut shell activated carbon is usually used in the pharmaceutical industry). After the treatment, the residual chlorine in the output water should be less than 0.1 ppm. The most important evaluation index for activated carbon is its ability of removing residual chlorine from the water. At the same time, activated carbon has some ability of adsorbing organic matters. As the activated carbon will retain some foreign matters being leaked from the upstream station and the friction between activated carbon particles will produce some powders, backwashing needs to be regularly performed for activated carbon filters. The research has shown that activated carbon filters can remove residual chlorine from the water very thoroughly. When activated carbon contacts the water containing residual chlorine, carbon radicals can decompose the

residual chlorine matters. The reaction formulas are as follows:

$$HClO + C^* \longrightarrow C^*O + Cl^- + H^+$$
$$OCl^- + C^* \longrightarrow C^*O + Cl^-$$

The total carbon amount of the activated carbon filter will decrease due to its catalyzing function, so the activated carbon should be replaced regularly to guarantee the chlorine removing effect.

As activated carbon, a porous material, has the property of adsorption, microorganisms will grow when a large amount of organic matters are adsorbed. If the microorganisms produced due to long term operation leak into the downstream treatment unit, the operation of the downstream treatment unit will be affected and there will be very large microbial contamination risk. Therefore, a high temperature disinfection system should be installed for the activated carbon filter, so that its microbial load can be effectively controlled. Pasteurization and steam disinfection are both effective for the disinfection of activated carbon filters. If the organic substance index of the raw water quality is not very high, chemicals dosing can be selected for reducing the residual chlorine, etc. in the water; this can be used as an alternative to an activated carbon filter. Generally, an oxidation-reduction potential meter (ORP meter) can be provided for controlling the dosing amount of sodium hydrogen sulfite into the water to ensure that the oxides in the water can be effectively reduced before being fed to the next treatment unit. The formula is as follows:

$$NaHSO_3 + HClO = NaHSO_4 + HCl$$

But the disadvantages are also very obvious. On one hand, the dosing amount is realized through the control of the dosing frequency of the dosing pump by use of instruments, but the control may be unstable and there may be a risk of leakage of residual chlorine because the instrument probe may not function properly and the oxidation-reduction potential indicated may correspond to a different residual chlorine value under different pH conditions; on the other hand, the reduction reaction happens due to the addition of chemicals, so the introduction of a large amount of external chemicals will consequently increase the treatment load of the downstream purification system; in a worse case, the service life of the RO membrane may be affected.

4.5 Softening Unit

Hard water may lead to scale formation in the water supply system. Water scales are mineral matters left after the water is removed or evaporated. Scale formation mainly occurs in the boiler, cooling tower, RO unit, pure steam generator, and water still. The softening unit is also called softener; its main function is to eliminate water hardness, e.g. calcium and magnesium ions. Softener usually consists of a vessel containing the resin, resin, valve or adjustor as well as a control system. The softening principle is as follows: calcium and magnesium ions in the water will be exchanged by sodium ions from the softening resin to prevent calcium and magnesium ions scaling on the surface of RO membrane. Generally, the hardness of the output water from the softener can be less than 3 ppm.

As the resin in the softener need regeneration to recover its exchangeability, a dual-stage series softening system is usually used to guarantee continuous operation of the purified water machine. When one softener is being regenerated, the other set can still be used for generating water. At the same time, this design can effectively avoid quick growth of microorganism in the water. The cylinder body of the vessel is usually made of fiber reinforced plastics or stainless steel; the pipeline should be made of PVC, PP/ABS, or stainless steel. The softener is automatically controlled by a PLC control system. The softening system should be provided with a salt water tank for the regeneration of the resins.

The softening resin is relatively sensitive to contamination with heavy metals. The contents of iron ions and manganese ions in the city water of individual regions may be out of standard, so the softening resin may be contaminated and the ion exchange ability of the softening resin may decrease or the resin may be out of function. At the same time, the RO membrane may be contaminated, so these ions must be removed before entering the softener. The traditional technology uses a manganese sand filter for removing irons and manganese or uses an oxidizing process; the basic working principle is as follows: dissolved ferrous iron or manganous ions in the water with a high content of iron ions or manganese ions can be oxidized into undissolved ferric iron or tetravalent manganese compounds respectively by oxidization (e.g. manganese sand filter, breakpoint chlorination, potassium hypermanganate, etc.); and the compounds will be filtered out by the manganese sand filter or subsequent mechanical filter.

$$4Fe_2^+ + O_2 + 10H_2O = 4Fe(OH)_3 + 8H^+$$

$$2Mn_2^{+} + O_2 + 2H_2O \longrightarrow 2MnO_2 + 4H^{+}$$

During the ion exchange process in the softener, Ca^{2+} ions and Mg^{2+} ions in the water will be retained in the resin after being exchanged for Na^{+} ions in the RNa resin, so the ion exchange resin has been changed from a RNa type to a R_2Ca or R_2Mg type. The ion exchange reaction formulas of the softening process are as follows:

$$Ca^{2+} + 2RNa \longrightarrow R_2Ca + 2Na^{+}$$

$$Mg^{2+} + 2RNa \longrightarrow R_2Mg + 2Na^{+}$$

After absorbing a certain amount of Ca^{2+} ions and Mg^{2+} ions, the ion resin must be regenerated. The regeneration of softener resin is done by reducing the converted resin by saline water, so that the Ca^{2+} ions and Mg^{2+} ions in the resin will be replaced by Na^{+} ions once again to regenerate RNa type ions and the ion exchange ability of the resin will be recovered; at the same time, the waste water will be drained. The ion exchange reaction formula for the regeneration is as follows:

$$R_2Ca + 2NaCl \longrightarrow 2RNa + CaCl_2$$

$$R_2Mg + 2NaCl \longrightarrow 2RNa + MgCl_2$$

The softening resin itself is not resistant to oxidization, which will cause the breakage of functional groups of the resins or even powderization and its original ion exchange ability will get lost. But the practice has shown that if the concentration of sodium hypochlorite is not higher than 1ppm, the detrimental effect of the oxidization of the resin is relatively small. When the concentration of sodium hypochlorite in the pretreatment system is controlled within 0.3 to 0.5 ppm and there is no other disinfection method for the softener, the softeners in series can be placed before the activated carbon filter, so that the disinfection function of sodium hypochlorite in the pretreatment system can be effectively used to prevent the rapid growth of microorganisms in the softener. Similarly, as the maximum operating temperature of the softening resin is 120 ℃, a pasteurization process can also be applied. If the pretreatment system is designed to use overall pasteurization, it is suggested to set up the softener after the activated carbon filter to prolong the service life of the softening resin.

4.6 Dosing Unit

In pharmaceutical water systems, the chemicals dosing is an essential unit. A good design of the dosing unit is not only the foundation for the long term and highly efficient operation of the system but also an important guarantee for meeting the process performance requirements (Fig 4.5). Generally, the chemicals dosing unit is designed to be installed in the pre-treatment system, which includes the raw water tank, raw water transfer pump, multi-media filter or ultra-filter, activated carbon filter, softener, safety filter, RO high pressure pump, RO, etc. City water, surface water, or ground water is usually used as the source water for the purified water machine. The water quality is relatively stable. In order to improve the treatment efficiency of the subsequent deionization unit, some necessary chemicals are dosed into the pretreatment system. Common chemicals include coagulants (polyaluminum chloride, PAC), disinfectants (sodium hypochlorite, NaClO), reducing agents (sodium hydrogen sulfite, $NaHSO_3$), and caustic-soda (sodium hydroxide, NaOH). Please refer to the relevant *Material Safety Data Sheet* (MSDS) for details about the chemical characteristics and some descriptions of the chemicals.



Fig 4.5 The Dosing Unit

Polyaluminum chloride is an inorganic polymer coagulant also known as polyaluminum; its English abbreviation is PAC. PAC is one of the inorganic polymer water treatment chemicals with large molecular weight and high electric charge that is produced by the bridging action of hydroxyl ions and polymerization of polyanions. The chemical formula is $[Al_2(OH)_nCl_{6-n}]_m$, in which m represents the polymerization degree, n represents the neutral degree of the PAC product. The purification principle of PAC is as follows: it achieves a water purification effect through the destabilization, aggregation, flocculation, coagulation, and settling of

fine suspended particles and gel ions in the water using such action mechanisms as compressing the thickness of the electric double layer, adsorption and charge neutralization, adsorption bridging and sediment trapping, etc.

In pharmaceutical water systems, the PAC dosing is usually arranged at the inlet of the filtration unit to improve the treatment performance of the filtration unit. PAC is usually provided in the form of 10% solution in a drum and will be regularly dosed by the operator into a PAC dosing tank at the site; it will be further dosed by an electric diaphragm pump into the pipeline at the inlet of the filtration unit at a concentration of 0.1 to 2 ppm. Considering bacterial control in the pharmaceutical factory and the stability of the chemicals, the design capacity of the PAC dosing tank is generally less than two weeks' consumption amount. It is suggested that a pipeline static mixer should be installed to improve the mixing efficiency of the PAC and raw water. The following factors should be taken into consideration for the design of the mixer: chemicals viscosity, density, liquid flow rate, pressure, etc. The specific dosing concentration should depend on the raw water quality. If the concentration of PAC is too low, it cannot purify the water body effectively, but if the concentration is too high, the water body will also be contaminated and the filtration unit will be blocked, which will lead to the contamination of the water tank and pipeline, frequent washing of filtration unit, or even the replacement of media or membrane modules. If the pretreatment unit is designed for operation in a continuous cycle and the water consumption is low, it should be noted that long term circulation may lead to too high accumulated PAC concentration. Generally, if the SDI value is less than 4 at the outlet of the filtration unit, it can be considered that the filtration effect is good. PAC dosing can be controlled by a diaphragm pump with the frequency being adjusted manually or automatically. Manual frequency adjustment is suitable for a system with stable flow rate and is economical. Automatic frequency adjustment can be designed to be interlocked with the feed water flow meter; and the frequency of the dosing pump can be adjusted in real time according to flow rate fluctuations, so that the dosing of chemicals with a stable concentration can be realized.

A sodium hypochlorite (NaClO) solution is a disinfectant containing chlorine and is a strong oxidant; when being dosed into water, it will decompose into hypochloric acid (HClO) and hypochlorite (ClO^-) rapidly; these two chemical substances are the major disinfecting components of a NaClO solution, which can react with cell water; furthermore, due to their features of having a small molecule and no electric charges, these substances can penetrate into the cell to oxidize protein or destroy phosphate dehydrogenase causing cellular metabolic disorders leading to cell death.

The sodium hypochlorite solution is widely accepted for pharmaceutical water treatment systems due to the following advantages: wide application range, highly efficient disinfection, relatively long disinfection interval, and low costs. The sodium hypochlorite solution is usually provided in the form of 10% solution in a drum and will be dosed regularly by the operator into a dosing tank on the site; then it will be further dosed by an electric diaphragm pump into the pretreatment system at a certain concentration. Considering the bacterial control in a pharmaceutical factory and the stability of the chemicals, the design capacity of the onsite dosing tank is generally less than two weeks' consumption amount. It is suggested that a pipeline static mixer should be installed to improve the mixing efficiency of the sodium hypochlorite solution and raw water. The following factors should be taken into consideration for the design of the mixer: chemicals viscosity, density, liquid flow rate, pressure, etc. The dosing amount of the sodium hypochlorite solution depends on the dosing points, raw water quality, and site commissioning and validation situation. Generally, if the concentration of residual chlorine in the supply water is less than 0.3 ppm, a sodium hypochlorite solution dosing system can be considered.

Generally, PID interlocking control will be used for the dosing amount of the sodium hypochlorite solution and subsequent residual chlorine sensor. The concentration will be controlled within 0.3 to 0.5 ppm; if the concentration is too low, there will be a risk of microbial growth; but if the concentration is too high, there will be too much consumption of reducing agent (sodium hydrogen sulfite solution) subsequently or even oxidization of the RO. Residual chlorine sensors should be installed at the outlet of raw water tank or raw water pump to monitor the concentration of residual chlorine; at this point, the concentration of residual chlorine should be controlled to no less than

0. 3 ppm.

An electrode sensor is usually used as the residual chlorine sensor, which will generate a signal proportional to the residual chlorine concentration of the water passing through a selective permeable membrane, work electrode, electrolyte, and reference electrode for measuring the content of residual chlorine in the water body, indicated in ppm or mg/L. The residual chlorine sensor is installed for bypass measuring; it should be ensured that the sampling flow rate will be constant, which is about 30 L/h. Its measurement is closely related to the temperature and pH value of the media. The residual chlorine sensor uses built-in temperature compensation, so that the measuring signal will not affected by the temperature of the water body; three-electrode technology is used to reduce the dependence on the pH-value effectively; and a good linearity relationship is shown in the range of pH 4 to 9. The sampling flow rate can be monitored through an optics flow switch.

The ORP (oxidation-reduction potential) represents the relative degree of oxidizability or reducibility of a water body. As residual chlorine has strong oxidizability, the ORP value will increase consequently if residual chlorine is introduced into the system. The ORP sensor uses a glass electrode; a corresponding potential difference will occur between a reference electrode and a work electrode according to the oxidization or reduction degree of the water body; and this potential difference is the actual ORP value, which is reported in mV.

RO membrane manufacturers recommend the maximum residual chlorine concentration should be generally no higher than 0. 1 ppm at the inlet of the RO membrane. If this concentration is exceeded, the performance and service life of the RO membrane will be affected severely; therefore, as a reducing agent of residual chlorine in water, a sodium hydrogen sulfite ($NaHSO_3$) solution is often used in pharmaceutical water systems. Sodium hydrogen sulfite is usually supplied in the form of 10% solution in a drum; it will be dosed regularly by the operator into a dosing tank at the site; and then it will be further dosed by an electric diaphragm pump into the system at a certain concentration. As the sodium hydrogen sulfite solution is not stable and if there are sulfate-reducing bacteria in water, sulfurous acid will become a nutrient substance and will help the growth of bacteria; therefore, it is suggested that the design capacity of the onsite dosing tank should be less than one week's consumption amount. The dosing point is generally located at the inlet of the safety filter. It is best to use a pipeline mixer to ensure sufficient time for the reaction between the sodium hydrogen sulfite solution and the residual chlorine in the water, which can also effectively prevent any detrimental effect on the RO unit due to foreign matters from the chemicals.

RO desalination efficiency is affected by pH value. If pH value is low, HCO^{3-} and CO_3^{2+} ions in water body will be converted into carbon dioxide (CO_2). As RO membrane has no ability for filtering gases, carbon dioxide gas in the water will permeate RO membrane and the conductivity of purified water will be affected. The dosing of sodium hydroxide (NaOH) solution is to increase pH value of the water properly, so that carbon dioxide (CO_2) can be converted into HCO^{3-} and CO_3^{2+} ions for being removed by RO membrane. Generally, pH value at the inlet of RO unit is controlled in the range of 7. 5-8. 5 to realize ideal desalination efficiency. Sodium hydroxide (NaOH) solution is usually dosed into RO system to increase pH value of RO inlet water. Sodium hydroxide (NaOH) is often dosed into onsite dosing tank in two forms: one is solid sodium hydroxide and the other is 10% sodium hydroxide solution; the former will be diluted into 10% solution for being dosed into the dosing tank at the site; the latter will be provided in chemical drum and then dosed regularly by the operator into the system with electric diaphragm pump. The design capacity of the dosing tank at the site is generally about two weeks' consumption amount. The dosing point of sodium hydroxide solution is generally located at the inlet of police filter. It is best to use a pipeline mixer together to ensure full reaction between the sodium hydroxide solution with residual chlorine in the water, which can also effectively prevent any ill effect on RO unit due to foreign matters in the chemicals. pH sensor will be installed after pipeline mixer and the dosing pump will be continuously controlled by PID. Some designer prefers to arrange the dosing point and pH sensor in the return pipeline of RO concentrate. As RO concentrate flow rate is relatively stable, this arrangement can also achieve good result. Furthermore, if pH value is too high (e. g. pH > 9. 5), there will be a risk of scaling in RO system, so pH 9. 5 is generally set as the limit value for RO alarm.

With the development of scientific technology, there is an ever-growing variety of online sensors for dosing operation. The introduction of multi-channel transmitter has provided more concise and flexible design for the control of multiple water quality parameters in pharmaceutical water systems. Fig 4.6 shows the multi-channel transmitter specially equipped for the dosing unit. It has the function for timed dosing and batch dosing. Multi-channel transmitter for the dosing unit consists of a standard main board and multiple extendable modules (conductivity, pH/ORP, input/output modules), nearly covering various sensors used during conventional purified water generation process, which include original signal sensors for output flow rate pulse, pH/ORP, conductivity, etc. as well as standard simulated signal sensors for output water (pressure, liquid level, residual chlorine, etc.). At the same time, this transmitter is also one multi-function controller, having up to seven standards and five optional computing and control functions; it can satisfy common requirements of water treatment system, e.g. computing RO recovery rate/desalination rate, ON/OFF control, PROP control, PID control, and timed/volumetric dosing control.

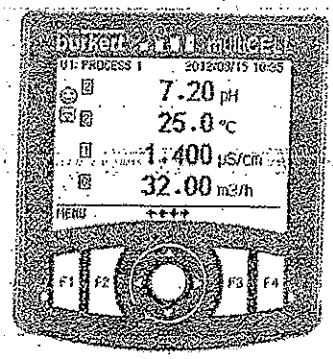


Fig 4.6 Example of multi-channel transmitter interface

4.7 Ultrafilter for Pretreatment

Ultrafilter for pretreatment (Fig 4.7) is a part of membrane filtration process and its filtration pore size is about 80,000to 150,000MWCO; it can replace mechanical filter in traditional pretreatment process and the output water quality is far better than that produced by mechanical filter. It can also retain some organic matters and microorganism effectively; microorganism removal ability can be over 10^4. It can be used when the turbidity of raw water is less than 100NTU and the output water turbidity is less than 0.1NTU. The usage of ultrafiltration can protect RO unit more effectively and prevent RO membrane from being contaminated. Generally, the service life can be prolonged to five years from three years or longer. At the same time, the recovery rate of RO membrane can be improved; more purified water will be produced at the same feed water flow rate, so the utilization rate of the water is increased.

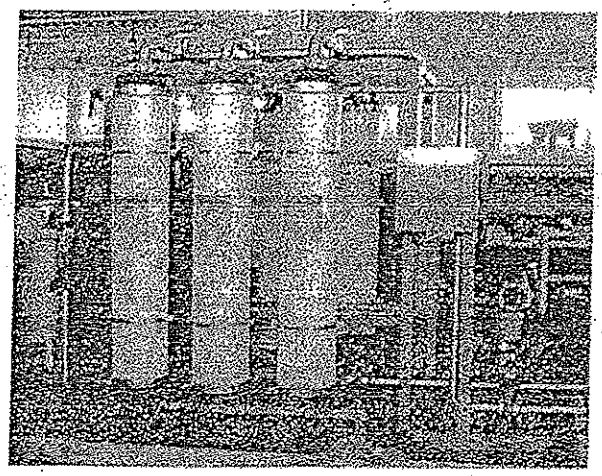


Fig 4.7 Ultrafilter for pretreatment

Ultrafiltration uses cross-flow technology similar to that for RO process; pressurized feed water flows toward porous membrane filtration surface in parallel; water flows through the membrane under the function of differential pressure. The retained matters such as particles, organic substances, microorganisms, and other contaminants will enter concentrate stream (usually 5% to 10% of the feed water) and be drained, so that the filter can be self-cleaned and the frequency of replacing filters can be reduced. Just like RO process, ultrafiltration cannot inhibit low molecular weight ionic contamination. Ultrafiltration cannot thoroughly remove the contaminants from the water; the removal of ions and organic matters varies with the structure and porosity of membrane material. It is very effective for the removal of many different organic matter molecules. In addition, ultrafiltration cannot retain dissolved gases. Most filtration process removes contaminants by continuous effluent decontamination; ultrafiltration flux and cleaning frequency vary with feed water quality and pretreatment process. Many ultrafiltration membranes are chlorine resistant and can resist a concentration of 100 ppm in a short term; therefore, it is not necessary to remove residual chlorine from feed water; and disinfection function of sodium hypochlorite can be realized.

Ultrafiltration system mainly consists of raw water

tank, raw water pump, disc filter (50 to 100 μm), ultrafilter, output water tank of ultrafilter, back-washing pump, oxidant dosing unit, etc. The membrane is made of polymer or ceramic; spiral membrane and hollow fiber membrane can be used for polymer membrane element. Ceramic module can be single-channel or multi-channel. A variety of disinfection methods can be used for ultrafiltration membrane; most polymer membranes can resist the washing of many chemicals, e.g. hypochlorite, hydrogen peroxide, peracid, and sodium hydroxide; some polymer membranes can be disinfected with hot water and some even can be disinfected with steam. Ceramic ultrafiltration material can resist all common chemicals, hot water, steam, or ozone disinfection.

4.8 Nanofilter

Nanofiltration (NF) is a kind of pressure-driven membrane separation method falling in between RO and ultrafiltration. NF membrane has a theoretical pore size of 1 nanometer (10^{-9} meter). Nano-membrane is sometimes called "softening membrane" and can remove anions and cations; in comparison to small anions (e.g. chlorides), it is easier to remove large anions (e.g. sulfate). Nanofiltration membrane has better retentive function for divalent anions and organic matter with a molecular weight of more than 200 Da, including chromoplast, trihalomethane precursor cell, sulfate, etc. But, nanofiltration has poor retentive ability for monovalent anions or non-ionic organic matter with a molecular weight of less than 150 Da.

Compared with other pressure-driven membrane separation process, nanofiltration is a relatively novel technology. Nanofiltration membranes are mostly derived from RO membrane, e.g. CA membrane, CTA membrane, PARA compound membrane, SPES membrane, etc. But in comparison to RO, the requirement for operation pressure is lower and generally 4.76 to 10.2 bars. Therefore, nanofiltration is also called "low pressure reverse osmosis" or "loose reverse osmosis". After nanofiltration treatment, the final output water conductivity is in the range of 40 to 200 μS/cm, but it also depends on total dissolved solids content in feed water and the variety of mineral substances; in comparison, the output water conductivity of one-stage RO unit is 5 to 20 μS/cm. At present, in respect of the prevailing design thought of purified water machine in China, nanofiltration technology has not been widely used or promoted.

4.9 Microfilter

Microfiltration is a membrane treatment process for removing fine particles and microorganisms. If the filter cartridges have same sizes and connection type, the housing of microporous filter is universal except for different filter cartridges and pore sizes. The pore size of terminal filter is generally 0.04 to 0.45 μm. Microfiltration has a wide range of applications. The filtration sterilization method accepted by *Chinese Pharmacopeia* is a typical microfiltration process. In purified water machine, microfilter is usually used as a police filter before RO unit mainly for preventing large particles into high pressure pump or RO module as well as any mechanical damage to the pump and membrane. Generally, a police filter uses a filter cartridge with filtration precision of 5 μm or 1 μm.

Microporous filter is usually used for retaining microorganisms after some modules in purified water system, where there is a risk of microbial growth. Microporous filter does a very good job in retaining microorganisms in this area; but some appropriate actions must be taken to ensure the integrity of filter cartridge during membrane installation and replacement process and further guarantee its inherent performance. Microporous filter is most suitable for the intermediate process of purified water generation system and is not applicable to circulating distribution pipework system. Filter should not be the only microorganism control unit in the system and should be one part of comprehensive microorganism control measures. Microfiltration has the same efficiency as ultrafiltration in reducing microorganisms and will not produce waste water; but unlike ultrafiltration, microfiltration cannot reduce the level of dissolved organic matters. Due to different pore sizes, microfiltration cannot remove smaller particles that can be removed by ultrafiltration. Another difference is that microfilter made of appropriate material can resist hot water disinfection and pure steam sterilization.

4.10 Degasser

A degasser in pharmaceutical purified water unit is mainly used for removing carbon dioxide from water. Carbon dioxide may have the following bad effect on subsequent EDI: to form carbonate ions which lead to

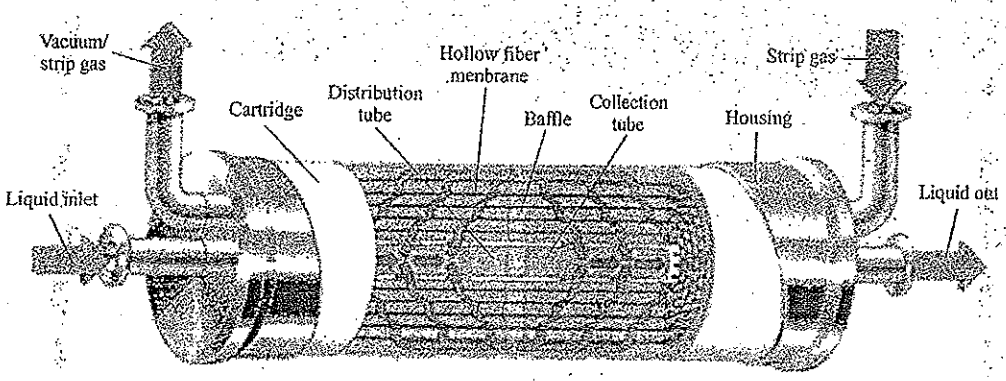


Fig 4.8 Membrane degasser

EDI module scaling or affect EDI output water conductivity; at the same time, carbon dioxide can reduce the efficiency of EDI for removing silicon and boron.

There are two main categories of degassing processes in pharmaceutical water systems. For category one, carbon dioxide is removed by the adjustment of pH value in combination with RO process; for category two, a membrane degasser is used for removing carbon dioxide; and its advantage is that it is not required to add other chemicals.

Theoretically, carbon dioxide and bicarbonate ions are kept in a balance in the range of pH 4.4 to 8.2; if pH value is 4.4, all alkaline matters are carbon dioxide; and if pH value is 8.2, all alkaline matters are bicarbonate ions; RO membrane has no ability to remove carbon dioxide but is very efficient in removing bicarbonate ions. Sodium hydroxide (NaOH) is dosed before RO unit to adjust pH value and convert carbon dioxide into bicarbonate ions for being removed by RO membrane and finally achieving the purpose of removing carbon dioxide.

Membrane degasser (Fig 4.8) consists of a hollow fiber membrane; one side of the membrane is liquid phase side and the other side is gas phase side; the removed gases can be collected by vacuum suction, gas purging, or a combination; the fiber membrane is hydrophobic, so water cannot permeate the membrane. Partial pressure of gas phase decreases due to gas removal, so gases will disperse through the membrane to turn into gas phase.

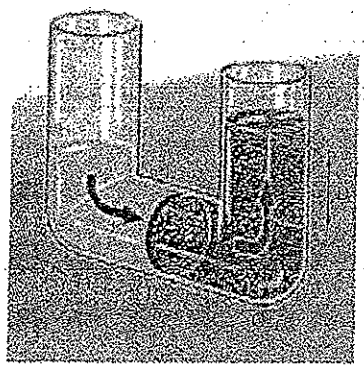
The degasser should use sanitary design; as hollow fiber is a kind of thin fiber, a police filter should be installed before membrane degasser. If hollow fiber membrane degasser is used in RO/EDI system, the most effective installation position should be after RO unit.

4.11 UV Lamp

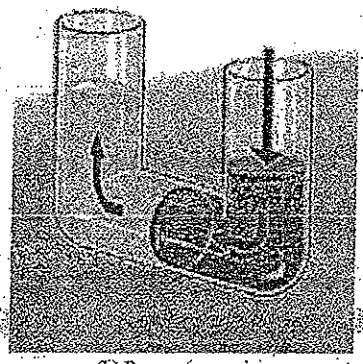
UV lamp is a commonly used, device in purified water, relevant content refer to Chapter 3.

4.12 RO Unit

Fig 4.9 shows the basic schematic drawings of permeation and Reverse Osmosis (RO). A piece of semi-permeable membrane (B) will be placed at the bottom of a U-shaped container; a semi-permeable membrane is a thin film with selective permeation performance and only water is allowed to permeate the semi-permeable membrane; and other saline matters



(a) Permeation



(b) Reverse osmosis

Fig 4.9 Working principle of permeation and RO

cannot permeate through it (strictly speaking, other saline matters can also permeate through it according to RO Dissolution-diffusion theory, but there is a big difference in permeation rate in comparison to water molecules). When purified water (A) and saline solution (C) are added into both sides of the semi-permeable membrane respectively, purified water will permeate into the saline solution side through the membrane, so the liquid level on saline solution side will rise and the liquid level on water side will decrease, until the pressure of the formed water column can counteract the migration of water molecules and the liquid levels on both sides will remain constant; the liquid level difference (D) at this time is the osmotic pressure; and this phenomenon is called permeation. Some pressure will be exerted on saline solution side to overcome osmotic pressure; when a pressure higher than natural permeation pressure is exerted on saline solution side, the flow direction of water molecules will be reversed; and some water molecules in saline solution will permeate through the semi-permeable membrane into pure water side; this phenomenon is called reverse osmosis (RO).

Since the end of 1950s to the beginning of 1960s, RO technical products have begun to commercialize and been launched into the market. RO is the most precise membrane liquid separation technology. It is a kind of semi-permeable membrane that only allows the permeation of water molecule but not the permeation of solute. It can retain all dissolved salts and organic matters with a molecular weight of more than 100 Da. Desalination rate of cellulose acetate RO membrane is generally more than 95% and that of RO composite membrane is generally more than 98%. They are widely used in the following applications: sea water and brackish water desalination, boiler feed water, industrial purified water and electronic ultrapure water generation, production of pure water for drinking, waste water treatment, special separation, etc. The structure of RO membrane can be classified into a symetric membrane and homogeneous membrane. Currently, the membrane used in purified water generation process is mainly made of cellulose acetate and aromatic polyamide. Membrane modules can be classified into hollow fiber, spiral-wound, plate-and-frame, and tubular types. Spiral-wound structure is the conventional RO membrane used in pharmaceutical industry (Fig 4. 10).

Typical RO system consists of RO feed water pump, anti-scalant dosing unit, reducing agent dosing unit, 5 μm police filter, heat exchanger, high pressure pump, RO unit, carbon dioxide degasser or NaOH dosing unit, and RO washing unit. When pretreated water enters RO system, most ions and bacteria can be removed; at the same time, microorganism and TOC can be effectively removed to realize constant low conductivity and low bacteria content so as to meet high standard water quality requirements.

The police filter before RO unit can prevent the permeation of particles of larger than 5 μm and protect RO membrane from being damaged. The function of high pressure pump is to increase feed water pressure to be higher than osmotic pressure. As the optimum working temperature of RO membrane is 25 ℃, the water output will decrease by 2% to 3% for each degree of temperature drop at the same operation pressure; therefore, a heat exchanger is used to heat the feed water of RO unit and the feed water temperature is adjusted to maintain at 25 ℃. The following types of heat exchangers need to be selected to prevent cross contamination: electric-driven heat exchanger, dual-plate plate heat exchanger, or dual-plate tubular heat exchanger. At the same time, the heat exchanger can also realize pasteurization function of RO/EDI system

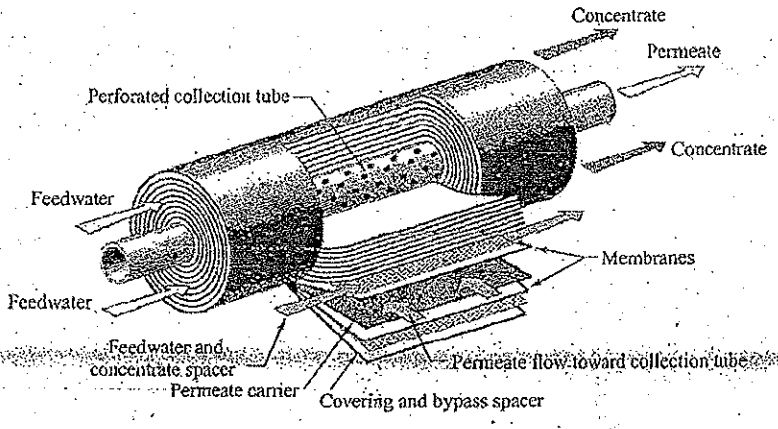


Fig 4. 10 Spiral-wound RO membrane

by a reasonable design.

The necessity of installing the dosing units for anti-scalant and reducing agents in purified water generation system depends on raw water quality, selection of pretreatment process, and the user's requirement. For a system with large water output, if the water hardness is reduced simply by a softener, the volume of the softener will be very large; the daily saline consumption and maintenance cost are very high; therefore, we can consider reducing the risk of scaling on concentrate side of RO membrane by adding anti-scalant to reduce calcium ions and magnesium ion. Anti-scalant is a kind of organic compound. Besides working at a Langelier saturation index (LSI) of 2.6, it can also prevent the scaling of sulfate. Its main function is to increase the solubility of scaling matters in the water to prevent the blockage of the membrane by calcium carbonate, calcium sulfate, etc. At the same time, it can also reduce the blockage of membrane by iron ions. RO membrane manufacturers will recommend some anti-scalants of certain brands and compositions. We can choose sodium hexametaphosphate or some other products accepted by NSF and FDA as anti-scalants.

The filtration performance of RO membrane for various ions has the following features: the permeation rate of monovalent ion is higher than that of divalent ion; and the permeation rate of divalent ions is higher than that of trivalent ions; for co-ions, the smaller the diameter of the element is, the permeation rate will be higher, e.g. $K^+ > Na^+ > Ca^{2+} > Mg^{2+} > Fe^{3+} > Al^{3+}$; the permeation rate of carbon dioxide and other non-condensable gases through RO membrane is almost 100%; therefore, if the content of carbon dioxide in raw water is too high, the conductivity of final RO output water will be relatively high, because the dissolution of carbon dioxide will have severe impact on the conductivity of the output water.

Besides RO principle, RO technology also makes use of selective adsorption of RO membrane and screening mechanism for organic matters. RO process cannot completely remove the contaminants from the water. It is very difficult or impossible to remove the dissolved organic matters with very small molecule weight; but RO unit can remove large amounts of bacteria, endotoxins, gels, and organic macromolecules. The pore size of RO membrane is mostly no more than 10×10^{-10} m. The objects being separated are the ions or organic matters in the water with a molecule weight of about several hundred. It can filter out various bacteria, e.g. one of the tiniest bacteria, *Pseudomonas aeruginosa* (3000×10^{-10} m); and it can also filter out all kinds of viruses, such as flu virus (800×10^{-10} m), Meningitis virus (200×10^{-10} m) as well as pyrogens [$(10 \text{ to } 500)\times10^{-10}$ m]. Now RO unit has become the top selection of pharmaceutical water treatment process due to the following advantages: simple operation, high desalination efficiency, high performance of depyrogenation, mature technology, and economical efficiency. RO technology is not only used in purified water generation process but also for producing WFI if being applied reasonably. Therefore, RO process has been accepted by USP as one of legal methods for producing WFI since USP19.

When RO unit stops working, the system will perform automatic flush for three to five minutes to remove the fouls on the surface of the membrane, so that the unit and RO membrane can be maintained effectively. After long term operation, some fouls hard to flush may deposit on the surface of the RO membrane to cause a drop in performance; such fouls must be removed by cleaning with chemicals to recover the performance of RO membrane. Chemical cleaning can be carried out with CIP unit, which usually consists of cleaning liquid tank, cleaning filter, cleaning pump, and the supporting pipeline, valves, and instruments. When the membrane module is contaminated, chemical cleaning of RO membrane module can be realized by CIP unit. The main reason for RO membrane deterioration is the oxidization of a certain membrane element and degradation by heating. Generally speaking, RO membrane is not chlorine-resistant, so the residual chlorine needs to be removed by activated carbon filter or decomposed by UV ray, or removed by dosing NaHSO3 during the pretreatment process.

Due to good separation performance of RO technology, its application range will become wider and wider. In the future, the comprehensive development trend of RO technology will be as follows: developing new types of membrane materials of anti-oxidation, acid and alkali-resistance, and with high water permeation; developing RO membrane element of low energy consumption, contamination resistance, high-temperature and high-pressure proof, and with special separation performance; combination application of RO membrane module with ultrafiltration, microfiltra-

tion, nanofiltration, and EDI modules; and development of new-type of gas membrane separation materials.

All RO membranes can be sanitized by chemicals, which vary with the different selection of membranes; but the continuous operation temperature of normal temperature RO membrane elements must be lower than 50 ℃; if this temperature is exceeded, the membrane will lose its normal performance very quickly. With the continuous development of pharmaceutical industry, more and more concerns are given to drug resistance of bacteria and chemical residues arising from chemical sanitization, so hot water sanitization water treatment system has become more and more widely used.

High temperature-resistant sanitary RO membrane is a kind of specially manufactured membrane. Pasteurization with hot water of about 80 ℃ can be used. It is mainly designed to satisfy the strict requirements of pharmaceutical and food processing for such hygienic indexes as bacteria and pyrogens. Typical high temperature RO membranes are covered by stainless steel housing for containing and protecting spiral membrane elements (Fig 4. 11).

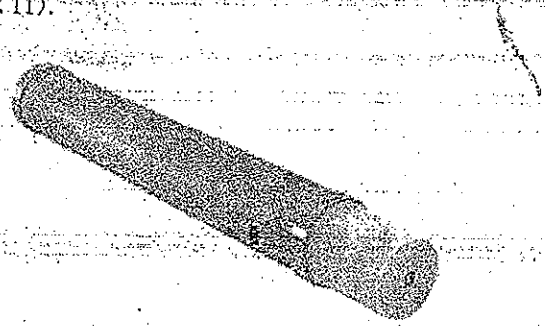


Fig 4. 11 Example of sanitary type membrane assembly

At present, the traditional rubber concentrate sealing ring has been cancelled for the relatively advanced high temperature RO membrane module. A small amount of fluid between the RO membrane and membrane housing has formed tangential flow bypass to prevent forming dead zone and the growth of bacteria and other microorganisms. At the same time, this design has improved the cleaning and sanitizing efficiency of the membrane element.

4. 13 EDI Unit

Electro De-ionization System is shorted as EDI system. It is a combination of electrodialysis process and ion exchange process. This ion exchange system uses one mixed resin bed and selective permeation membrane; it is used for further desalination. EDI system mainly consists of EDI unit, relevant valves, connecting pipeline, instruments, and control system.

The working principle of EDI is to adsorb cations and anions in the water by use of mixed ion-exchange resin; at the same time, these adsorbed ions will permeate through cation and anion exchange membranes respectively and be removed under the function of direct current electric field. A dilute chamber is formed between the anion exchange membrane facing towards anode (only allowing the permeation of cations) and cation exchange membrane facing towards cathode (only allowing the permeation of anions); and a concentrate chamber is formed between the anion exchange membrane facing towards cathode and cation exchange membrane facing towards anode. There are anion and cation resins between dilute chamber and concentrate chamber. When the water flows through the dilute chamber and concentrate chamber, the ions in the water will be adsorbed by ion exchange resin; the electrodes on both sides of EDI module can provide transverse direct current electric field, which can drive the adsorbed ions to permeate through ion exchange resin, so that ions concentration in dilute chamber will be reduced and ions concentration in concentrate chamber will be increased to make water purity in dilute chamber higher and higher. At the same time, some water will be electrolyzed into hydrogen and hydroxide ions by electric potential energy, so that the resins can be continuously regenerated without adding regenerant (Fig 4. 12).

EDI system has two operation modes: co-current operation and counter current operation. When the dilute and the concentrate have the same feed water direction, it is called co-current operation; when the dilute and the concentrate have reverse feed water directions, it is called counter current operation; the installation, monitoring and operation of EDI module under co-current operation are relatively simple; but, if the feed water load of EDI is relatively high and particularly the feed water has higher hardness, counter-current operation will have some advantages, which can reduce the rapid flow of high concentration water drawn from dilute chamber through the concentrate chamber, so that the scaling probability in concentrate chamber can be reduced and the service life of the module can be prolonged. There is a pair of electrolyte water compartments inside EDI, i. e. anode compartment

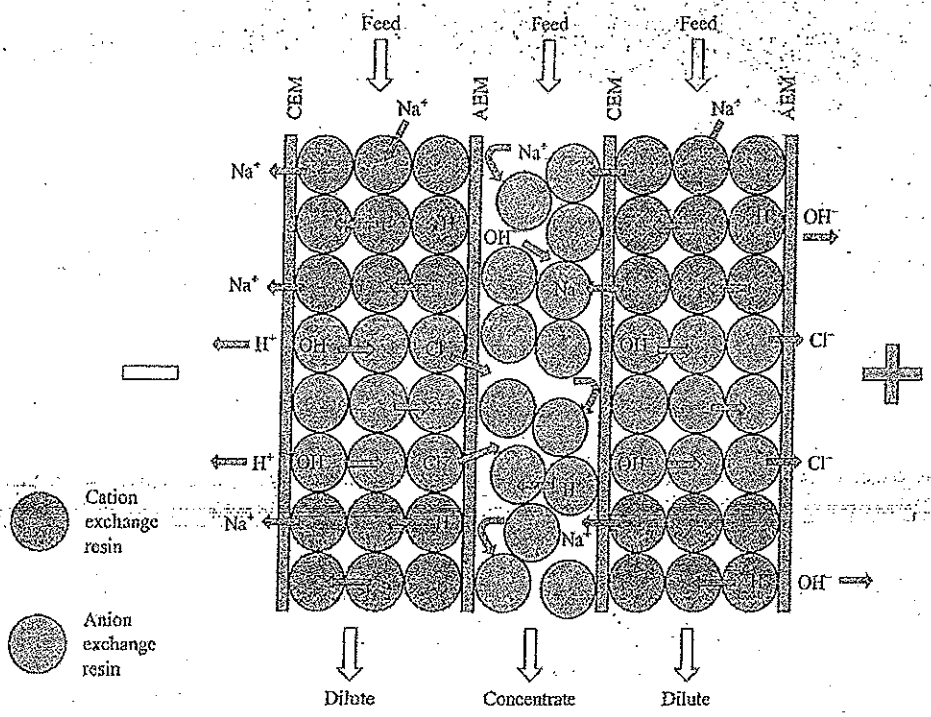


Fig 4.12 Operation principle of EDI

and cathode compartment. A series of electrochemical reactions will happen in electrolyte water compartment with the migration of ions.

Chemical reaction in cathode compartment:

$$2H_2O + 2e^- = 2OH^-(aq) + H_2(g)$$

Chemical reaction in anode compartment:

$$2H_2O = 4H^+(aq) + O_2(g) + 4e^-$$

$$2Cl^-(aq) = Cl_2(g) + 2e^-$$

As is shown in above chemical formula, a small quantity of dangerous gases will be produced in electrolyte water compartment during the normal operation of EDI. At the same time, as the electrolyte water compartment is adjacent to direct current electrode, the operation temperature is relatively high and constant water flow is needed to reduce the temperature; therefore, low electrolyte water flow protection will usually be set up in the design to prevent EDI module being burned out due to lack of water. A separate drainage system should be designed for the electrolyte water to guarantee production safety of the workshop.

Local pH value in dilute chamber will vary with the increment of EDI electric current density and the continuous production of hydrogen and hydroxide ions due to the electrolysis of some water on the surface of resin in the dilute chamber to create an environment beneficial for inhibiting the quick growth of bacteria. At the same time, there are positive charges on the surface of anion exchange resin and bacteria (particularly gram-negative bacteria) carry negative charges to make them very easy to be adsorbed on the surface of anion exchange resin; and the bacteria are in a most active area for water electrolysis, so the growth of bacteria can be inhibited or even killed to greatly alleviate the contamination level of EDI output water by bacterial endotoxins.

Similar to RO membrane, EDI modules can also be classified into normal temperature type and high temperature type. Fig 4.13 shows a typical purified water generating system using pasteurization.

EDI technology combines electrodialysis process with ion exchange process; the directional migration of ions can be realized under direct current electric field by means of selective permeation of cations and anions through cation and anion exchange membrane and ions exchange function of ion exchange resins, so that though desalination of the water can be finished and water resistivity can be more than 10 MΩ · cm. At the same time, ions exchange resins will be regenerated by hydrogen and hydroxide ions from electrolyzed water; therefore, ultrapure water can be continuously produced without using acid and alkaline chemicals for regeneration. Compared with traditional mixed-bed technology, EDI process has abandoned conventional ions exchange technology being accompanied with spent acid and spent alkali pollution. It has many advantages as follows: no chemical pollution, continuous regeneration,

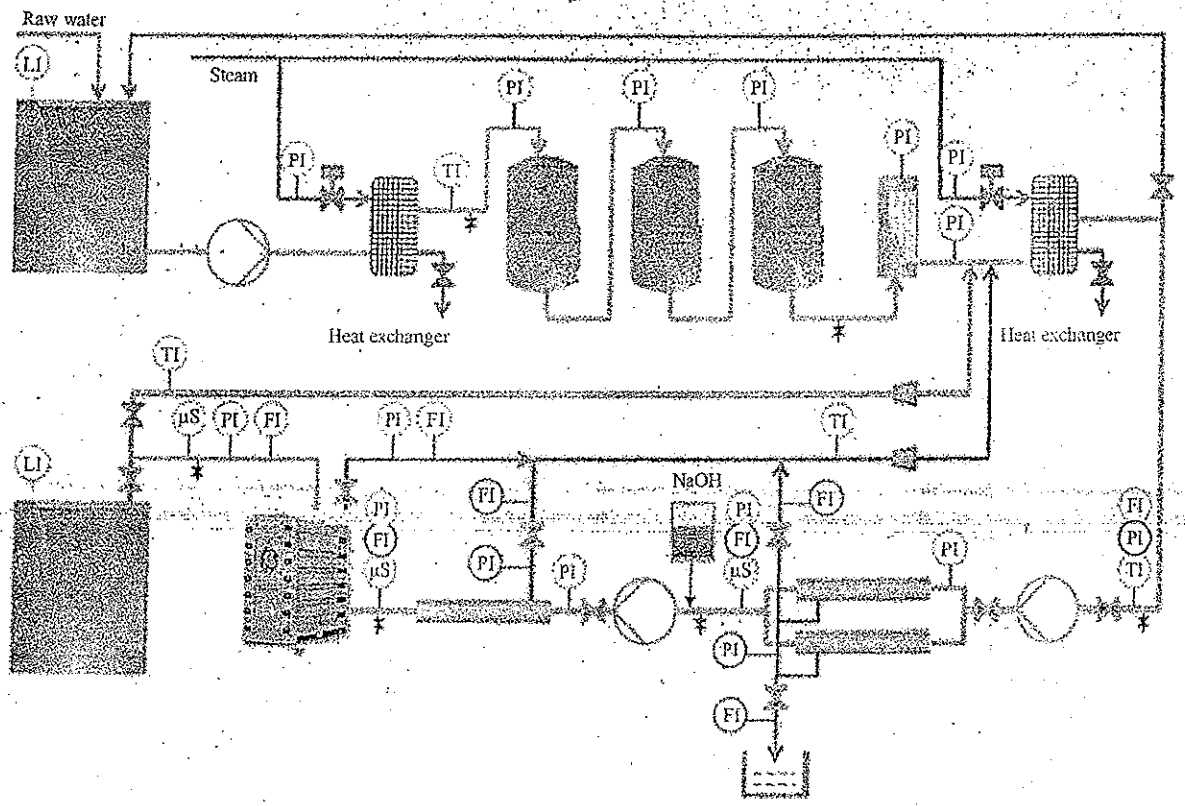


Fig 4. 13 Purified water generation system using pasteurization

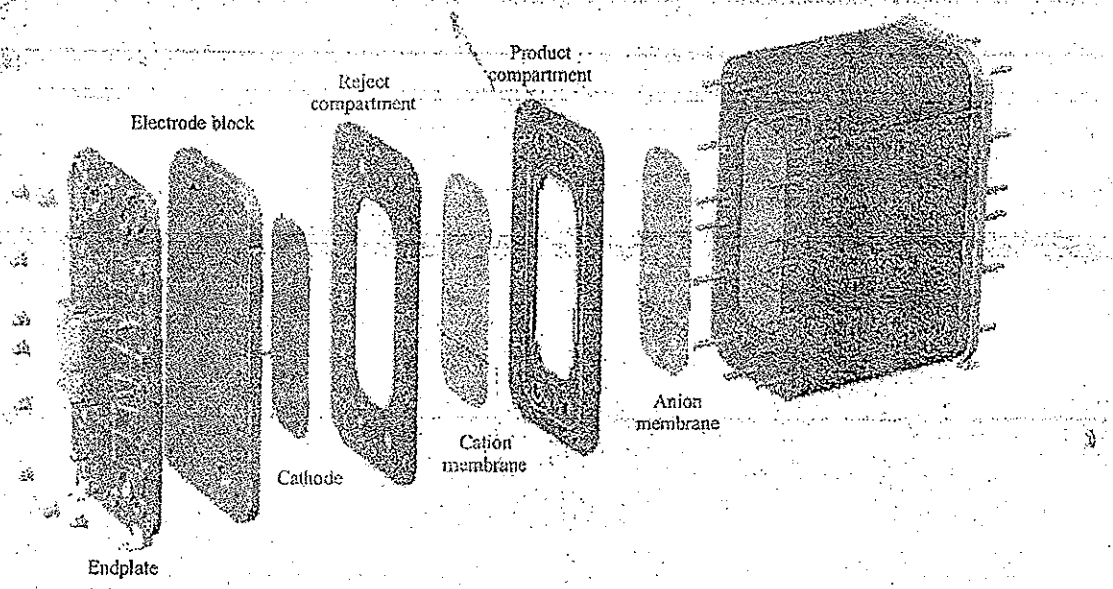


Fig 4. 14 Structure of plate-and-frame EDI

simple startup and operation, module replacement convenience, output water with higher purity, higher recovery rate, small floor occupation area, low risk of microbial contamination, etc. therefore, it is very favorable for environment protection and energy conservation. At the same time, the resin consumption of EDI system is only 5% of that of traditional mixed-bed process, so EDI system is economical and high efficient. As most gases that dissolving in water (e. g. carbon dioxide) have weak ionization characteristics, EDI system can remove them effectively.

EDI unit has now been widely accepted by and used in pharmaceutical industry. At present, EDI unit can be classified into plate-and-frame type and spiral-wound type according to the structure. Fig 4. 14 shows the internal structure of a typical plate-and-frame EDI unit. There are recycling of concentrate and recycling of non-concentrate according to the operation process;

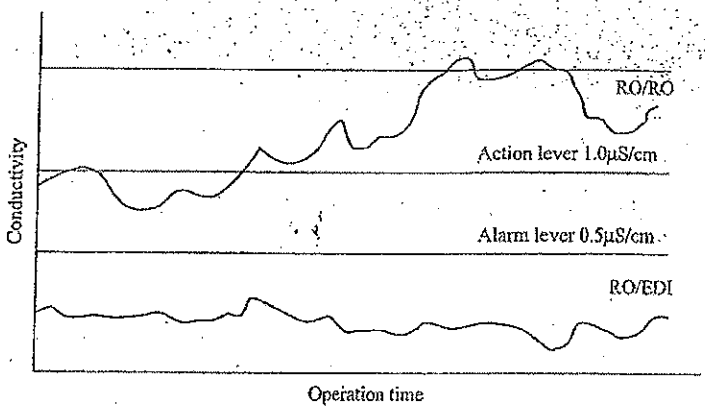


Fig 4. 15 RO/EDI and RO/RO

there are also high-voltage and low-current as well as low-voltage and high-current according to different power supply requirements; the customer can make reasonable selection according to the actual situation.

According to USP, the conductivity of purified water should not be higher than 1. 3 μS/cm (25 ℃); compared with RO/RO system, the conductivity value of RO/EDI system is more stable and remains at a lower level (Fig 4. 15); therefore, RO/EDI has been widely used and promoted by more and more pharmaceutical enterprises in order to realize more safe and stable purified water quality.

Chapter 5

Generation of Water for Injection

WFI is one of the most important and widely-used raw materials for sterile production processes. At the same time, a large amount of WFI is used for washing the equipment or system. According to the US FDA cGMP stipulations, WFI in compliance with pharmacopeia standards must be used as the final rinse water for sterile pharmaceutical production. Each country or region has different requirements for WFI quality indexes; please refer to the Table 5.1 below for main WFI quality indexes of each country or region's pharmacopeia, including the *US Pharmacopeia* (USP), *European Pharmacopeia* (EP), *Chinese Pharmacopeia* (ChP), *Indian Pharmacopeia* (IP), and *Japanese Pharmacopeia* (JP). Appropriate technology should be selected to control WFI quality indexes to guarantee that the pharmacopeia requirements can be met. For example, filters in the main pipeline of a water system may become the ideal places for microorganism growth due to improper management; therefore, it is not recommended to install the main pipeline filter at the outlet of the purified water tank. Due to the peculiarities of pharmaceutical products, enough measures should be taken when designing WFI generation machines for controlling inorganic matters, organic matters, microorganisms, and endotoxins in the water; at the same time, reasonable and effective actions should be taken for risk prevention and rectification.

The following factors should be taken into consideration for the selection of a WFI generation process: raw water quality, output water quality, reliability of the machine process operation, prevention and disinfection measures for system microbial contamination, professional qualifications of machine operators, reliability and adaptability to variations of raw water quality,

Table 5.1 Pharmacopeia standards for WFI

Parameters①	USP	EP	CP	IP	JP
Conductivity(at 25 ℃)②/(μS/cm)	1.3(Three-step method)	1.3(Three-step method)	Same with EP	Same with USP	Same with USP
TOC/(mg/L)	0.5③	Same with USP	Same with USP	Same with USP	Same with USP
Total number of colonies④/(CFU/mL)	10	10	10	10	10
Nitrate/ppm	0.25	0.25	0.25	0.25	0.25
Heavy metal/ppm	—	0.2	0.06	0.2	—
Acidity	—	—	0.1	According to PW requirement	—
Nitrite/ppm	—	—	—	Indicator	—
Ammonium/ppm	—	—	5.0-7.0	—	—
Readily oxidizable substance/(/100 mL)	—	—	—	—	—
Nonvolatile matters/(mg/ml)	—	—	1/100	—	—

Note:

① Unless otherwise stated, all data are the maximum values.

② Conductivity limit values have a relationship with temperature. For three-step test method in USP, it is allowed to use laboratory test method if online conductivity test value exceeds the limit. Please refer to <645> *Conductivity* for the details.

③ Real response value of limit value is the one that being obtained after standard solution parameter value is subtracted by that of blank water. Please refer to <643> *TOC* for the details.

④ The requirements for microbial testing are the same for all pharmacopeias except that EP has included test requirements into Production section; please refer to USP<1231> for the details.

convenience for routine equipment maintenance, output water recovery rate and blowdown treatment, daily operation and maintenance costs, and system monitoring ability. A WFI generation system is mainly used for transforming raw water into WFI in compliance with Pharmacopeia requirements through various "purification" processes. As a WFI storage and distribution unit has no purification function, the output water quality of a WFI generation system should be higher than pharmacopeia requirements. For example, the limit value of endotoxin content is 0.25 EU/ml according to the USP, so the enterprises will generally have a limit value of 0.1 EU/ml as the output water quality requirement for WFI generation system.

WFI can be generated by distillation, purification (in combination of RO and terminal ultrafiltration), etc. Each country has very specific stipulations on WFI production methods:

- According to the *US Pharmacopeia*, WFI should be produced by distillation or some equivalent or better purification technology with respect to the removal of chemicals and microorganisms;
- According to the *Chinese Pharmacopeia*, WFI is the water produced from purified water by distillation.
- According to the *European Pharmacopeia*, WFI should be produced from drinking water meeting regulatory standards or produced by distillation of purified water. The parts of the distillation equipment in contact with water should be made of neutral glass, quartz, or appropriate metals; it should be equipped with devices for effectively preventing entrainment of liquid droplets.

If the endotoxin content in injections exceeds the limit specified in the Pharmacopeia, there is a possibility for pyrogen reaction. The major function of a water distiller is to remove endotoxins from the water; at the same time, the microbial content in the water can be significantly controlled.

An internationally established method for producing WFI is by distilling raw water, i.e. drinking water or purified water; according to the ChP and EP, the feed water of a water distiller must be purified water; according to the USP, the feed water should be at least drinking water. A water distiller is a reliable machine that is based on phase change and sometimes operates at high temperature. Pure steam can be generated by the same water distiller or a separate pure steam generator. There are a variety of water distillers, which have a similar basic structure; they generally consist of evaporator, separator, condenser, etc.

For a long term, the production of WFI has been restricted to the distillation method. With the development of the pharmaceutical industry and the establishment of quality management systems, some purification technologies (such as terminal ultrafiltration and reverse osmosis) can now be used for WFI production in the US, Japan, and other countries or regions only if such technologies can be verified to be as effective and reliable as the distillation method. However, as WFI generation by RO and ultrafiltration is done by membrane filtration at normal temperature, the breeding of microorganisms cannot be inhibited effectively in comparison to the high temperature WFI produced by the distillation method. The enterprises must perform a lot of maintenance work and pay close attention to the risk of microbial contamination.

In 2016, the Chinese Pharmacopoeia Commission has widely solicited comments from the pharmaceutical industry; many pharmaceutical enterprises, engineering companies, equipment manufacturers, and SFDA professionals participated in the discussion to prepare for the revision of the new pharmacopeia standards for pharmaceutical water. With the development of pharmaceutical water system products in China, new types of WFI processes combining ultrafiltration and purification will be considered and promoted in the future.

5.1 Pyrogens

WFI is one of the most critical and essential raw materials for producing injections; and pyrogen control is particularly critical. Pyrogen refers to a type of pyrogenic substance that can cause an abnormal body temperature rise of warm-blooded animals. Generally speaking, pyrogens mainly come from the releasing matters of the inclusion body after the death of bacteria. The most important administration mode of sterile injections is intravenous injection; if the injection solution contains some pyrogens, a pyrogenic reaction is very likely to happen. Main symptoms of pyrogenic reaction occurring during perfusion or after perfusion are as follows: the patients will feel cold and shiver, have pale face, cold limbs, and high body temperature of over 40 ℃; in severe cases, the patient

may feel like vomiting, have headaches, and joint pain in the four limbs, grey and pale skin, low blood pressure, are in a state of coma and shock, which can even be life threatening. Generally, if the content of bacterial endotoxins from an injection solution injected into the human body is 1 μg/kg, a pyrogenic reaction may occur.

Pyrogens consist of bacterial pyrogens, endogenous macromolecule pyrogens, endogenous micromolecule pyrogens, and chemical pyrogens. The term "pyrogen" mentioned in this book mainly refers to bacterial pyrogens, which are the metabolic products of some bacteria, dead bacteria, and endotoxins. The products of gram-negative bacilli have the most powerful pyrogenicity; gram-positive bacilli rank the second; gram positive cocci are a little weaker; moulds, yeasts, and even viruses can also produce pyrogens. Bacterial endotoxins can combine with live microorganisms, dead microorganism fragments, or free molecules. Free endotoxins can be released from the surface of cells or the biofilm produced by the pharmaceutical water systems; or enter the pharmaceutical solution preparation system from the raw water.

Bacterial endotoxins are compounds of lipopolysaccharides and micro-proteins in the cell wall of gram negative bacteria (Fig 5.1). They are not bacteria or metabolic products of bacteria, but matters with endotoxin bioactivity being released after the death or decomposition of bacteria. The amount of bacterial endotoxin can be measured in EU; 1 EU is equivalent to 1 IU (international unit of endotoxin).

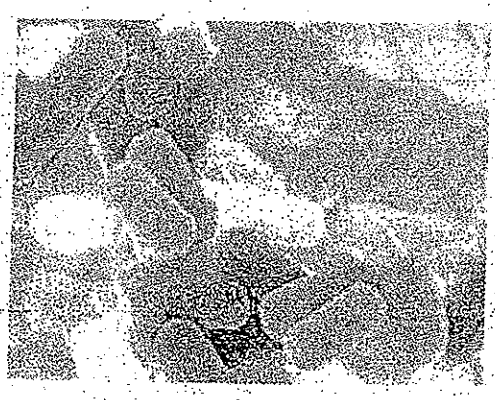


Fig 5.1 Bacterial endotoxin

Endotoxins are one type of pyrogens, but not all pyrogens are endotoxins. The European Pharmacopoeia Commission has pointed out: *"Strictly speaking, not all pyrogens have lipopolysaccharides structure, but all known bacterial endotoxin lipopolysaccharides have pyrogenic activity"*. Therefore, pyrogens and bacterial endotoxins not only have a lot in common but also some differences. There are corresponding inspection methods for both pyrogens and bacterial endotoxins. The pyrogen testing method is as follows: intravenously inject a certain dose of test solution into a rabbit's body; and observe the increase of the rabbit's body temperature at a specified time to determine if the limit of pyrogens in the test solution meets the stipulation. The bacterial endotoxins testing method refers to the inspection or quantification of bacterial endotoxins produced from gram-negative bacteria using tachypleus amebocyte lysate (TAL) to determine if the limit of bacterial endotoxins in the test solution meets the stipulation.

In comparison to the pyrogen inspection method using a rabbit, the bacterial endotoxins inspection method has the following advantages: good sensitivity, quickness, simple operation, good reproducibility, and accurate results. At present, the bacterial endotoxins testing method is widely used in the western medicine and biological products. But it should also be pointed out that the bacterial endotoxins test is a complex enzymatic reaction process; subtle changes of the production process may cause an increase of interference. Generally, the traditional pyrogens testing method using a rabbit is used for TCM injections due to their complex composition, multiple influencing factors, etc. Moreover, for some drugs with detoxification and body temperature decrease effects, the drug will interfere with the physiological activity of the rabbit and cause a body temperature decrease; the testing method with the rabbit may not be accurate; therefore, the bacterial endotoxins testing method should be considered.

There are two bacterial endotoxins testing methods, i.e. the sol-gel process and the photometric method; either method can be used for the testing of test solutions; in case of any conflict, the results of the sol-gel process will prevail unless otherwise specified. The sol-gel process is a method which uses the agglutination reaction between TAL and endotoxins to inspect or semi-quantify endotoxins. Photometric methods include turbidimetry and the chromogenic technique; turbidimetry refers to a method of determining the endotoxins content by inspecting the turbidity change during the reaction process of TAL and endotoxins; the chromogenic technique refers to a determination method using

the coagulase produced during the reaction process of TAL and endotoxins; the coagulase can release chromogen enabling a specific substrate to develop color.

During the bacterial endotoxins testing process, microorganisms and endotoxins contamination should be avoided. The water used for bacterial endotoxin testing is sterilized WFI with endotoxin content of less than 0.015 EU/ml (for sol-gel process) or 0.005 EU/ml (for photometric method) and without interference to endotoxins testing; the utensils to be used should be treated to remove any potential exogenous endotoxins; dry-heat sterilization is normally used for heat resistant utensils for a period of over 30 minutes at 250 ℃; other appropriate methods without interference with the bacterial endotoxins testing can also be used. If plastic instruments (e.g. micro-hole plate and nipples for microloader) are used, they should be specified to be free from endotoxins and have no interference with the testing.

The bacterial endotoxin limit of drugs and biological products is generally determined according to $L = K/M$, in which, L is the bacterial endotoxins limit of the test solution, usually represented by EU/ml, EU/mg or EU/U (active unit); K is the maximum acceptable endotoxin dosage for each kg of human body weight per hour, being represented by EU/(kg · h); for injections, $K = 5$ EU/(kg · h); for radiopharmaceutical injections, $K = 2.5$ EU/(kg · h); for intrathecal injections, $K = 0.2$ EU/(kg · h); M is the maximum dosage of the test solution for each kg of human body weight per hour, being represented by ml/(kg · h), mg/(kg · h) or U/(kg · h); it is assumed that the average human body weight is 60 kg and the average human body surface area is 1.62 m^2. The injection time will be considered one hour if it is less than one hour; the dosage of the test solution for each square meter of human body surface area is multiplied by 0.027 to obtain the dosage of each kg of human body weight (M).

Different from the microbial limit of sterile products, the limit of the bacterial endotoxins of injections is not zero; during the production process of sterile injections, various effective actions need to be taken to control the level of bacterial endotoxins in the final products. The limits of bacterial endotoxins of different injections vary from each other; for example, the limit of bacterial endotoxins of the pethidine hydrochloride injection is 0.20 EU/ml, that of sterile WFI is 0.25 EU/ml, and that of sodium chloride injections is 0.50 EU/ml. The combined usage of several drugs is not considered for the bacterial endotoxin limit; but the content of endotoxins in the drug is generally far lower than the limit; and the internal control standards of drug manufacturers are stricter than the registered standard, so the limit of endotoxins stipulated in pharmacopeia is also called the maximum allowed endotoxins concentration.

Bacterial endotoxins mainly have the following characteristics: ①bacterial endotoxins can dissolve in water, some measures should be taken to remove bacterial endotoxins from injections with water as a solvent; ②bacterial endotoxins have a small size in the range of 1 to 5 nm, so they can be removed by a ultrafiltration or RO membrane; activated carbon filters can adsorb and filter out bacterial endotoxins; ③endotoxins are non-volatile matters but can dissolve in water, so they can enter distilled water with water steam drops during the distillation process; ④bacterial endotoxins are highly heat resistant and will not be affected after being heated for one hour at 60 ℃; and most endotoxins will not degrade at 100 ℃; bacterial endotoxins can only be thoroughly destroyed when being heated for 3 to 4 hours at 180 ℃, for 30 to 45 minutes at 250 ℃, or for 1 minute at 650 ℃. The sterilizing conditions used for general injections cannot thoroughly destroy bacterial endotoxins; ⑤ bacterial endotoxins can be destroyed by strong acids, strong alkali, strong oxidizers, ultrasonic waves, etc. and ions exchange resins can adsorb bacterial endotoxins.

Pyrogens treatment can be classified into two categories: inactivation processes and separation processes. Inactivation processes mainly include dry heat sterilization, acid treatment, alkali treatment, oxidant treatment, alkylating agent treatment, etc. For example, a dry heat sterilizer can eliminate bacterial endotoxins at 250 ℃ for a period of over 30 minutes; a CIP workstation can eliminate bacterial endotoxins in pharmaceutical solution preparation systems by means of recycled washing with a 2% alkaline solution. Separation processes mainly include adsorption, membrane separation, and distillation; for example, when purified water is generated, bacterial endotoxins are controlled by activated carbon adsorption, ultrafiltration, RO treatment, and distillation; moreover, adsorption, membrane separation, and distillation methods have been proven in the routine operation of WFI production

processes for removing bacterial endotoxins in the raw water.

a. The adsorption method. It can effectively remove pyrogens; common adsorption materials include activated carbon, anion exchange resins, barium sulfate, asbestos, etc. The *US Pharmacopeia* (USP) has incorporated the methods for removing pyrogens by use of activated carbon and macromolecule anion exchange resins. In purified water generation processes, activated carbon adsorption is the most common method for removing pyrogens and is usually used in combination with a membrane filter to prevent activated carbon entering the next working procedure; if the contamination level of bacterial endotoxins in the raw water is relatively low, the usage of a macromplecule anion exchange resin will be more appropriate for removing pyrogens.

b. Membrane separation. Ultrafiltration, microporous membrane filtration, and RO treatment are all membrane separation technologies; they are different processes, but there is no distinct limit between them; one end of ultrafiltration membrane with larger pore size overlaps with microporous filtration membrane; while the other end with smaller pore size overlaps with RO membrane. The USP and JP regard the combination method of RO and ultrafiltration as the legal method for producing WFI. At the same time, the *EU Pharmacopeia* has passed a resolution to permit the application of membrane filtration in producing WFI and this resolution will formally take effect in April, 2017, which underscores the maturity of the membrane separation technology used in removing pyrogens. RO treatment, ultrafiltration, and microporous membrane filtration have some similarities; that is, particles as ions, molecules, gels, pyrogens, and microorganisms in the water will be separated using the specific performance characteristics of various membranes with a differential pressure; but their separation mechanisms and targets are different.

RO membranes have the smallest pore sizes, generally in the range of 100 to 200 Da based on the molecular weight of the blocked contaminants (including pyrogens). The molecular weight of pyrogens is over 50,000 Da and the diameter is generally in the range of 1 to 50 μm, so the pyrogens can be effectively removed. A RO membrane only allows the separation of inorganic ions of below 1 nm, so it has a good desalination function; but ultrafiltration and microporous membrane filtration don't have a desalination function.

Microporous membrane filtration has a limited role in removing pyrogens and can retain the pyrogenic substances with larger diameter by use of screening, static absorption, and bridging principles. It should be pointed out that this method is not perfect, as pyrogenic substances with a smaller diameter will pass through a 0.22 μm microporous filtration membrane; very small size pyrogens can penetrate a 0.025 μm filtration membrane; and the tiniest pyrogens can even penetrate all microporous filtration membranes. The pyrogenicity will increase with the molecular weight of the pyrogen, so from an objective viewpoint, microporous filtration membrane can play a positive role in retaining some pyrogens, but it cannot be used separately as a reliable method; therefore, the enterprises should control the indexes of bacterial endotoxins during the production process to comply with the pharmacopeia's limit requirements.

As shown in the electronic scanning image of a non-homogeneous ultrafiltration membrane, the ultrafiltration media has a structure similar to a screen, but filtration only happens on the surface of the filtration membrane. Different from the RO process, ultrafiltration removes endotoxins mainly relying on a mechanical method; the following three processes happen simultaneously during ultrafiltration; the matters to be separated are adsorbed and retained, they are also captured or entrapped on the membrane surface, and then are retained by the screen. The pore size of an ultrafiltration membrane is roughly in the range of 0.005 to 1 μm and the sizes of bacteria are in the range of 0.2 to 800 μm, so an ultrafiltration membrane can eliminate bacteria. Furthermore, the molecular weight of pyrogens having pyrogenic effect on the human body is in the range of 800,000 to 1,000,000 Da; the naturally existing pyrogen colony is a mixed body; and the smaller parts are only 1 to 3 μm; therefore, the molecular weight level of an ultrafiltration membrane for retaining pyrogens should be in the range of 10,000 to 80,000 Da for effectively eliminating pyrogens. The difference between ultrafiltration and microporous filtration is as follows; microporous membrane filtration is a static filtration process; the solution will be agitated to eliminate the layer of concentration polarization; while ultrafiltration is a dynamic process; the surface of the ultrafiltration surface will be flushed continuously by flowing solution, so it is not easy to form a layer of concentra-

tion polarization.

c. The distillation method. As bacterial endotoxins are non-volatile, the distillation method is always the most effective, safest, and most commonly used method; distillation is a purification process for removing chemicals and organisms from feed water using the principle of the liquid-vapor phase change and physical separation method. Through the distillation process, endotoxin content in feed water can be reduced by at least 99.99%.

5.2 The Distillation Method

According to the ChP, JP, EP, and USP, the content of endotoxins in WFI must not exceed 0.25 EU/ml; distillation and membrane filtration are two main methods for producing WFI; and distillation is the preferred method for producing WFI.

WFI generation equipment for generating WFI by use of distillation mainly includes tower type water distillers, thermocompression water distillers, and multi-effect water stills (see Table 5.2). Before the 1950s, the single-effect /tower type distilled water machine was mainly used in foreign countries; it was a first-generation distilled water machine with a high energy consumption index and serious resources waste; moreover, the generated distillate had poor quality due to the now outdated production process and demister. Since the 1960s, the thermocompression water distiller has been developed in foreign countries; compared with tower type distilled water machine, it has such obvious advantages as wide range of output, energy conservation, and water saving. The advantages of a thermocompression water distiller are even more prominent when high production capacity is required. With the continuous development of the compressor technology, the operation of thermocompression water distillers is becoming more stable. At present, thermocompression water distillers have a relatively wide application in foreign countries and have been gradually accepted and promoted in China. In 1971, the first multi-effect water still in the world was successfully developed and has the following advantages: advanced technological process, high performance-price ratio, simple and reliable operation, low noise, and energy conservation. Compared with the first generation thermocompression water distiller, the maintenance of a multi-effect water still is very convenient and the operation is stable. Therefore, the multi-effect water still has been highly regarded by global pharmaceutical enterprises since it was initially launched in the market. Now it has become the most prevalent WFI production machine.

Table 5.2 Comparison of distilled water machines

Performance	Single-effect water still	Thermocompression water distiller	Multi-effect water still
Electric energy consumption	Low	High	Low
Steam consumption	Very high	Low	High
Cooling water consumption	Very high	Low	High
Raw water requirement	High	Moderate	High
Investment cost	Low	Moderate①	Moderate
Energy consumption	High	Low	Moderate
Operation temperature	Middle	Middle	High
Capacity of a single machine	Low	High②	Moderate②
Machine noise	Low	Relatively high③	Low
Scaling risk	Middle	Middle	High
Maintenance of the compressor	None	Yes	None

① The performance-price ratio of the investment increases with the production capacity of the thermocompression water distiller;

② The maximum capacity of a thermocompression water distiller may exceed 20000 L/h and that of a multi-effect water still is about 10000 L/h;

③ The noise level of a thermocompression water distiller is related to the type of the compressor; the noise produced by a low speed direct-driven compressor is relatively low; and that of a high speed centrifugal compressor is relatively high.

Single-effect water stills and multi-effect water stills generate WFI mainly by consuming plant steam, but a thermocompression water distiller produces WFI mainly by consuming electric energy and an appropriate amount of plant steam. A study done by a foreign competent authority shows: if the raw water temperature of a single-effect water still is 60 °F (15.6 ℃), the required consumption of plant steam energy is 2,701 kJ/kg for producing one pound of high temperature WFI (82 ℃); the consumption of plant steam energy of a five-effect water still is 988 kJ/kg for producing one pound of high temperature WFI; and that of a thermocompression water distiller is only 320 kJ/kg for producing one pound of high temperature WFI; if the

output water is at normal temperature, the consumption of plant steam energy of the thermocompression water distiller is only 119 kJ/kg for producing one pound of WFI.

5.2.1 Single-effect Water Still

A single-effect water still is also known as a tower type water distiller and is mainly used by laboratories or scientific institutions for producing a small quantity of WFI. The basic structure of a tower type water distiller is as shown in Fig 5.2 and mainly consists of an evaporation kettle, demister, and condenser.

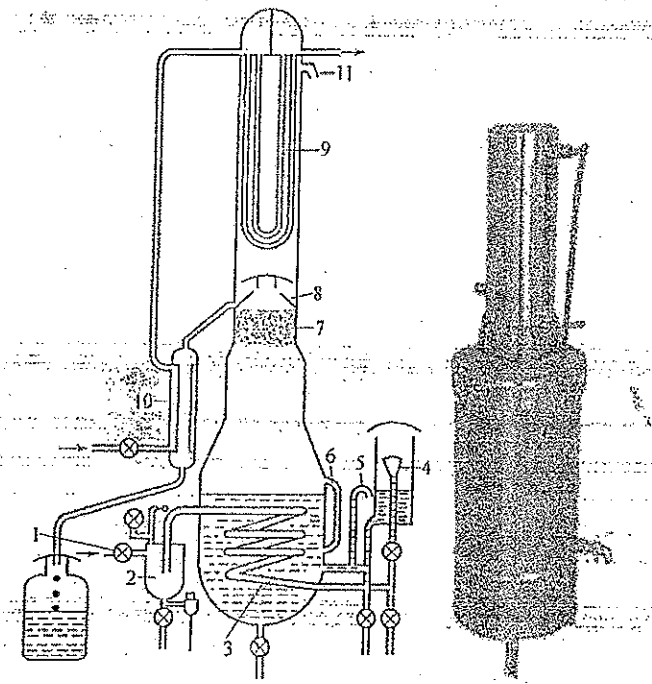


Fig 5.2 Structural schematic drawing of a tower type water distiller

1—steam inlet; 2—steam selector; 3—heating coil; 4—waste gas vent; 5—overflow pipe; 6—gauge glass; 7—demister; 8—water shield; 9—primary condenser; 10—secondary condenser; 11—vent hole

The production steps of a single-effect water still are relatively simple; first, the evaporation kettle is filled with deionized water or purified water until almost full. Plant steam is introduced from the inlet and goes through the steam selector to remove entrained water droplets before entering the heating coil for heat exchange; after the heat is released, the plant steam will be transformed into steam condensate and sprayed into a waste gas remover; the remover (which is filled with neutral rigid short glass fiber) is used to increase the contact surface between the steam condensate and air; the condensate gas and volatile gas (e.g. carbon dioxide) will escape; the steam condensate flows into the evaporation kettle again to supplement some water in the kettle for evaporation; surplus water will be drained from the overflow pipe; the distillate in the kettle will continue evaporating due to being heated by the coil and the vapor will go through the demister (consisting of baffle plate and neutral glass tube); the steam will pass through the barrier layer; the boiling foam and most droplets will be blocked by the barrier and flow towards the evaporation kettle; the steam will rise continuously; when it meets the arc-shaped water shield, the droplets will once again be retained and separated, but the steam will bypass the baffle plate and continue rising; the rising steam will first be condensed into water in the U-shaped condenser (primary condenser) on the top of the tower; the condensate will drop on the water shield and will be accumulated in the groove around the water shield; then it will flow into the secondary condenser for being further cooled into double-distilled water; non-condensable gases from the primary condenser will be exhausted from the vent hole on the top of the tower; as a tower-type water distiller only has one evaporation process, it has relatively high steam consumption; it has been prohibited to be used for industrial production in China.

5.2.2 Multi-effect Water Still

The working principle of a multi-effect water still is as follows: fully-preheated purified water goes through multi-stage evaporation and condensation to remove non-condensable gases and foreign matters to obtain high purity WFI. A multi-effect water still is superior to the single-effect water still with respect to energy conservation and environmental protection; compared to single-effect water stills, multi-effect water stills have improved the utilization rate of plant steam and cooling water and greatly improved the production capacity to energy consumption ratio; at the same time, the temperature of the output water of multi-effect water still is relatively high, which is favorable for inhibiting the growth of microorganisms in WFI; the occupation area of the machine is small and the maintenance is relatively simple; now it has become the prevailing equipment for producing WFI in the pharmaceutical industry.

A multi-effect water still usually consists of multi-

ple evaporative heat exchangers, separator, preheater, two condensers, valves, instruments, and control devices. During the multi-stage evaporation and condensation process, only the first-effect evaporator needs external heat sources for heating; the condensation of pure steam from the last effect evaporator and WFI from each effect of the evaporator is achieved through the cooling of external cooling media; therefore, it has a very evident energy-saving effect.

Ina multi-effect water still, the purified steam from each effect of the evaporator is used for heating and evaporating the feed water and is consequently transformed into WFI due to phase change. The number of effects for a conventional multi-effect water still is three to eight; each effect consists of one evaporator, one separator, and one preheater; the energy-saving result increases with the number of effects. Certainly, if it is required to reduce the consumption of steam and cooling water with a constant WFI output, the number of effects must be increased, so the investment cost will also be increased. Due to such considerations, a joint decision should be made by the user and the manufacturer for choosing an appropriate number of effects.

In order to prevent cross contamination in the system, the first-effect evaporator, all preheaters and condensers should adopt a double-tube sheet design. The most advanced double-expansion joint technology in the world is used for the inner tube sheet and outer tube sheet (Fig 5.3); it is a physical machining method. The tube is connected to the tube sheet by the tube expander; the machining precision should be high; and this technology can be applied to clean machines or systems with a working pressure of no more than 10 bar. As welding operations are avoided, the double-expansion joint method can completely eliminate chemical intergranular corrosion due to the welding of the heat exchanger and the risk of leakage from the heat exchanger is extremely low; therefore, the service life of a multi-effect water still is greatly extended.

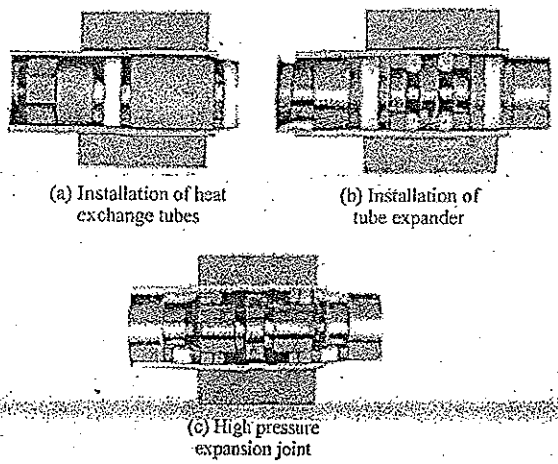


Fig 5.3 Double-expansion joint technology

The typical working principle of a multi-effect water still (Fig 5.4) is as follows: the raw water is heated by the mixture of pure steam and distillate in the second-effect condenser and then fed to each effect preheater for being heated by secondary steam and distillate; after that, it goes through the distributor on the top of the first-effect column evaporator for removing non-condensable gases and being uniformly distributed into evaporation tubes; and a layer of uniform liquid film will be formed in the evaporation tubes; it will exchange heat with the plant steam flowing on the outer wall of the tubes to evaporate into steam rapidly, which will move downwards to the bottom of the column under differential pressure; unevaporated raw water will be transported to the next effect as the feed water of the next effect evaporator; the subsequent effects have a similar operation process; unevaporated water will be fed to the next effect; the liquid remained unevaporated in the last effect of evaporator will be removed as blowdown. The raw water will be evaporated into pure steam, which will be led into a pure steam pipeline from the steam-liquid separator at the bottom of the evaporator as the heat source of the next effect; the steam will be condensed into WFI after releasing heat in the next effect evaporator; each effect has a similar operation process. The mixture of WFI and pure steam will become WFI with a set temperature after passing through the first stage cooling (with purified water as coolant) and the second stage cooling (with cooling water as coolant); the distillate is tested by an online conductivity meter and if qualified will be discharged as WFI; unqualified distillate will be automatically drained.

The heat energy of the steam from the first-effect evaporation column will be used for heating the next effect evaporation column; the repetitive usage of heat energy remarkably reduces energy consumption. The non-evaporated feed water of the first column will be used as the preheated feed water for the next column. The steam generated in the last column will be condensed mainly by the cooling of the feed water; therefore, only a small amount of cooling water is required.

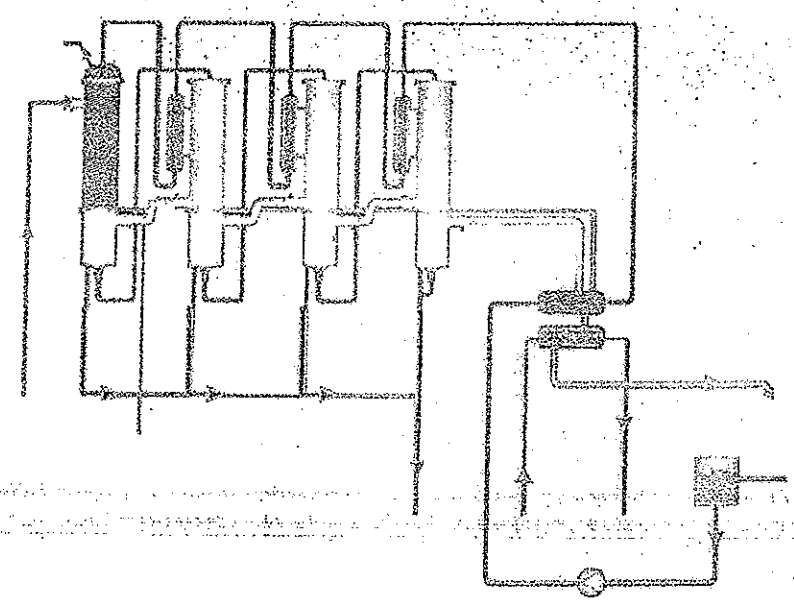


Fig 5.4 Schematic drawing of multi-effect water still

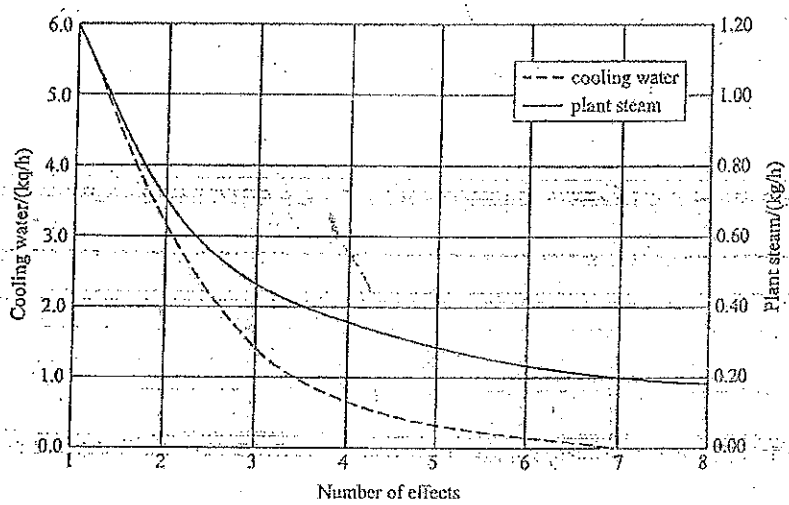


Fig 5.5 Performance curve of a multi-effect water still

The feed water will be preheated gradually by the preheaters between various evaporation columns, reducing energy consumption. The efficiency of a multi-effect water still depends on the pressure of the heating steam and the number of effects. The output of distillate increases with the pressure of the plant steam; and the utilization rate of heat energy increases with the number of effects. Fig 5.5 shows the typical performance curve of one multi-effect water still, which is based on 15 ℃ feed water and cooling water, 8 bar plant steam, and 99 ℃ WFI output water. It can be seen from the figure that the consumption of utilities and cooling water can be reduced by an increase of the number of effects. It is generally suggested that a multi-effect water still of higher production capacity should have more columns to reduce utilities consumption and daily operation costs.

Liquid film-forming is a key technology of the multi-effect water still. The quality of liquid film-forming in the tubes of a MWS is very important for enhancing the heat exchange effect, reducing energy consumption, and improving steam quality. Taking the first effect evaporation column as an example, the purified water is added from the top of the heating section and flows uniformly into the heating tubes through the liquid distributor at the tube end; the solution will form a liquid film on the inner wall of the tubes and flow downwards under gravity and is evaporated. In order to form an uniform film on the tube wall, a proper liquid distributor must be installed on the top of the heater to form the uniform liquid film, increase evaporation efficiency, and reduce mist entrainment.

Steam-liquid separation is another key technology of a multi-effect water still. Distillation has a good function of removing non-volatile organic and inorganic matters from raw water, including suspended matters, gels, bacteria, viruses, pyrogens, and other foreign matters. At present, the major separation technologies for MWS include gravity separation, impaction separation by guide plate, and spiral separation.

a. Gravity separation. It is a method for steam-liquid separation using of the gravity of the droplets. After high-speed steam stream from the tubes passes through the flash chamber, the speed is reduced to a certain value. The steam stream flows upward after a 180° turn; and a certain part of the droplets will be separated from the stream and settle down. Gravity separation can reduce the residual droplets in the steam stream to less than 3%; but gravity settling only applies to droplets with a diameter of more than 50 μm.

b. Impact separation by guide plate. It is a type of separation technology with better separation effect. When a steam stream with liquid droplets passes through the channel, the droplets will impact the guide plate and be left on it; finally, they will be drained from the drainage pipe in the form of a liquid film. The impact separator by guide plate has a large steam operation resistance; as this technology is relatively outdated and the quality risk is quite large, its usage in MWS is now very rare.

c. Spiral separation. It is a physical separation method and can effectively achieve steam-liquid separation. Pyrogens are soluble in water and only present in water and the steam/water mixed droplets. Due to the density difference between the liquid droplets and the steam, there will be a very large difference between the centrifugal forces acting on the liquid droplets and steam during high speed movement along a spiral trajectory; therefore, steam-liquid separation can be realized. Spiral separation can be classified into inner spiral separation and outer spiral separation according to the radius of the spiral trajectory and the difference of achievable centrifugal forces.

Due to the structural restriction of the inner spiral separation, its centrifugal acceleration is lower than that of the outer spiral separation and its demisting efficiency is not high, so a wire mesh demister is usually required for further separation. The wire mesh demister can realize the separation purpose using inertial impaction, gas adsorption, retaining function, and electrostatic adsorption. For liquid droplets of over 5 μm, the separation efficiency by wire mesh demister can be more than 98%; due to larger steam operation resistance, the heat energy loss of a wire mesh demister is relatively large; at the same time, in order to guarantee the demisting effect of a wire mesh demister, there must be enough air flow flux, so the volume of the heat exchange column will be relatively larger.

The outer spiral type is a more advanced and efficient steam-liquid separating unit; after the steam stream passes through the separator, the swirling air flow will produce a very large centrifugal force enough to separate the liquid droplets; a very good separation result can be achieved. At present, the most advanced MWS in the world produce WFI mainly by the combined use of falling film flash evaporation, 180° directional change and gravity separation, and outer spiral centrifugal separation. The endotoxins content in the output water is less than 0.01 EU/ml and very stable, which can effectively guarantee the quality of WFI.

5.2.3 Vapor Compression Water Distiller

The mechanical vapor compression water distiller is also known as vapor compression still; it uses an electric motor as the power source for steam compression. Vapor compression distillation is a method of evaporating water in which the energy in the evaporated water vapor is enhanced by compression and is recovered to produce additional vapor. Water vapor generated from liquid boiled inside a bank of tubes is withdrawn by a compressor and discharged, at an increased pressure and temperature, to the outside of the tube bank. The latent heat of the condensing water vapor is transferred through the tubes where it is utilized as heat of vaporization to boil additional liquid. More vapor is thus generated, and a continuous process is sustained. WFI will be produced.

MVR is an energy saving technology; it reuses the energy of the steam produced by the machine itself reducing the requirements for the external energy source. The working principle is as follows: a steam compressor is used for compressing the steam generated by the evaporation system to increase the steam enthalpy; the compressed steam with high enthalpy enters the evaporation system as a heat source, this is a conservation of the latent heat. This recycling of the latent

heat will reduce the usage of plant steam. Plant steam will only be used for the initial startup of the system, supplementing heat loss, and supplementing the required enthalpy for the temperature difference between feed water and inlet water into the evaporator, so that the consumption of plant steam for the evaporator can be remarkably reduced to achieve energy conservation.

Ina well-insulated compressor, the vapor is compressed adiabatically. For most applications using vapor compression distillation in the temperature range of 100 ℃ or lower, water vapor can be assumed to behave as an ideal gas. Using this assumption, the specific energy input to the vapor by the compressor can be evaluated using the relation $PV/T=$ constant. Where P represents gas pressure, V represents gas volume and T is the adiabatic index. For a reversible adiabatic process, the temperature of the steam increases as pressure increases and the volume decreases during compression. The higher-pressure steam then condenses to release the latent heat for steam production in the evaporator section.

The most critical equipment for MVR technology is the compressor for increasing gas pressure. Compressor refers to the machinery for compressing the gases to increase gas pressure or deliver the gases. A compressor is also called "gas compressing machine" or "gas pump". It is called "ventilator" if the exhaust pressure is less than 0.02 MPa; it is called "blower" if the exhaust pressure is in the range of 0.02 to 0.2 MPa; and it is called "compressor" only when the exhaust pressure is more than 0.2 MPa (Table 5.3).

Table 5.3 Classification of compressors

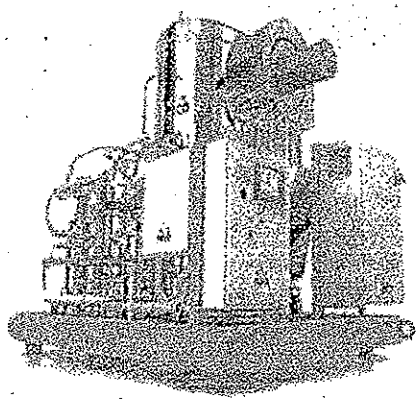
Type	Name	Exhaust pressure (gauge pressure)
Fan	Ventilator	Less than 0.02 MPa
	Blower	0.02 to 0.2 MPa
Compressor	Low pressure compressor	0.2 to 1.0 MPa
	Medium pressure compressor	1.0 to 10 MPa
	High pressure compressor	10 to 100 MPa
	Ultrahigh pressure compressor	Higher than100 MPa

Compressors can be classified into positive displacement compressors and power compressors according to the working principle. A positive displacement compressor directly compresses the gases with variable volume to reduce the volume of the gases and therefore increase the pressure of the gases; the compressor has a working chamber with periodical change of its volume; a power compressor is also called speed-type compressor; it first causes a rise of the gas flow rate, which means the kinetic energy of the gas molecules will be increased; then the gas flow rate will be reduced progressively, so that the kinetic energy can be turned into pressure energy; at the same time, the gas volume will be consequently reduced; the compressor has an impeller for driving the gases to attain the required flow rate.

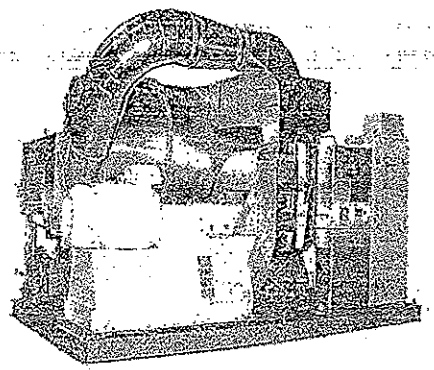
A vapor compression water distiller mainly consists of an evaporator, a centrifugal compressor, a deaerator, heat exchangers, pumps, valves, instruments, controls, a pretreatment system (if necessary) and associated piping.

a. The evaporator. The evaporator is mainly used for heat exchange between the feed water and the compressed steam from the compressor. The compressed steam temperature is higher than that of the feed water; the steam will condense in the evaporator and release latent heat; The pre-heated feed water in the evaporator will absorb the latent heat and evaporate into steam; a large number of heat exchange tubes in the evaporator provides the area for heat exchanging, which is one of the essential factors for the heat exchanging process. Vapor compression water distillers can be classified into vertical type and horizontal type according to the type of evaporator (Fig 5.6). Both types can produce up to 30 ton per hour of WFI. The vertical design is more frequently selected due to design advantages.

b. Compressor. The compressor withdraws the steam produced from the feed water of the evaporator; the mechanical energy will be transformed into steam heat energy using the impeller or other types of compression structures, so that the compressor can realize the transformation from electric energy to mechanical energy and then from mechanical energy to heat energy. Vapor compression distillation is a method of evaporating water in which the energy in the evaporated water vapor is enhanced by compression and is recovered to produce additional vapor. Water vapor generated from liquid boiled inside a bank of tubes is withdrawn by a compressor and discharged, at an increased pressure and temperature, to the outside of the tube bank. The latent heat of the condensing water vapor is transferred through the tubes where it is utilized as heat of vaporization to boil additional liquid.



(a) Vertical type



(b) Horizontal type

Fig 5.6 Types of vapor compression water distiller

Table 5.4 The compressors for vapor Compression Water distillers

Components	Industrial fan	Belt-driven compressor	Direct-drive compressor
Impeller	Air fan with large diameter	Centrifugal compressor with small diameter	
Axial speed of compressor	Slow	Quick	Quick
RPM of the motor	Same with axial speed of the compressor	Standard	Same with axial speed of the compressor
Integrated components	Coupling, gearbox, pipeline system	Motor, compressor pulley, belt	None
System volume	Separate brake	Separate motor and compressor	Compressor with the motor
Lubrication type for compressor bearing	Oil immersion	Oil immersion	Metering oil, Oil Mist system
Maintenance of lubrication system	Frequently	Frequently	Seldom

More vapor is thus generated, and a continuous process is sustained. The high speed centrifugal compressor and low speed centrifugal compressor are the two common and most important types of compressors.

It is traditionally thought that compressors always involve maintenance and reliability problems; but with the demand for high production capacity of WFI, the economic effect brought by a vapor compression water distiller always exceeds the concerns of the enterprises for the compressor; in this case, proper maintenance measures should be taken to alleviate the issues related to compressors; therefore, the core issue for a vapor compression water distiller is how to design the structure of the compressor to improve its efficiency and reliability. The development of the compressors for vapor compression water distillers has gone through three major phases: air blower/industrial fan, belt-driven centrifugal compressor, and variable frequency direct-drive centrifugal compressor (Table 5.4).

In the 1940s to the 1960s, the Roots air blower was used in vapor compression water distillers; afterwards, industrial air fan technology was introduced in succession; the rotating speed of industrial air fans could reach 1,750 to 3,600 r/min; if it was driven by a frequency inverter, the motor speed could be increased to 4,500 r/min; as the above-mentioned technology didn't comply with sanitary requirements, it has been discarded in the pharmaceutical industry; in the late 1960s, the belt-driven centrifugal compressor was developed; it can run at a high speed in the range of 4,500 to 22,000 r/min; a centrifugal compressor is driven by a standard motor belt; compared to a gear drive or other methods, the belt drive has the advantages of relatively low cost and easy replacement. The belt is installed on a pulley; the belt and lubricant oil need to be replaced every 12 months; proper calibration and belt tension are very important for maintaining a long service life; a too tight belt may lead to early failure of the belt, seals, and bearing. Similar to industrial fans, a belt-driven compressor has a noise level of about 85 to 90 dB at a distance of one meter. Over fifty years ago, the invention of the variable frequency direct-driven centrifugal compressor brought new vitality to the development of the vapor compression water distiller; the motor housing of a direct-driven centrifugal compressor is designed to directly receive the impeller axial load; therefore, it doesn't require the intermediate bearing box, which is a common part

of the industrial fan; some heat will be produced during the motor running and the operation process; the motor needs to be cooled by the evaporator through a cooling water pipe in the motor housing; in this way, the noise from the cooling fan can be eliminated; the noise level of new type direct-driven compressors has been reduced to less than 80 dB at full speed operation from the conventional 85 to 90 dB. The machine noise can be fully avoided when controlled by frequency inverter and under lower work load.

The new directly driven variable speed compressor drives have significantly improved the process of vapor compression distillation and how it is used within the pharmaceutical and biotech industries for the production of USP purified water and water for injection. The energy consumption of a given plant is improved by eliminating the inrush current associated with across the line starting and matching the compressor speed to the output demand of the system.

Reductions in maintenance and improvements in reliability can be realized through the elimination of numerous components. These components include belts and sheaves or gears & couplings, intermediate bearing blocks, bearings and seals as well as the re-circulating oil system with its associated filters, coolers, pumps and instrumentation. The direct drive is not dependent upon an operator to properly tension belts or align gears eliminating a possible source of operator induced failure. Eliminating these external transmission systems has reduced the number of bearings and seals within the compressor drive and eliminated the external forces they previously imparted onto the compressor. As a result, the L10 bearing life of a fewer number of smaller bearings has improved to 60,000 hours.

The use of a once through oil mist system in lieu of recirculating large volumes of oil has eliminated the issue of oil leaks. Maintenance is limited to refilling an oil reservoir every six months. The noise associated with earlier systems has been reduced to less than 80 dB by eliminating transmission systems and motor fan cooling. This advancement in technology has significantly improved the VC system such that the economic benefits of the process can exist at lower flow rates because the absolute value of the operational savings is no longer outweighed by concerns associated with maintenance and reliability.

At present, vapor compression water distillers mostly use centrifugal compressors, a type of turbine compressor. During the operation of a centrifugal compressor, the gases in the compressor have a radial movement, which is perpendicular to the compressor shaft. The working principle is as follows: the working wheel with blades rotates on the compressor shaft; the gases entering the working wheel will rotate along with it, which can increase the kinetic energy (speed) and static head (pressure).

c. The preheating unit. It can solve the energy recovery problem very well by using several heat exchangers with different functions. Feed water only has a temperature of about 20 to 25 ℃ when being fed to the vapor compression water distiller; the evaporation temperature of the evaporator is about 100 ℃; the WFI output water temperature is about 80 ℃; and it will be better for the drainage of the concentrate with a lower temperature. Feed water will be finally transformed into WFI and concentrate after being fed into the vapor compression water distiller; before leaving the vapor compression water distiller, the WFI and concentrate will pass through the preheater for transferring the heat to the feed water as much as possible, reducing the consumption of steam for evaporation; at the same time, non-condensing gases will release their heat to the feed water through the decarbonator before being vented; it is required that these heat exchangers adopt a double tube sheet structure or other special design, so that cross contamination between the two media exchanging heat can be avoided.

A mechanical vapor compression process has its major components including an evaporator/condenser, a centrifugal compressor, a deaerator, heat exchangers, pumps, valves, instruments, controls, pretreatment systems and associated piping (Fig 5.7).

In the above described design, a typical VC unit is used for pharmaceutical distillation; softened and dechlorinated water (at a minimum) is boiled inside a bank of tubes. The generated vapor then passes through a mist separator to remove any impurities within the vapor generated from the feed water supply. The pure vapor enters the compressor, at a controlled saturation pressure (and consequently temperature), where compression takes place resulting in a higher saturation pressure. The higher-pressure (and temperature) compressed steam is discharged into the evaporator onto the outside of the tubes, where it condenses and gives up its latent heat energy to the boiling water inside the tubes. The process is very efficient

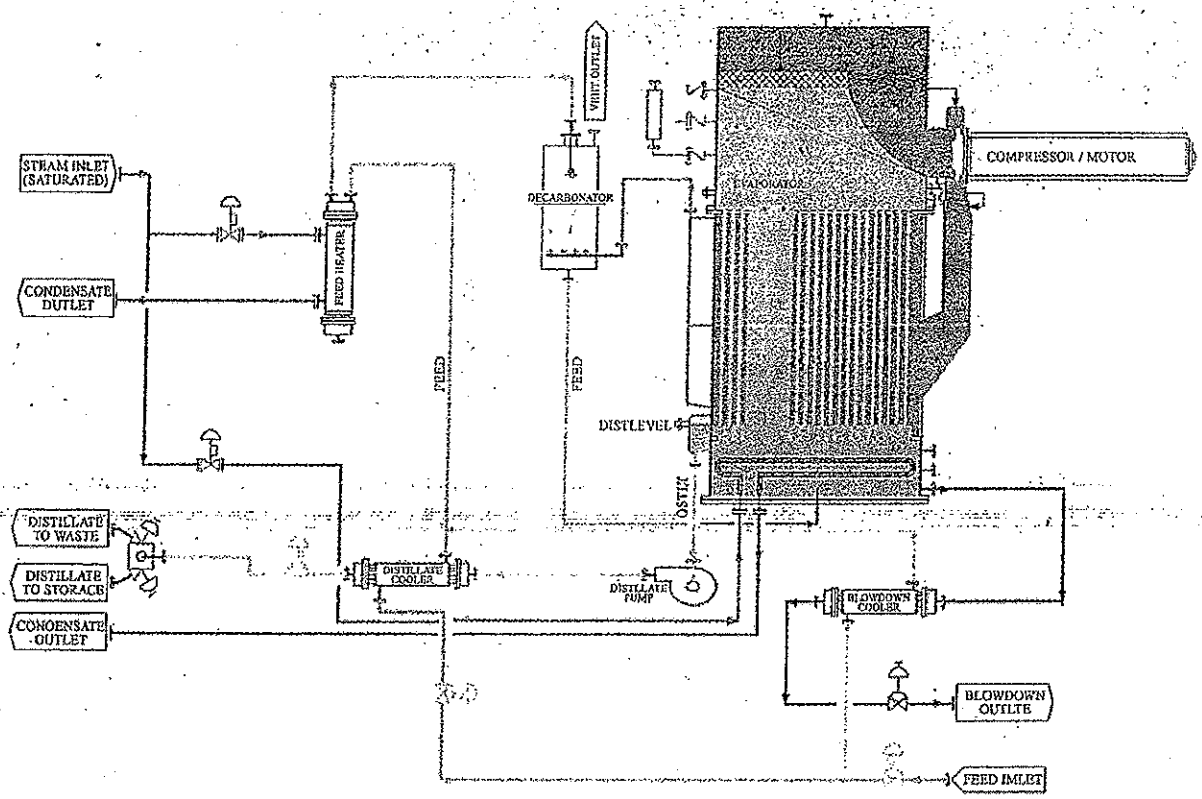


Fig 5.7 Schematic drawing of a vapor compression water distiller

thermodynamically, since only about 10-15 BTU (11-16 kJ) of compressor work is used to recycle approximately 1000 BTU (1056 kJ) of the latent heat energy contained in the released vapors.

Additional vapor is generated and the process continues. The vapor, which condenses on the outside of the tubes, is collected, and drawn off by the distillate pump and pumped through a heat exchanger. The excess feed water (blowdown) is also pumped through a heat exchanger. The distillate and blowdown are cooled in the respective heat exchangers while simultaneously preheating the incoming feed water. The heat exchangers help to minimize the energy consumption of the system.

Some make-up heat is required for continuous operation to replace losses within the system, including the terminal temperature difference in the heat exchangers and the heat lost to radiation and venting. This make-up heat is generally provided by an existing steam supply or alternatively by electric immersion heaters.

According to the actual requirements of the customers, vapor compression water distillers can produce high temperature WFI (70 to 80 ℃), normal temperature WFI or purified water (20 to 32 ℃) or simultaneously produce pharmaceutical water at two different temperatures in compliance with the requirements of various countries' Pharmacopeias.

A vapor compression water distiller uses its compressed steam as the primary heat energy, which can remarkably increase working efficiency; and pressure vessel supervision, inspection, management, and control rules are not applicable to its evaporator. The required energy mainly comes from electric power; the consumption of electric energy may differ depending on the structural design of each vapor compression water distiller. A study by an R&D institute made a comparison between a vapor compression water distiller and a five-effect distiller from the same pharmaceutical end user with the same WFI capacity. It was found that the vapor compression water distiller consumed 50% less plant steam than the five-effect distiller did, but for each ton of WFI being produced, the vapor compression water distiller consumed an additional 10 kW of electric energy.

Full pre-treatment must be done for the distillation technology to prevent or reduce equipment corrosion or scaling; the scope of the pretreatment differs depending on the raw water source and used distillation method; generally speaking, after softening treatment and chlorine removal, the raw water can satisfy the requirements for feed water of a vapor compression water

distiller; There are no strict requirements for conductivity and TDS in the raw water because vapor compression water distillers and single-effect water stills have relatively low operation temperatures and therefore are less prone to scaling; on the contrary, as a multi-effect water still has a relatively high operation temperature, it has a more strict requirement for the content of dissolved mineral matters in raw water.

In many cases, the formation of silica scale can be prevented by ensuring an adequate blowdown rate and maintaining the silica concentration below the saturation concentration; for example, the blowdown rate of a multi-effect water still is generally controlled in the range of 10% to 15%; but a vapor compression water distiller with lower operation temperature can resist more silica content in raw water; therefore, its blowdown rate can be relatively lower.

The latent heat of a vapor compression water distiller will be reused; therefore, unlike a multi-effect water still, it is not necessary to install a separate condenser for reducing the temperature of the output water at the end of the equipment. At the same time, the effective production capacity of a vapor compression water distiller can reach over 20,000 L/h, easily satisfying the requirement for high output of WFI of some chemical injections, traditional Chinese medicine injections, and biological products enterprises in China.

Compared with a multi-effect water still, a vapor compression water distiller has more adjusting valves and a more complex structural design; and more caution will be required for maintenance and operation stability. As the evaporator of a vapor compression water distiller is not a pressure vessel, its service life will be longer compared to the evaporator of a multi-effect water still; therefore, during the initial period of installation and positioning, the maintenance space and maintenance measures should be taken into consideration for the heat exchange tubes in the evaporator for long term operation; the technical requirements for the maintenance personnel of a vapor compression water distiller is high as there are some compressor parts working at high speed and with a high load; the compressor should have a pre-warning device so that any fault can be found in advance and safety can be ensured; the compressor bearing and seals must be replaced when the service life period expires; it is also very important to maintain the dynamic balance of the compressor impeller; with the increase of service time, it should be guaranteed that the impeller dynamic balance should be always maintained in the acceptable range; at the same time, professional maintenance should be conducted each year for the large power frequency inverter cabinet by professional staff to avoid short circuits of electrical equipment or any failure due to dampness.

5.3 Purification Process

The USP states that "*WFI is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms*". It is required by the USP, EP, and ChP that the content of bacterial endotoxins in WFI should be less than 0.25 IU/ml or 0.25 EU/ml; at the same time, a specific requirement has been put forward for the microbial contamination level; that is, the total aerobic germ count in 100 ml test solution should not exceed 10 CFU. Therefore, in order to produce WFI in compliance with USP/EP/ChP requirements, effective control of the raw water content of microorganisms and endotoxins should be achieved. The ultrafiltration technique is a more technologically mature purification process for producing WFI. The main purpose of a terminal ultrafilter in the pharmaceutical water system is to reduce the burden of microorganisms and endotoxins; in combination with RO, EDI, etc. the output water-quality can meet the requirements of WFI.

In 1988, when the eleventh revision of the *Japanese Pharmacopeia* (JP) was emended, the ultrafiltration method was formally recorded in the pharmacopeia as an important method for producing WFI. The JP has accepted tangential flow filtration-ultrafiltration (TFF-UF) with a precision of 6,000 MWCO as an important method for producing WFI. In Europe and the US, the ultrafiltration method is used by some manufacturers as one of the depyrogenation methods. However, this method hasn't been accepted by the ChP and EP in the application of WFI production. In March, 2016, the European Pharmacopeia Commission passed the revised monograph (0169) for WFI; it is stated in this revision that WFI can be produced by a purification technology equivalent to the distillation method, e.g. RO and additional appropriate technology. This revision will be effective in April, 2017, which means that the terminal ultrafiltration process (membrane treatment)

will be gradually accepted by the regulatory body of each country in the near future for producing WFI. The terminal ultrafilter will be more and more widely applied.

For a terminal ultrafiltration process (Fig 5.8), an ultrafiltration membrane module with molecular weight cutoff below 6,000 Da can be used for processing purified water to obtain WFI. According to the trial test results for microorganisms and endotoxins, the output water quality of a terminal ultrafiltration process can fully meets the requirement for WFI. In comparison to the traditional distillation method, the energy consumption of the devices will be greatly reduced; a ultrafiltration process can be operated normally if an adequate purified water flow rate and appropriate pressure are provided; however, a multi-effect water still needs a large amount of plant steam and a certain amount of cooling water in addition to the power for the water pump.

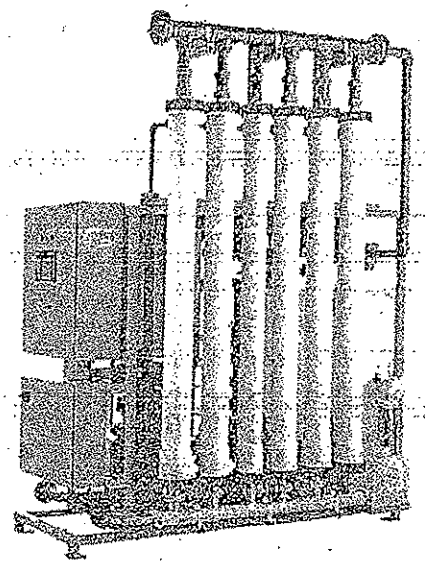


Fig 5.8 Terminal ultrafilter

Besides TFF-UF units, some direct-flow filters (positive Zeta potential, e.g. NFZ) depth filter (e.g. SUPRA EK1P), etc. also have a relatively good capability for removing microorganisms and endotoxins in WFI in the pharmaceutical water preparation systems.

5.3.1 Tangential Flow Filtration-ultrafiltration

Ultrafiltration membrane modules can be structurally classified into hollow fiber type and flat-sheet membrane cassettes type, which have specific features and can be used according to different applications of the UF membrane module. At present, the hollow fiber ultrafiltration membrane module has a relatively wide application in pharmaceutical water preparation systems; the terminal ultrafiltration membrane module is located in the final "product terminal", so the sanitation requirements are relatively high. Fig 5.9 shows the working schematic drawing of a TFF-UF unit with a retention rating of 6,000 MWCO; the standard name is hollow fiber module, which is abbreviated as HF.

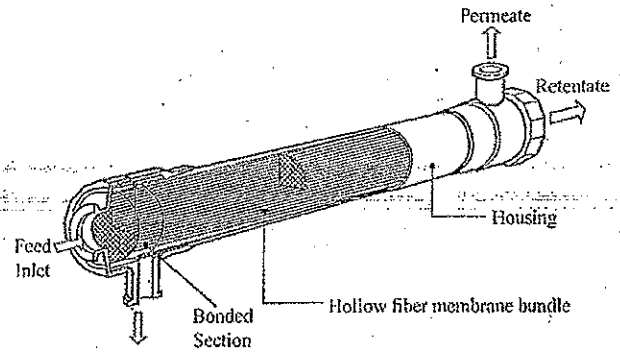


Fig 5.9 TFF-UF unit

As the retention rating is high, a TFF-UF unit generally has excellent performance for microbial control; for example, one small HF module with an effective filtration area of about 0.017 m^2 can reduce *B. diminuta* and the bacteriophage PP7 by lg reduction values (LRV) of 6.4×10^5 and approximately 4×10^7, respectively. (please refer to *Pall Microza Hollow Fibers for Endotoxin Removal*, *Laboratory to Process*, April 25, 2006, M. Fushijima for details); therefore, the purified WFI could meet the requirement of less than 10 CFU/100 ml in the ChP. This type of filter usually has a double-layer membrane structure (Fig 5.10), which not only has a double retention function for impurities removal but also can withstand forward and reverse washing, so that the service life of the device can be effectively prolonged.

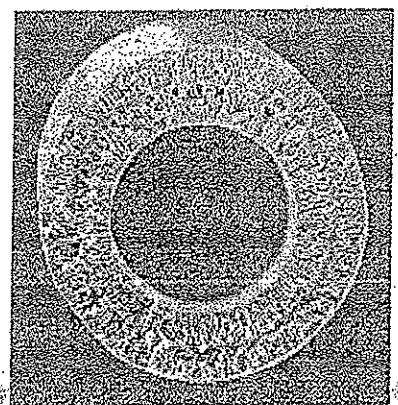


Fig 5.10 Double-layer membrane structure of a TFF-UF unit

Further studies have shown that a 6,000 MWCO HF module exposed to a long term bacterial challenge of more than 6 months could keep the filtrate sterile (Table 5.5, the microorganism control capacity of a TFF-UF with a 6,000 MWCO HF module, with reference to TR-944, *Validation Guide for Pall Microza Polysulfone 6,000 Molecular Weight Cut-off Ultrafiltration Modules*).

Table 5.5 Microorganism control capacity of TFF-UF unit with 6,000 MWCO

Module serial number	Forward flow at 30 psig air, 60/40 IPA /water wet /(ml/min)	*P. diminuta* Challenge Results (Input= 6.4×10⁵-1.2×10⁷ CFU/ml)	PP7 Bacteriophage Challenge Results (Input= 4×10⁷-8.6×10⁹ PFU/ml)
		Serile permeate samples①	Sterile permeate samples②
024042	0.15	YES	YES
023042	0.17	YES	YES
198032	0.18	YES	YES
202032	0.19	YES	YES
172032	0.22	YES	YES
030042	0.22	YES	YES
022042	0.24	YES	YES
171032	0.29	YES	YES
163032	0.35	YES	YES
161032	0.40	YES	YES

① Titre Reduction was>6.4×10⁵ for all samples.
② Titre Reduction was>4×10⁷ for all samples.

A TFF-UF device with a retention rating of 6,000 MWCO can control endotoxins effectively. Research shows that the 6,000 MWCO HF module (4.7 m² for a single HF module) can maintain a low endotoxins level (lower than 0.03 EU/ml) in the filtrate under different working temperatures (22 to 90 ℃) with the feed endotoxins level at one order of magnitude (it means Con. $_{feed}$ = 10^1). Table 5.6 shows the endotoxins removal capacity of a 6,000 MWCO TFF-UF module at different temperatures.

Further studies were performed, and for all of 0.19 m² 6,000 MWCO HF modules, the endotoxins removal capacity was 4 orders of magnitude (5×10^4), and all test results showed that the endotoxins level was lower than 0.125 EU/ml in the filtrate. This means the total endotoxins trial level is approximately 10^5 EU (Table 5.7).

Table 5.6 Endotoxin removal capacity of a TFF-UF module

Sample	Temperature /℃	Feed /(EU/ml)	Permeate /(EU/ml)
1	22	13.0	<0.03
2	60	40.7	<0.03
3	90	56.1	<0.03
4	60	79.6	<0.03
5	22	14.5	<0.03

Table 5.7 Endotoxins trial level of a TFF-UF unit

SIP-1013(S/N 027100)		
Filtration time/min	Feed /EU	Permeate /(EU/ml)
3	4.1×10^8	<0.125
13.5	2.4×10^9	<0.125
20	4.5×10^9	<0.125
SIP-1023(S/N 010049)		
Filtration time/min	Feed /EU	Permeate /(EU/ml)
3	3.9×10^8	<0.125
15	2.6×10^8	<0.125
27.5	9.4×10^9	<0.125

Other experimental data shows that a single 0.19 m² HF module can keep the endotoxins level lower than 0.08 EU/ml in the filtrate for over 2,000 hours in one trial with the feed endotoxins concentration at 1 order of magnitude (10^1, 25 ℃) (Table 5.8).

Table 5.8 Long term capacity of a TFF-UF module for endotoxins removal

Filtration time/h	Endotoxin Analysis Results	
	Feed/(EU/ml)	Permeate/(EU/ml)
Start Up	22	<0.08
100	18	<0.08
200	24	<0.08
400	27	<0.08

cont

Filtration time/h	Endotoxin Analysis Results	
	Feed/(EU/ml)	Permeate/(EU/ml)
600	23	<0.08
800	24	<0.08
1000	29	<0.08
1200	25	<0.08
1400	19	<0.08
2000	22	<0.08

Additionally, due to the strict regulatory requirements for the approval of devices in the pharmaceutical industry, high temperature treatments (such as steam in place, abbr. SIP) should be carefully considered. The 6,000 MWCO HF module mentioned above can withstand SIP at 121 ℃, and successfully meets the requirements for Class VI (121 ℃) Plastics in the USP (Fig 5.11).

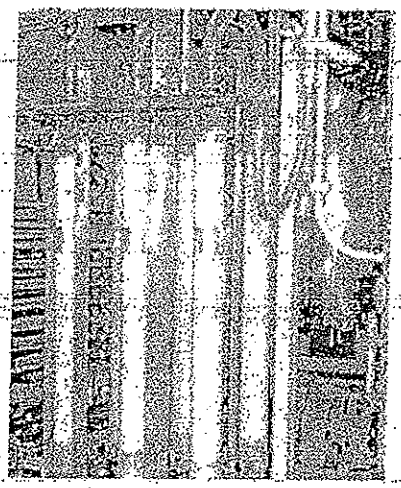


Fig 5.11 SIP for TFF-UF HF module and system

5.3.2 Sterilizing Grade Filter

The *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing* (2004) defined a sterilized-grade filter as a filter that, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent. The 1987 version of this guidance also described a quantitative standard which has been mentioned before (as at least a trial concentration of organisms at 10^7 CFU/cm^2, and resulting in no passage.). All these requirements are almost the same with the standard of sterilizing filtration in the ChP, and that is the LRV should not be less than 7/cm^2 with *B. diminuta* as the trial microorganism. At present, sterilizing-grade filters are commonly used globally, and all sterilizing-grade filters must successfully pass the previously described bacterial test. In the WFI preparation process, sterilizing-grade filters could be used as the aseptic barrier.

At the same time, there are some Zeta positive charged sterilizing-grade filters in the industry that can not only be used as an aseptic barrier, but can also absorb negative charged impurities such as endotoxins. Fig 5.12 shows different models of sterilizing grade filters with Zeta positive charged membrane; please refer to Kleenpak™ Nova Capsule Filters, USD 2176; Pall Solutions for the Biopharmaceutical Industry, USD2337 for details.

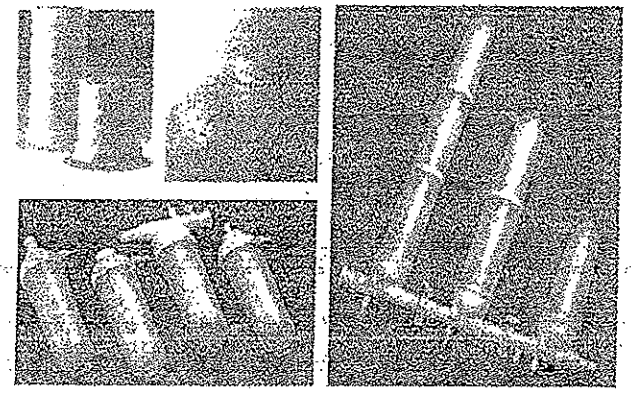


Fig 5.12 Zeta positive charged sterilizing-grade filters

When using the Zeta positively charged membrane DFF filter in the preparation process of WFI, the negatively charged endotoxins are adsorbed by the membrane due to the principle of electro adsorption (Fig 5.13).

Fig 5.14 shows the endotoxins removal ability of the filters with Zeta positive charged membrane at different pH values (with reference to Validation of endotoxins removal capabilities of Pall positively charged filters, USTR 1421); another favorable factor associated with the adsorption of positive and negative charges principle is enabling the removal of foreign matters with a size of less than the pore size of the filtration membrane, so that a better filtration result can be achieved.

Based on experiments on filters with Zeta positive charged membrane we found, a single 10 inch Posidyne® NFZ filter (sterilizing-grade, retention rating of 0.2 μm, effective filtration area 0.78 m^2) could supply 8 orders of magnitude (10^8 EU) for endotoxins removal capacity, and the endotoxins level of the

The retention rating of a depth filter is usually defined with μm as its unit, and this rating unit is not an absolute rating in the industry. Table 5.9 shows the retention rating classification (with reference to Seitz® P-series Depth Filter Sheets, USD 2205e). Even though the description of the precision is not very accurate, this will not influence the control of the retention capacity of the depth filter by adjusting the content of the components and modifying membrane porosity.

Table 5.9 The retention rating distribution of a depth filter

Depth filter type	Retention rating/μm
EKX-P	0.05-0.2
EKS-P	0.1-0.3
EKM-P	0.2-0.5
SUPRA EK 1P	0.2-0.5
KS 50 P	0.4-0.8
K 100 P	1.0-3.0
SUPRA 80 P	1.0-3.0
V 100 P	2.0-4.0
K 200 P	3.0-6.0
K 250 P	4.0-9.0
K 700 P	6.0-15.0
K 900 P	8.0-20.0

Considering all parameters of the depth filter membrane in Table 5.10 (with reference to Validation Guide, Seitz® P-series Depth Filter Media, USTR 2366b), it can be seen that a higher retention rating membrane could have a higher bacteria retention capacity for pore sizes smaller than 1 μm. Thus, a high retention rating depth filter membrane could perform very well for microbial control, and could be effectively used together with other sterilizing methods.

Depth Filters have different mechanisms for the impurity removal filtration steps. So, it is no doubt that these mechanisms (such as electrokinetic adsorption) could also affect on the endotoxins removal aspect especially with a high retention rating and positive charged depth filter membrane. Table 5.11 shows that one type of depth filter (SUPRA EK1P 60, retention rating at 0.2 to 0.5 μm) reduces a total of 6 orders of magnitude for endotoxins removal, and it means that it can its membrane intercept a large quantity of endotoxins at about 3.14×10^{7} EU/cm².

All the tests results show that some depth filters can be applied in the endotoxins removal step for the preparation of WFI, and have a sufficient margin of safety. Depth filters can be used in combination with other methods to achieve the purpose of effectively controlling the endotoxins content. Although the depth filter application in the water preparation industry may face some limits for maximum throughput and reuse etc., the protection ability and the practicability in the water using point is appealing.

Table 5.10 Relevant parameters of a depth filter

Seitz P-series depth filter media grade	Permeability at 100kPa /[L/(m²·min)]	Weight per unit area/(g/m²)	Thickness /mm	Ash content /%	Adsorption of azorubin red/(g/m²)	Log reduction value(LRV)
EKX P	24	1550	3.6	62	2.5	9.0①
EKS P	29	1400	3.7	58	2.5	8.5①
EKM P	41	1400	3.7	51	2.5	8.0①
SUPRA EK 1 P	64	1300	3.6	47	10	7.5②
KS 50 P	93	1350	3.7	46	2.5	6.5①
K 100 P	149	1350	3.7	46	2.5	
V 100 P	149	1350	3.7	52	<1	
SUPRA 80 P	159	1300	3.7	49	10	
K 200 P	217	1350	3.9	46	2.5	
K 250 P	535	1250	4.0	46	2.5	
K 700 P	935	1250	4.1	46	2.5	
K 900 P	1980	1200	4.1	46	2.5	

① Tested with *Brevundimonas diminuta* (ATCC 19146).
② Tested with *Serratia marcescens* (ATCC 14756).

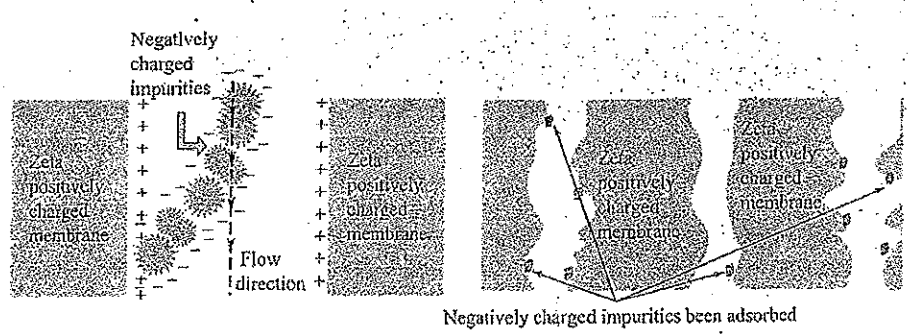


Fig 5. 13 The electro adsorption mechanism of a zeta positive charged membrane

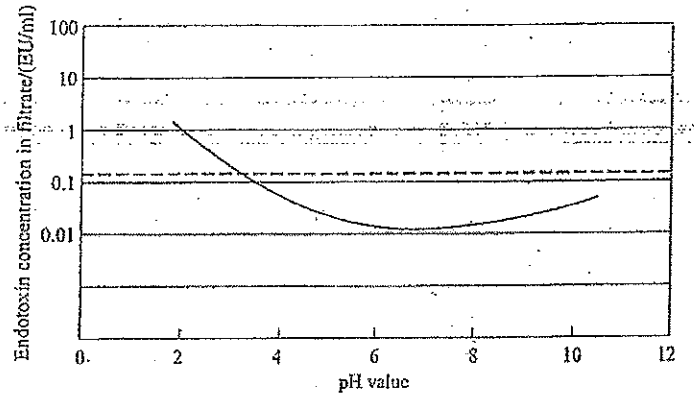


Fig 5. 14 The endotoxin removal capacity of the Zeta positive charged membrane in different pH value environments

filtrate was lower than 0. 125 EU/ml (Fig 5. 15). So, this type of filter could effectively remove the endotoxins in WFI with a very low original concentration on the feed side.

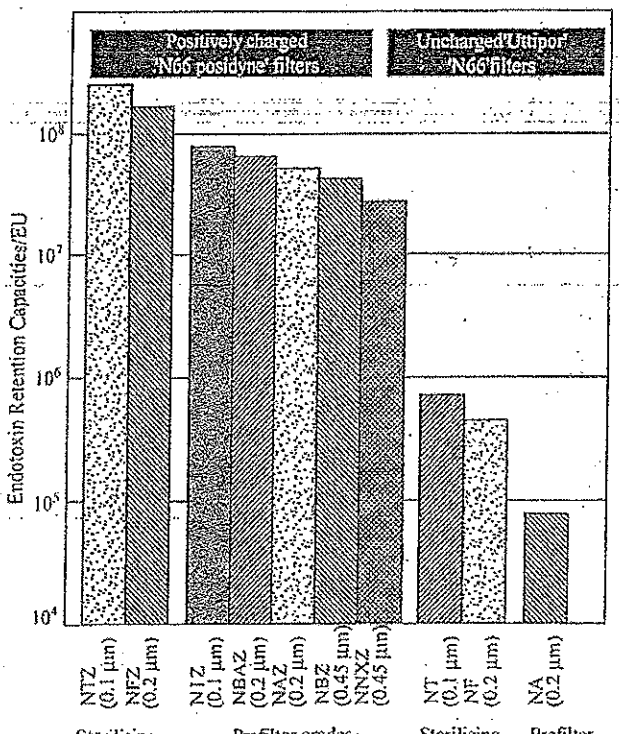


Fig 5. 15 The endotoxin removal capacity of filters with Zeta positive charged membrane

5. 3. 3 Depth Filter

A depth filter is a high retention capacity filter device with a certain thickness and high permeability pore membrane. The main retention mechanisms for impurities are direct surface retention and inertial impaction.

Depth filters are composed of a cellulose matrix, filtration aid and resins. The cellulose matrix is usually generated from natural cellulose fiber, and provides a high permeability structure; filtration aids usually include perlite, diatom earth and microcrystalline cellulose, which combined with the cellulose matrix, enhances retention and adsorption capabilities; resins are positively charged particulates that can increase the wet strength of the whole membrane and can adsorb negatively charged impurities. A electrokinetic adsorption effect will be produced between bacterial particles and the passages inside the depth filter membrane layer made of cellulosic material as a result of static adsorption, hydrophobic interaction, and surface charges interaction due to ionic strength.

Table 5.11 The endotoxin removal capacity of a depth filter

Depth filter	Endotoxin content(EU/ml)		Logarithmic endotoxin reduction	Endotoxin challenge (EU/cm^2)	Total endotoxin retention (EU/cm^2)
	UNFIURAIE	FILTRATE			
SUPRA EK 1 P 60	6.06	3	282	282	
	600	<0.06	>4	3.11×10^5	3.11×10^3
	6000	<0.06	>5	3.14×10^4	3.14×10^4
	6×10^4	<0.06	>6	3.14×10^5	3.14×10^5
	6×10^5	$<6\times10^5$	0	3.14×10^6	0

Lipopolysaocharide: *E. coli* 055 : B5 Filtration flow rate: 460 L/(m^2 · h)

Endoroxin reduction: $\frac{\text{EU ml unfiltrare}}{\text{EU ml filtrate}}$ Endotoxin retention: $\frac{(\text{EU ml unfiltrate}-\text{EU ml filtrate})\times\text{ml filtrate quantity}}{\text{cm}^2\text{ filter area}}$

Sensitivity of reagent: 0.03 EU/ml Medium: pure water

Chapter 6

Storage and Distribution Systems

6.1 Overview

The pharmaceutical water storage and distribution systems includes the storage unit, distribution unit and point of use pipeline (Fig 6.1). The design of a good storage and distribution systems should take regulations, system quality safety, investment, practicality and other aspects into full consideration, and eliminate the occurrence of insufficient or excessive design. It should adopt the design features which can reduce operation and microbial contamination risks to the maximum on the premise of the most reasonable cost. The selection of the design features should be based on the concept of "return on investment", in which, "return" mainly refers to the reduction of risk. This concept will help control the system cost and evaluate different design forms. The capacity of the system to continuously transfer water complying with pharmacopoeia requirements to the point of use can be used to measure whether the system design is successful. Therefore, one challenge faced by the pharmaceutical engineering is to select design features that achieve the required water quality standard with the highest rate of return on investment.

The correct design of the storage and distribution systems are of great importance to the success of a pharmaceutical water system. Any pharmaceutical water storage and distribution systems must achieve the following three goals:

- Maintain the quality of pharmaceutical water within the range required by the pharmacopoeia.
- Transfer pharmaceutical water with required flow rate, pressure and temperature to each point of use of the process.
- Ensure the initial investment is reasonably matched with the operating cost.

The design alternatives of a pharmaceutical water storage and distribution systems are diverse, which design is adopted mainly depends on the user and production requirements. Over or under-designing are fre-

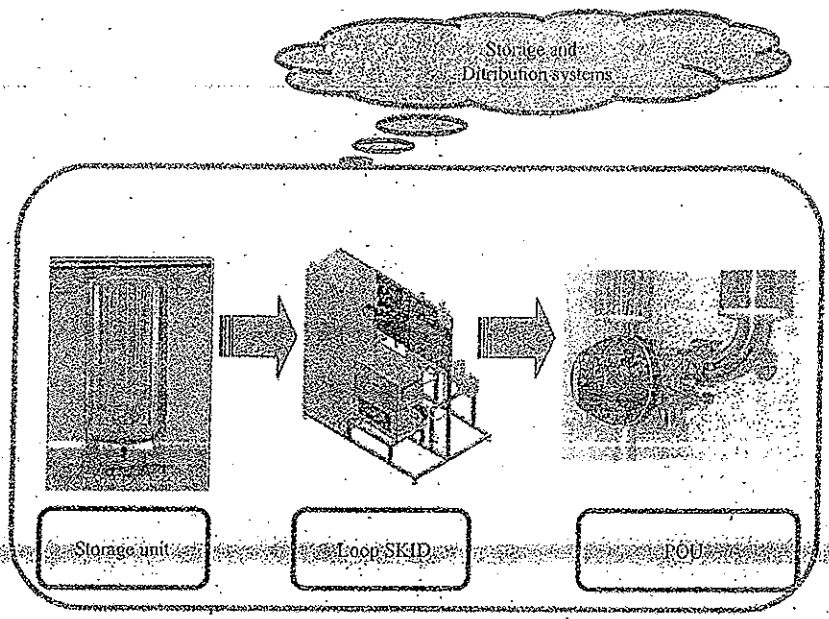


Fig 6.1 The storage and distribution systems

quently encountered problems for pharmaceutical water storage and distribution systems. For example, GMP requires the quality of pharmaceutical water at the point of use to be kept within the range required by pharmacopoeia, although there may be a small quantity of carbon dioxide dissolved in water through the vent filter resulting in an increase of the conductivity of water for injection, the conductivity index is still very safe. For common pharmaceutical products, if nitrogen protection is adopted in order to avoid the impact of carbon dioxide on conductivity, it will be highly effective, but its operating cost is very high. From the perspective of investment, it might be unwarranted. But for anaerobic "special pharmaceutical products" such as amino acid large volume injection, nitrogen blanketing should be taken into consideration. Another example is the sterilization of vent filters on purified water tanks. Risk analysis indicates that the vent filter of the purified water tanks does not require frequent online sterilization by pure steam, periodic replacement of the vent filter element for the purified water tank is also a very safe method, but for vent filters installed in water for injection systems, the risk level is higher than that of purified water systems. It is recommended to incorporate online sterilization and online integrity testing thus reducing the risk of contamination from the vent filter used for the water for injection.

With the technology improvements and increasing importance paid on pharmaceutical water by enterprises, many design features, such as high temperature storage, continuous turbulence circulation, sanitary connections, pipe polishing, automatic track welding technology, periodic disinfection or sterilization, application of diaphragm valve, etc., have been widely accepted and applied. When all the new design features are integrated into one design protocol, the safety of the system is usually very high, but the cost will be increased. Using very high quality components and design increases the safety level, but may not be necessary in some cases. Many systems, even if one or more design features not implemented, can work adequately, in these circumstances, the cumulative effect of other design features is sufficient to ensure the safety of the system as a whole. For example, for purified water systems and sterile gas systems, the implementation of high temperature storage, continuous turbulence circulation, sanitary connections, mechanical polishing of pipelines, automatic track welding technology, periodic disinfection or sterilization and diaphragm valves in storage and distribution systems, has controlled the system's safety risk very well, it is unnecessary to use electro polished stainless steel pipelines to increase the safety factor further. If so, the costs will be higher, without a significant increase in the system's safety level.

For storage and distribution systems, the ratio of the tank volume to the flow rate of the transfer pump is called tank turnover or cycle turnover, for example, if the water for injection tank volume is 5 m^3, the water for injection pump flow rate is 10 m^3/h, then the tank turnover time is 30 min. For production, storage and distribution systems, the ratio of the tank volume to the capacity of the water generation equipment is called system turnover or replacement turnover, e.g., the water for injection tank volume is 5 m^3, the capacity of the distilled water machine is 0.5 m^3/h, then the system turnover is 10 h (Fig 6.2).

6.1.1 Storage Unit

The storage unit is used to store pharmacopoeia compliant pharmaceutical water and meet the maximum peak requirement for water usage of the system. The storage systems must keep the quality of the water supply to ensure the quality of the water used in the final product. It allows the use of a generation system with smaller output and less cost, but meeting the maximum production requirements. The internal surface of the storage tank is in contact with slow water flow, which makes it easy for a loose biological film to adhere, therefore, it is very important to disinfect the storage tank and ensure the continuous circulation of the water in the tank. Installing a spray ball in the tank will result in water circulating continuously and wetting the internal surface of the top of the storage tank thus further reducing the formation of biological film. Smaller storage tanks are better than larger ones, when considering slowing the bacterial reproduction. That is because the circulation rate of the system is relatively high, which reduces the possibility of fast bacterial reproduction. The operation of smaller generation systems is close to a continuous dynamic turbulence status. Generally, the vacant times for the storage systems will be 1 to 5 times/h, it is recommended to be 2 to 3 times/h, that is equivalent to a storage tank turnover time of 20-30 minutes. As for storage and distribution systems disinfected by ozone, the reduction of the tank

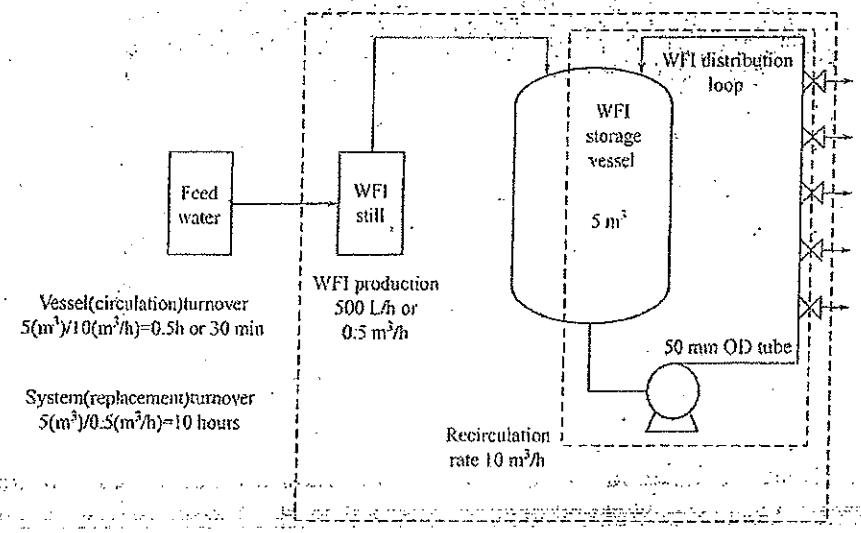


Fig 6.2 System turnover and tank turnover

volume results in reducing the internal surface area of the tank, which facilitates the fast dissolution of ozone in the water.

The selection of the storage tank is usually based on economic considerations and the pretreatment volume. A smaller generation unit equipped with a larger storage tank or a larger generation unit equipped with a smaller storage tank can meet the production requirements for the same production workshop. Generally, the system turnover time is controlled within 1 to 2 hours. The excessive output of the water generator means increasing the investment, while the excessive volume of the storage tank means the vacant times of the tank are limited and the risk of microbial contamination is increased. The effective volume ratio refers to the proportion of the effective volume of the tank to the actual total volume. The storage tank of pharmaceutical water systems usually has an effective volume ratio of 0.8 to 0.85. For example, the total tank volume will be 10,000 L when the company requires the purified water storage tank to store 8,000 L of purified water.

The storage tank can be positioned either vertically or horizontally; the selection criteria should take full consideration of the tank volume, installation requirements, requirements for the tank itself, investment and design requirements. Usually, the vertical tank is preferred, because the lowest discharge point of vertical tank is a "point", which makes it easy to meet the requirement of "draining out the whole system", while the "lowest discharge point" of a horizontal tank is not as good as for a vertical tank, and if they have the same liquid level when the pump stops, the residual water in the horizontal tank is more than that in the vertical tank, but the horizontal tank is acceptable in the following conditions;

- The tank volume is exceedingly large, e.g., the effective volume exceeds 10,000 L.
- The tank height is restricted by the water generation room's height.
- The position of the water distiller's outlet is lower than the position of the inlet of the vertical tank.
- The cost of the horizontal tank is much lower than that of the vertical tank for the same volume.

When the storage systems and distribution systems are designed for pasteurization, the tank is usually made of 316L stainless steel and designed for atmospheric pressure or for different pressure applications. It is designed and constructed as per ASME BPE standards. The external wall of tank is equipped with an insulating layer to maintain the temperature and prevent the personnel from excessive heat. The accessories of the tank include: spray ball, pressure transducer, temperature sensor, vent filter with electrical heating jacket, liquid level sensor, and tank bottom drain valve.

When the storage systems and distribution systems are designed for ozone sterilization, the tank is usually made of 316L stainless steel, with atmospheric pressure or a different pressure design. It is designed and constructed as per ASME BPE standards. The insulating layer on the external wall of the tank may not be necessary. The accessories of the tank include: pressure transducer, temperature sensor, vent filter, liquid level sensor, tank bottom drain valve, etc. Meanwhile, it is recommended to install an ozone breaker at the outlet of the vent filter for environmental and personnel safety.

When the storage and distribution systems are designed to use saturated steam with a pressure of more than 0.1 MPa for sterilization, the storage tank should be designed as a pressure vessel. If the system is disinfected with pure steam or superheated water, the tank is usually made of 316L stainless steel with the design pressure of 1-3 bar, designed and constructed as per ASME BPE standard, and will be provided with the whole set of documents required by the local boiler pressure vessel approval organization. The external wall of the tank has an insulating layer to maintain temperature and prevent personnel from excessive heat. The accessories of the tank will include: spray ball, rupture disk, pressure tranducer, temperature sensor, vent filter with electrical heating jacket, liquid level sensor, and tank bottom drain valve. The vent filter should pass the online heating sterilization and online integrity test. For a storage unit which needs heating of the tank itself in order to maintain the water temperature, the tank shall be designed with an industrial steam jacket.

The main purpose of the spray ball is to ensure continuous self-cleaning and wetting of the tank, and the continuous uniform temperature of the whole system for pasteurization or superheated water disinfection. With the exception of the vent filter connector, the tank accessory connectors (pressure relief device connector, instrumentation tap, etc.) at the top of the storage tank should be as close as possible to the top to simplify the design of the spray ball and obtain a better spraying effect. The tank vent filter should be as far away from the storage tank as possible to prevent the spray water from the spray ball from blocking the filter element. If a pipe or other instrument is inserted vertically inside the tank from the upper end, then multiple spray balls may be used to avoid forming "shadow" spray patterns. For an ozone disinfection system, the spraying action of the spray ball will accelerate the precipitation of ozone; therefore, a spray ball is usually not used. As an alternative method, a return water inlet should be installed at the appropriate position with regard to the liquid level to maximize the ozone contact area.

The tank pressure transducer is used mainly to detect the real-time pressure in the tank, provide the basis for the command of opening or closing the vent filter when the tank is sterilizing. The pressure in the tank will be controlled and monitored by PLC. Some domestic enterprises adopt pure steam sterilization for purified water systems with normal pressure tanks or water for injection tanks which are not resistant to negative pressure, which has a very large risk of implosion. Therefore, when the system is sterilized by pure steam or superheated water, it is a must to design a pressure tank that is resistant to negative pressure to avoid unnecessary potential safety hazards.

The tank temperature sensor is mainly used to monitor the water temperature in real time. In order to control the microbial propagation effectively, the temperature in the tank will be monitored and controlled by PLC. It is recommended to maintain the water temperature in the purified water tank at 18-25 ℃, and the temperature of the injection water should be maintained at 75-85 ℃. If the temperature of the purified water exceeds 25 ℃, the system has a larger risk of microbial propagation, if the temperature of the water for injection is higher than 85 ℃; the system has a larger risk of rouging.

A rupture disk (Fig 6.3) is mainly used in a pressure-bearing tank, it is a substitute for a traditional safety valve, and usually has a counter-arched design. Its advantage is the tri-clamp connection, made of 316L stainless steel, which eliminates the dead leg risk present in outdated safety valves. The WHO GMP requires the rupture disk to be equipped with an alarm device, so as to be alerted and find the blast in the system in a timely manner. For purified water tanks at normal pressure, the rigorous pharmaceutical enterprise will consider installing a few negative pressure rupture discs for early detection of the occurrence the of the tank operating at negative pressure, and avoid implosion in the event of a blocked vent filter.

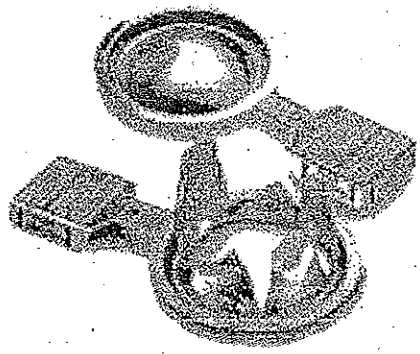


Fig 6.3 Blasting device

The tank vent filter is one of the basic elements mentioned in all GMPs; its main purpose is to eliminate the impact of outside particles and microor-

ganisms on the tank water quality. The bore diameter of filter element is 0.22 μm, and it is made of polytetrafluoroethylene (PTFE). When the system is operating at high temperature (e.g., pasteurized purified water storage tank, pure steam or superheated water sterilized water for injection tank), condensate water can easily accumulate on the filter membrane and result in blocking of the vent filter. The use of a vent filter equipped with electrical heating jacket or steam tracing, and self-draining port can prevent tank implosions and reduce the probability of microbial contamination to the vent filter effectively. For ozone disinfected purified water systems, there isn't any risk of blocking for the vent filter. The vent filter is protected by ozone for a long term; therefore, it is unnecessary to install an electrical heating jacket.

Depending on the system operation requirements, the design of the vent filter in pharmaceutical water storage tanks can be very simple or complex. It can be designed as a simple combination of a disposable filter element and filter shell, or designed as a vent filter equipped with online sterilization and integrity test functions, and electrical heating jacket. Consideration should be given to installing a redundant vent filter and valve to prevent the water in the storage tank from exposure to the outside environment or contacting the testing reagent when that is replaced or an integrity test is conducted. The design of the vent filter mainly depends on the operating parameters and the requirements for the periodical maintenance of the storage tank, combined with the risk analysis, microbial propagation in the purified water vent filter can prevented by offline sterilization or periodical change of the filter element, while for the water for injection system, it is recommended to use online sterilization to prevent microbial propagation. When the online sterilization of the vent filter is done in forward or reverse direction, the actual pressure differential for the inside and outside of the membrane should not be higher than the maximum tolerance for the pressure differential of the membrane itself. If the carbon dioxide that enters the storage tank has an adverse effect on the water conductivity, several countermeasures are available: purification by electro deionization, filling the top of the storage tank with an inert gas (e.g. nitrogen), using a vent filter equipped with carbon dioxide absorber, injecting fresh water or changing the water.

The vent filter used in the storage tank of pharmaceutical water systems should undergo an integrity test after the filter element is installed, that is not required for validation for a sterile filter. It is a must to conduct a test and visual inspection, including an integrity test conducted at the end of the system operation. The purpose of the integrity test is to verify whether the vent filter is blocked or leaked when it is removed from the system, and demonstrate the taken preventive maintenance plan is correct. The commonly used filter integrity test methods include: the bubble point method, diffusion flow method and water invasion method. These methods vary with filter manufacturers, application and filter element type. Appropriate procedures should be established depending on the specific failure that may occur while testing the used filter element.

The liquid level sensor is another important accessory of the tank. Its function is mainly to provide the start-stop signal for the water generator and prevent the centrifugal pump at rear end from idling. The liquid level in the tank will be monitored and controlled by PLC. In the traditional design, the liquid level sensor has a 4-20 mA signal output, and the signal is classified into several levels as high liquid level, high liquid level, low liquid level, low low liquid level and pump stop liquid level. The start/stop of the water generator is mainly triggered by the high liquid level and low liquid level, while the pump stop liquid level is mainly used to protect the centrifugal pump for water transfer at the rear end, and prevent it from idling. The liquid level sensor types that can be used for a pharmaceutical water storage tank mainly include: static pressure liquid level sensor, capacitive liquid level sensor and differential pressure liquid level sensor, they all have tri-clamp connections and can resist high temperature disinfection or sterilization.

The pharmaceutical water in the storage tank is in a state of "relative rest", and the tank has the largest risk of microbial propagation in the whole storage and distribution systems, therefore, the internal wall of tank shall have an adequate surface finish, (not necessary if periodic disinfection or sterilization of the storage systems are performed), to effectively prevent the microorganism from attaching to the tank wall and form a biological film which is difficult to remove. It is generally recommended that the tank surface finish *Ra* is not more than 0.6 μm, and it is better to use electrolytic polishing with the polish *Ra* of 0.4 μm. Multi-

ple distribution pipe network systems of some workshops may share a storage unit to save floor area and investment. For example, a preparations workshop is designed with two floors, in which, the first floor is the stock solution workshop, and the second floor is the preparations workshop. For such a system, the purified water systems can use a shared purified water tank and two sets of separate distribution and delivery systems to supply water for the first floor and second floor respectively. It is better to have separate ports for the connectors of the transfer pump of each set of the delivery systems at the bottom of the purified water tank to prevent transfer pumps from "competing for water".

6.1.2 Distribution Unit

The distribution unit of pharmaceutical water systems is the core unit of the whole storage and distribution systems. The main function of the distribution systems is to transfer the pharmaceutical water complying with pharmacopoeia requirements to the process points of use, and ensure its pressure, flow and temperature meet the requirements of the production process or cleaning. The distribution systems has online detection instruments for flow, pressure, temperature, TOC, conductivity, ozone, etc., that conduct real-time monitoring and trend analysis of the water quality, and control the bioburden in the water effectively by means of periodic disinfection or sterilization. As required by quality control protocols, the main supply and main return pipelines of the whole distribution system should have a sampling valve installed for water quality analysis. Fig 6.4 is a representation of a typical water for injection storage and distribution system.

The distribution systems are mainly composed by the following elements: transfer pump with frequency converting control, heat exchanger and its heating or cooling regulating apparatus; sampling valve, diaphragm valve, pipelines and fittings made of 316L stainless steel, temperature sensor, pressure transducer, conductivity sensor and transmitter, TOC sensor and matched integrated control system (including control cabinet, I/O module, touch screen, paper recorder, etc.). Fig 6.5 refers to typical distribution systems.

Sampling is very important aspect of the performance qualification for pharmaceutical water systems. As stipulated by the FDA, the sampling volume of water for injection should not be less than 100 ml, and 100-300 ml is preferred. In order to ensure the safety of sampling, and prevent cross contamination, ISPE recommended the use of sanitary dedicated sampling valves to conduct offline sampling for purified water and water for injection (Fig 6.6). The sampling valve is mainly installed at the outlet of the water generation equipment, main supply and main return pipelines of the distribution systems. The point of use fixed connection cannot be dismantled at any time.

The process analysis technology (PAT) is widely used in pharmaceutical water systems, and the distribution system is usually equipped with temperature sensor, pressure transducer, flow sensor, ozone sensor, conductivity sensor and TOC sensor for monito-

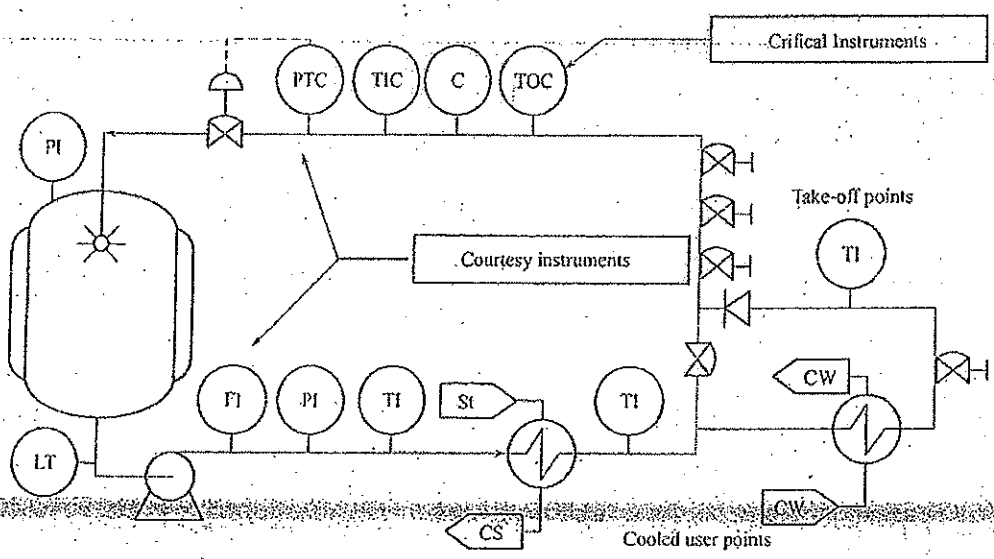


Fig 6.4 Water for injection storage and distribution systems

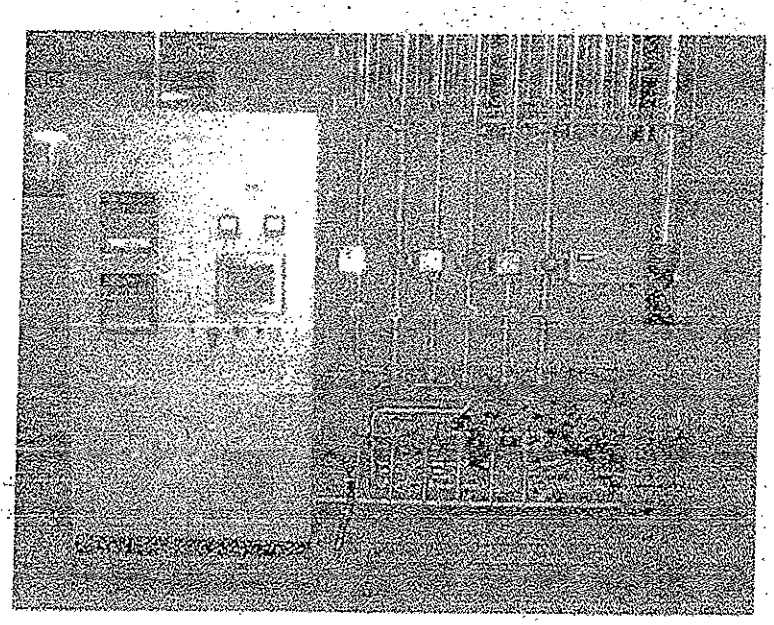


Fig 6.5 Typical distribution systems

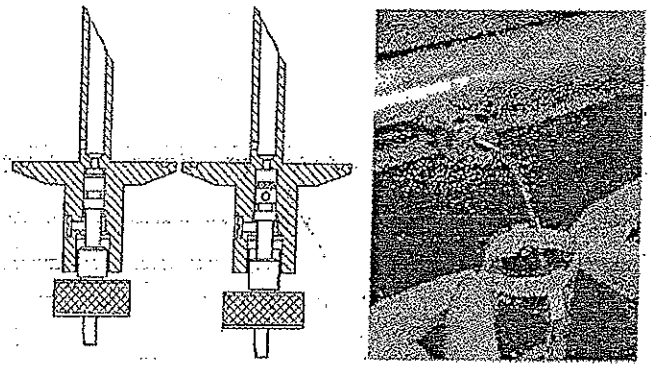


Fig 6.6 Dedicated sampling valve

ring the water quality and operational state.

a. The temperature sensor is usually installed before or behind the main heat exchanger, and has control linkage with the proportioning valve for heating or cooling, which provides assistance for real-time temperature monitoring and periodic disinfection or sterilization of the pipe network. When purified water systems are pasteurized, the system temperature is maintained at 85 ℃ for 1-2 h, and when a water for injection system is sterilized by pure steam or superheated water, the system temperature is maintained at 121 ℃ for 30 min. Temperature sensor is has a sanitary type design, has a 4-20 mA signal output function, and tri-clamp connection, its measuring range usually is 0-150 ℃. For water for injection storage and distribution systems, temperature is a key parameter in addition to conductivity and TOC.

b. The pressure transducer is usually installed at the return water terminal, and mainly used for monitoring the pressure of the return water pipeline, when the return water pressure is lower than a set value, an alarm will be triggered, the operator will inspect whether there is inappropriate use of water at any point of use. As demonstrated by risk analysis, lower return water pressure has higher risk of contamination for the system. When a water point of use with large water consumption is opened, it is possible to have air suck-back resulting in contamination of the water systems. To ensure the return water spray ball can be normally opened, it is better to control the return water pressure within 1-2 bar, and set the alarm pressure at about 0.5 bar. Some pharmaceutical water systems will adopt a counterbalance valve to adjust the return water pressure; its purpose is to ensure the system is always maintained at a state of positive pressure. The pressure transducer will have a sanitary type design, with a 4-20 mA signal output function, and adopts tri-clamp connection. Its measuring range is usually 0-6

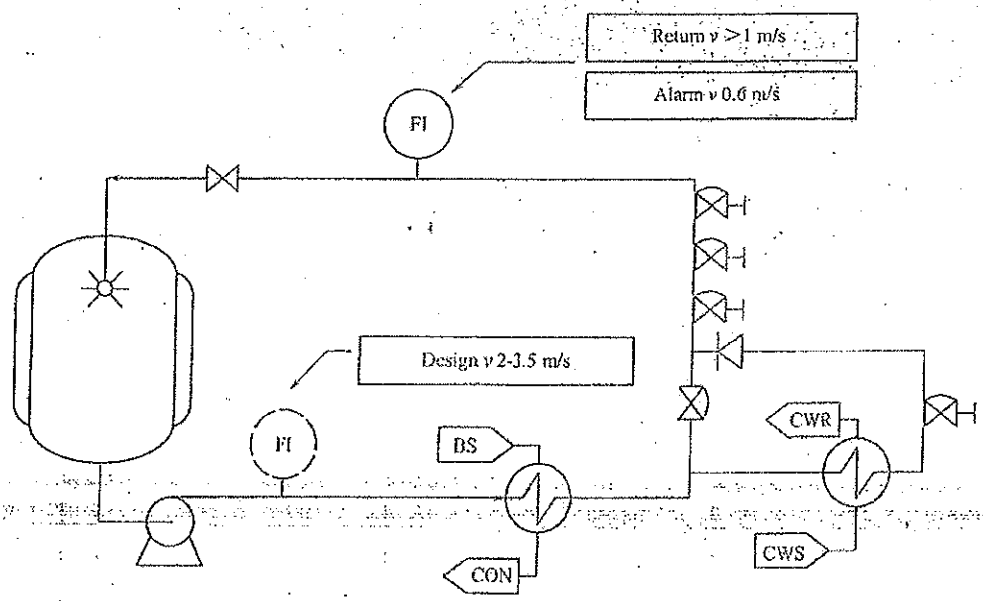


Fig 6.7 Return water flow and alarm flow

bar or −1 to 5 bar.

c. The flow sensor is usually installed at the return water terminal, and mainly used for monitoring the flow of the return water pipeline. The system flow is related to the pressure. The centrifugal pump in pharmaceutical water systems has a frequency conversion linkage with the return water flow or pressure. Most of the pump frequency conversion is linked with the flow for control. Normally, the return water flow at the system terminal should be kept at not lower than 1 m/s, and the pump frequency conversion flow shall be always set at about 1.2-1.5 m/s. Flow is crucial to the long-term stability of water quality, when the system use level is at peak value, the system flow lower than 1 m/s for a short time will not cause fast microbial propagation in the system, but it is possible that a too low flow will increase the risk of system contamination; therefore, 0.6 m/s is usually adopted as the alarm flow for the return water pipeline (Fig 6.7). The flow sensor will have a sanitary type design, with a 4-20 mA signal output function, and a tri-clamp connection, its measuring range is usually matched with the pump flow. The commonly used types of flow sensor in distribution systems are metal rotor flow sensor, vortex flow sensor, etc.

The designed flow of pharmaceutical water systems refers to the actual flow of the main pipeline at the pump outlet. In order to ensure the safe operation of system pipeline, it is recommended, from an engineering standpoint, that the maximum designed flow is not more than 3.5 m/s, and 2-3 m/s is preferred. The designed flow can be obtained from the conversion of the proportional relationship of the pump flow and main pipe diameter. Table 6.1 is the corresponding flow value at the flow rate of 1 m/s for different pipe diameters of ASME BPE and SAM3008 standard pipeline. ASME BPE standard pipeline is taken as an example. When the designed flow of centrifugal pump is 10 m^3/h, the pipe diameter should be selected as DN40, and the designed flow of the main pipeline should be 2.92 m^3/h. If the flow of the centrifugal pump is increased to 18 m^3/h, and the pipe diameter is still selected as DN40, the designed flow of the main pipeline reaches 5.26 m^3/h; the design is not reasonable. Therefore, when the pump flow is 18 m^3/h, it is recommended to select the pipe diameter as DN50, and the designed flow is 2.82 m^3/h.

Table 6.1 Pipe specification and flow rate

	Pipe specification/mm		Flow(1 m/s)/m^3/h	
	ASME BPE standard	SMS 3008 standard	ASME BPE standard	SMS 3008 standard
DN25	25.4×1.65	25.0×1.2	1.38	1.44
DN40	38.1×1.65	38×1.2	3.42	3.58
DN50	50.8×1.65	651×1.2	6.38	6.67
DN65	63.5×1.65	63.5×1.6	10.24	10.28
DN80	76.2×1.65	76.1×1.6	15.61	15.69

d. The conductivity sensor. The installation location of the conductivity meter must reflect the quality of the water in use, and the optimal location for online detection is usually behind the valve of last "point of

use" in the pipeline, and in the main pipeline, before the return to the storage tank. Although the conductivity sensor is nonionic, conductivity is still an important indicator for determining the total ion concentration of the water; therefore, it is a critical parameter for many water systems. It is required that the conductivity indicators of purified water and water for injection are as specified in the pharmacopeia; therefore, the online conductivity monitor is one of the "key" instruments in the whole distribution system. Bubbles will cause the reading of conductivity to be lower than the expected value, and solid particles will affect the conductivity of the system seriously; in order to work normally, an L-type triple valve can be used to install a conductivity probe, and ensure water can pass through the conductivity probe continuously to prevent bubbles or solid particles from becoming captured on the electrode.

e. The TOC sensor is installed at the same location as the conductivity meter; the online TOC sensor in the distribution systems is usually installed behind the valve of last "point of use" in the pipeline, and in the main pipeline before the return to the storage tank. It is required that the TOC indicators of purified water and water for injection are as specified in the pharmacopeia; it is another "key" instrument in the whole distribution system. The pharmacopeia requires the TOC reading to be not higher than 500 ppb, the TOC alarm value is normally set at 100 ppb, the TOC action value is 250 ppb. It is of great significance to use a TOC analyzer to indicate endotoxin contamination, but when the endotoxin contamination results in higher TOC content, the linear relation between endotoxin and TOC is no longer present. Additionally, the TOC test result cannot substitute for microbial test or endotoxin test.

TOC can be detected by online monitoring (Fig 6.8) and offline sampling and analysis. The installation of a TOC online analyzer can be decided by the enterprise itself; it will help the enterprise perform real-time monitoring of water quality and conduct reasonable trend analysis.

f. The online ozone sensor is usually installed in the purified water systems disinfected by ozone to monitor the ozone concentration in the water. The ozone sensor determines the ozone concentration by means of an oxygen dissolving cell. An ORP analyzer cannot distinguish ozone from other oxidizing agents in the water; therefore, the ozone sensor used in the water systems cannot be replaced by an ORP analyzer.

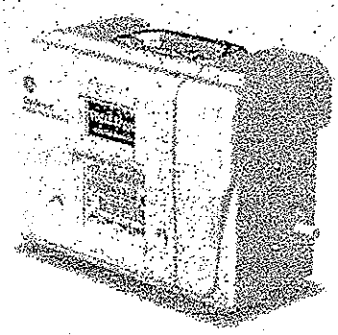


Fig 6.8 TOC online analyzer

A pharmaceutical water storage and distribution unit has a separate electrical control system, including control components such as programmable logic controller (PLC) and color touch screen, electrical components such as power supply, switches, buttons, contactors, relays, frequency converter, indicator lights, cabinets, terminal strip, cables and trunking, DP communication module and other necessary components. The control system is used to control the operation of the circuit so it will run correctly. The system is directly installed in the frame of the storage and distribution systems to facilitate operation, monitoring and control of the equipment. The operator interface terminal (OIT) is a monitoring panel that displays and allows for setting the operating parameters of the equipment. Alarm, action and sterilization steps, process set points and process values can be displayed on the operator interface terminal.

After the system is run for one cycle, the disinfection procedure can be started to sterilize the whole system, at that moment, the system will feed back the temperature or ozone concentration signal to a programmable logic controller through the sensor, and make it maintain a certain temperature or concentration, and operate as per set disinfection time.

Routine functions of control system:

- Frequency converting control of transfer pump. The pump is conducting frequency converting control based on the return water flow, at the same time, it has pump stopping at low liquid level and alarm protection functions.
- Water temperature control. The temperature of the water systems is controlled automatically allowing regulation of heating and cooling of the heat exchanger and ensuring the water temperature is within the set

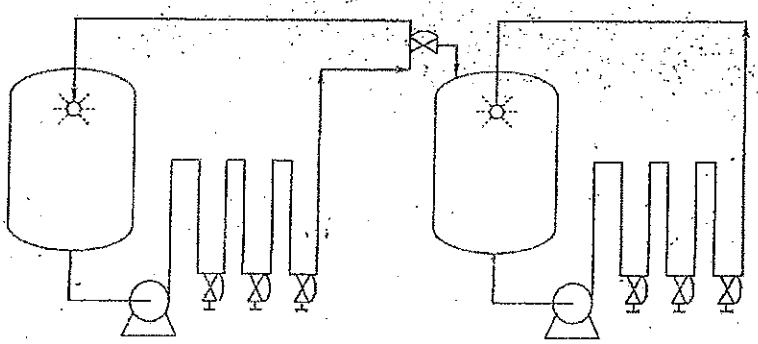


Fig 6.9 Reasonable distribution and design of pipeline

range.

• Monitor return water temperature, pressure, conductivity, TOC, flow, storage tank liquid level, temperature and other parameters, and print and store data automatically. It has trend analysis, historical record storage and parameter over-limit alarm functions.

• Critical parameters can be set, such as conductivity, TOC, return water temperature, sterilization temperature, return water flow, etc.

• Production and sterilization operation can be controlled automatically with online recording and printing functions, sterilization time can be timed automatically.

• The system has three levels of access control: Operator, administrator and supervisor or higher level. It allows for setting different user names and passwords to prevent unauthorized persons from accessing the system to modify the data.

• It can adopt touch screen or upper computer for control.

• The touch screen can display the system flow interface, process and parameter set interface, historical data query interface, etc.

6.1.3 Point of Use Pipeline

The point of use pipeline starts from the distribution unit in the water generation room, passes through all process points of use, and returns to the distribution systems of water generation room; its main function is to transfer pharmaceutical water complying with pharmacopoeia requirements to each point of use through pipelines. The point of use pipeline is mainly composed of the following components: sampling valves, diaphragm valves, pipe fittings, supports and auxiliary materials, thermal insulation materials, etc. For water for injection systems, it also includes a cooling module point of use. The pipe fittings of the point of use pipeline are mainly composed of piping, elbows, tee joints, U-tubes, reducing nipples, clamps, chucks and gaskets.

In order to control the system quality and facilitate management, it is recommended that the total length of pipeline of typical distribution pipeline systems is not more than 400 m. If there are too many points of use, and the pipeline is too long, the independent distribution pipeline design, as illustrated in Fig 6.9, can be adopted as a reasonable alternative.

The points of use of pharmaceutical water are mainly divided into open points of use and fixedly connected points of use. For example, the purified water point of use in a sanitary appliance room is an open point of use (Fig 6.10), the valve at the point of use has the function of sampling, while the water replenishing valve of the preparation tank is a fixedly connected point of use. The point of use will have installed an independent sampling valve for sampling, and the sampling valve should be rinsed before sampling.

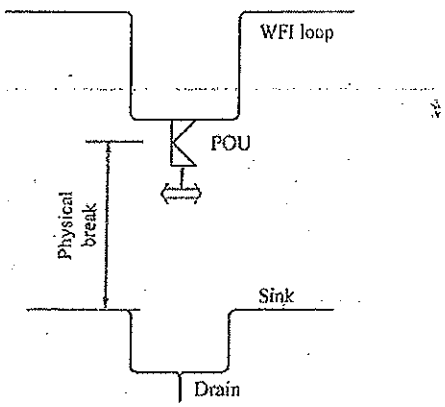


Fig 6.10 Open point of use

The fixedly connected points of use can be divided into direct docking points of use and indirect docking point of uses (Fig 6.11). The valve of a direct docking point of use is at a very short distance from the process equipment, while there is a relatively long pipeline be-

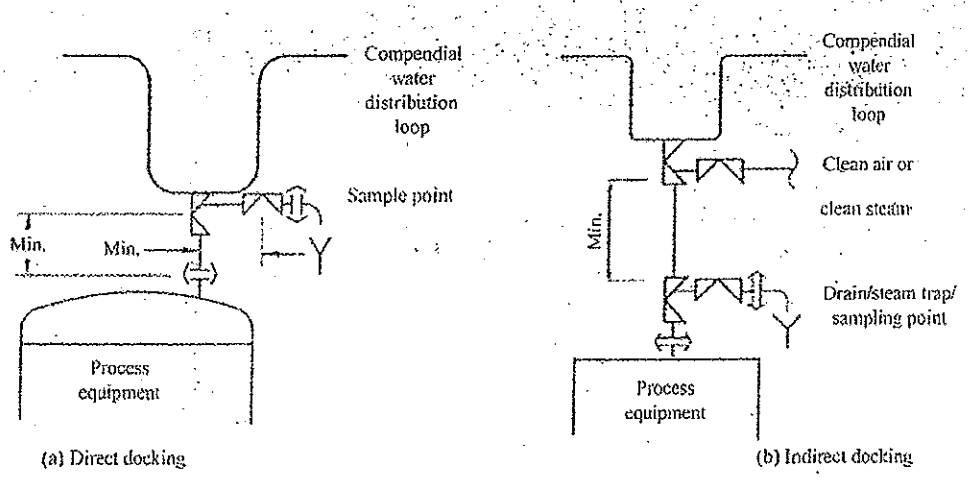


Fig 6.11 Fixedly connected point of use

tween the valve of indirect docking point of use and the process equipment. To avoid microbial contamination, clean gas or pure steam is usually used to purge or sterilize the pipeline.

The fluid process system can be connected by flange, clamp, welding, screw thread and screw joint; high quality welding is the safest sterile connection method, and has the minimum risk of microbial propagation; therefore, the pipeline installation of pharmaceutical water systems should use the welding method as large an extent as possible. When the system components, (e.g., transfer pump, instrument and meter, etc.), require frequent disassembly or maintenance, the tri-clamp or sterile flange connection can be used.

A tri-clamp connection is composed of two chucks, one plastic seal ring and one stainless steel clamp. The plastic seal ring is a wearing part, and should be replaced regularly. Under the production conditions of the biopharmaceutical industry, which has very strict sterility requirements, the plastic seal ring of tri-clamp may cause potential cross contamination due to excessive or insufficient extrusion force exerted on the clamp. Meanwhile, the thermal expansion effect of stainless steel is very distinct when the system undergoes online sterilization, and the difference of cooling rates of the stainless steel connector and the plastic seal ring is relatively large, which may also result in a minor gap appearing between the seal ring and connector. In order to solve the many problems brought by the deformation of the seal ring and frequent replacement, NEUMO, a German company, launched its patented product Connect-S (Fig 6.12) in 2001.

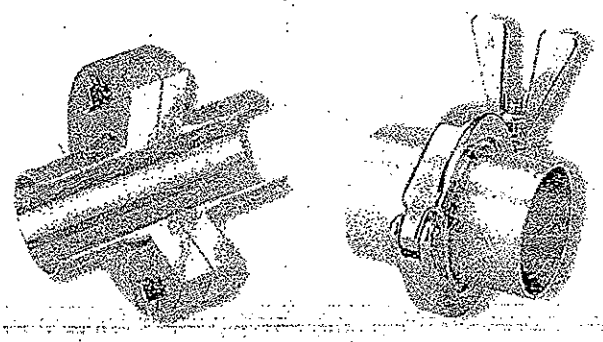


Fig 6.12 Connect-S connector

The Connect-S sterile connector requires no plastic seal ring; it nearly matches the sterility degree of welding, while eliminating many problems such as replacement of the seal ring. The two ends of the Connect-S connector have two different S-type designs, and go through eight precision-machined treatment points, to achieve the metal contact and completely seal the two ends of the connector. As illustrated in Fig 6.13, the concave-convex area with a width of 0.389 mm has achieved a complete sealing.

The design of the Connect-S takes full advantage of the flexibility of stainless steel. At the preliminary stage of the Connect-S installation, due to the non-elastic deformation of stainless steel, one end of the connector has a protuberance of 0.05 mm which can be felt by touching. After about 10 min of installation, the connector will return to the original shape due to the tenacity of stainless steel, to form a perfect sealing (Fig 6.14).

It should be noted that Connect-S has very high requirements for the precision of mechanical processing; if the quality of the mechanical processing is not adequate, it can easily develop leaks. Under normal operating conditions, it can complete thousands of repeated in-

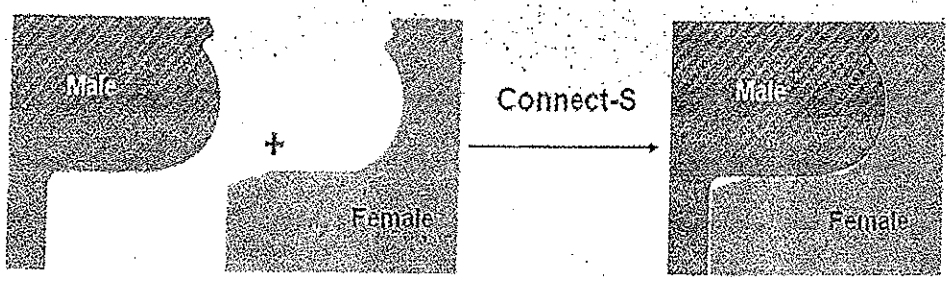


Fig 6.13 The Connect-S connector

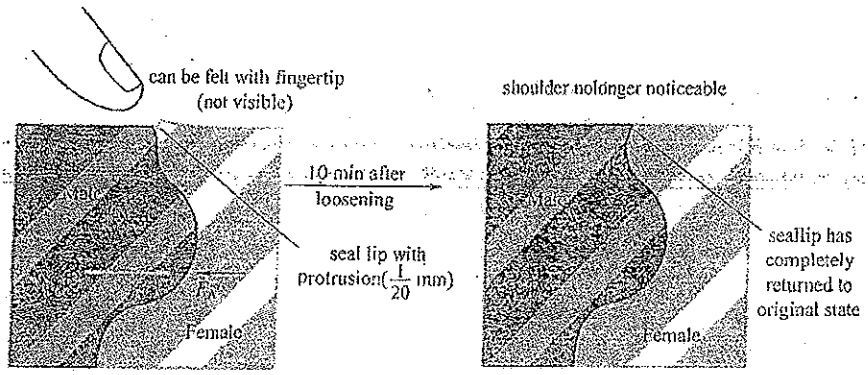


Fig 6.14 Sealing principle of Connect-S

stallations, with no leaking within limit operation conditions of 400 ℃ and 10 MPa. Accompanying the development of science and technology and the advancement of pharmaceutical engineering industry, Connect-S will be an ideal sterile connector for the pharmaceutical liquid process systems.

6.2 Decision Flow Chart

A pharmaceutical water storage and distribution systems can have three different design configurations for high temperature circulation, normal temperature circulation and low temperature circulation according to the different operating temperatures. The selection of the design protocol is not restricted by laws and regulations, the enterprise can select a design protocol complying with its own actual requirements by combining the temperature requirements of the points of use, disinfection method and the scale of system. Meanwhile, the enterprise should take the product dosage form, investment cost, water-use efficiency, energy consumption, operation and maintenance, operation risk and other elements into consideration. The design philosophy of storage and distribution systems can be summarized as eight alternatives; at present, the following fundamental design principles are routinely employed: ① batch storage and distribution systems; ②branched/one way distribution; ③parallel distribution loops from single tank; ④heat storage and distribution systems; ⑤ambient or reduced temperature storage and distribution systems; ⑥heat storage, cooled and reheated distribution systems; ⑦heat storage, cooled bypass circulating distribution systems; ⑧point of use cooled systems.

The two basic concepts of the pharmaceutical water distribution are "batch distribution" and "dynamic/continuous distribution" [Fig 6.15(a)]. "Batch distribution" requires at least two storage tanks, one provides pharmaceutical water complying with pharmacopeia requirements for points of use, the other is replenishing or testing water. The advantage of "batch distribution" is the management of pharmaceutical water by means of batch processing, it is tested before use, and the storage tank is posted with a QA/QC release label to ensure the water of each production batch can be traced and identified. The first one of the above mentioned eight design principles is the "batch distribution" system.

The "dynamic/continuous distribution" only requires one storage tank, and adopts the concept of "process control". The whole storage and distribution system is in a state of 24-hour continuous operation, the storage tank liquid level is linked with the replenishing valve of the water generator to ensure the actual

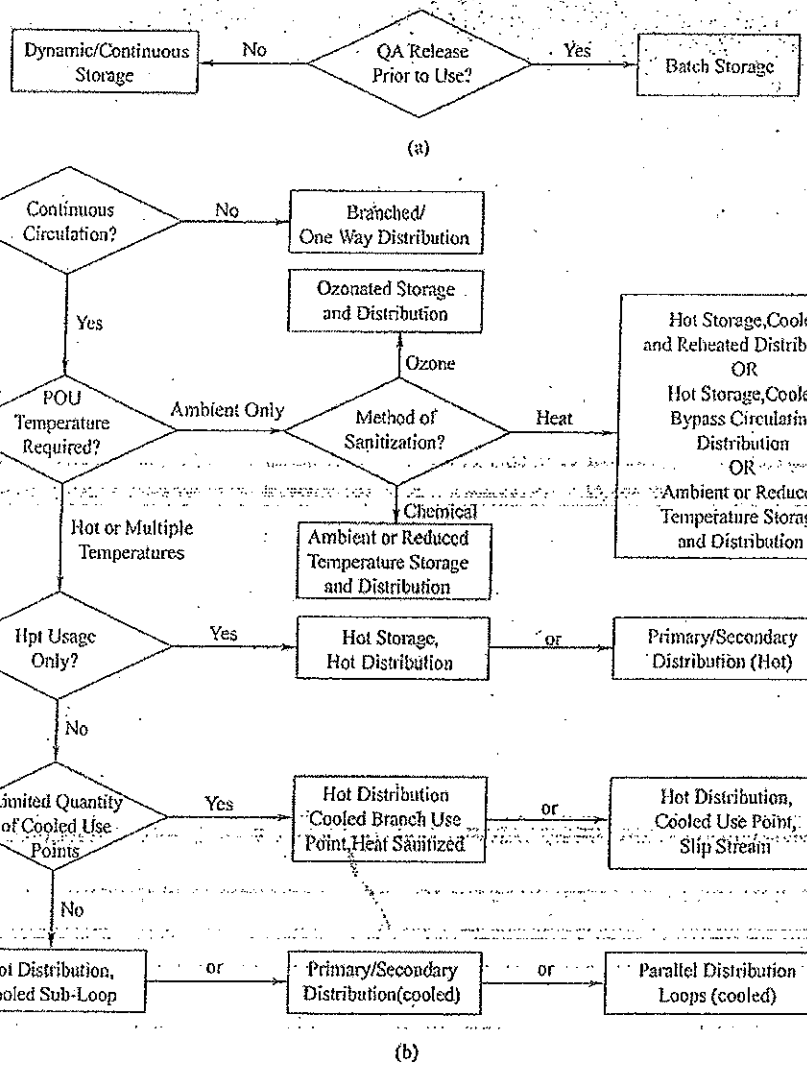


Fig 6.15 Distribution systems-decision tree

water demand is met, and maintain the water quality within pharmacopeia requirements. The "dynamic/continuous distribution" has the advantage of a simple system design, low investment and operation management cost; it can meet the requirements of peak use amount effectively during production by using the tank buffer capacity. The third to seventh design principles are "dynamic/continuous distribution" systems. It is recommended by ISPE that the design protocol of a storage and distribution system is selected using a distribution system decision tree[Fig 6.15(b)].

6.2.1 Batch Storage and Distribution Systems

A batch storage and distribution systems (Fig 6.16) can't start production until the water quality is determined and released by the quality department. When one tank is in use, the other tank will be replenished and water quality monitoring will be conducted by the quality department. The main advantage of the design it that it makes tracing the production water batch, (a certain amount of water), possible, but its disadvantages are also obvious, mainly including higher initial investment cost (requiring multiple storage

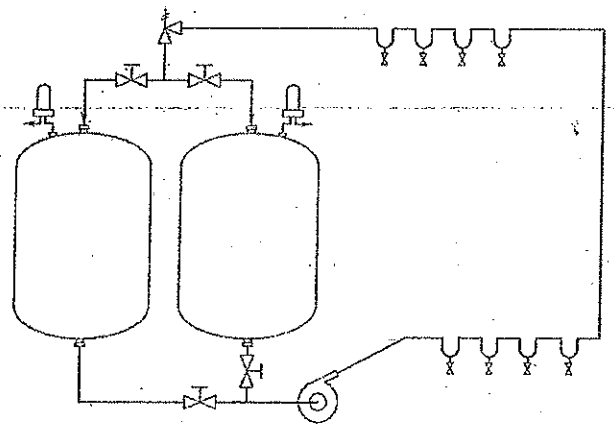


Fig 6.16 Batch storage and distribution systems

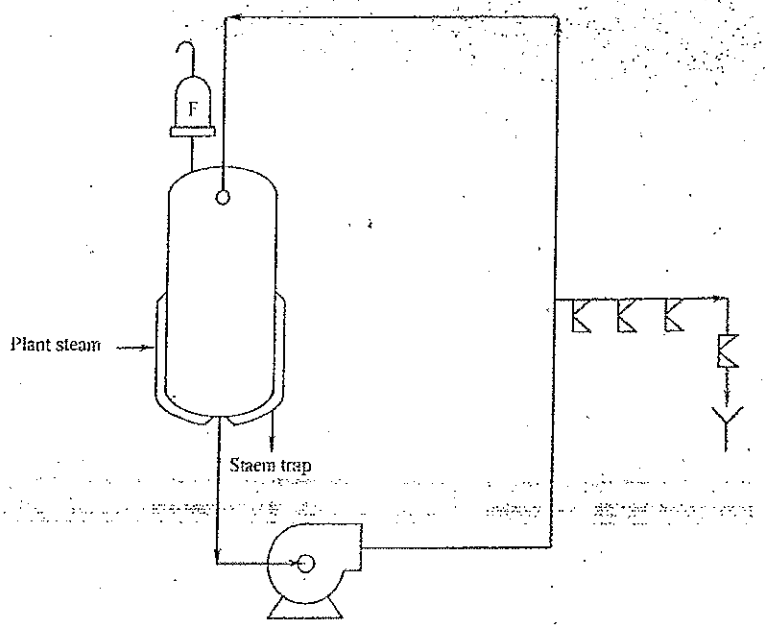


Fig 6.17 Branched/one way distribution

tanks) and operating cost (labor intensive), it is necessary to wait for the water sample test result, entailing the possibility for potential water supply delay, etc.. In the pharmaceutical industry, the "Batch storage and distribution system" is usually used when operating with a large water quantity and low temperature, such as a 4 °C low temperature water for injection systems, used in solution preparation center for blood products facility.

6.2.2 Branched/one Way Distribution

The "branched/one way distribution" (Fig 6.17) is mainly applicable for operation with a low requirement for the microbial limit and continuous water demand, such as softened water systems and potable water systems. When the number of points of use is limited and water demand is concentrated, the structure has certain advantages; the initial investment cost of the design is relatively low. But when the water is used dispersedly and irregularly, the structure has no advantage, it may cause microbial contamination when the water flow is stopped at the point of use. The microbial control is difficult to be maintained; it is a must to implement a cleaning and disinfection/sterilization plan for the loop, in order to control the microbial contamination within an acceptable range. For example, if it is stipulated that the system needs to be rinsed every day, and the system may require higher disinfection or sterilization frequency, this will increase the operating cost, moreover, it is difficult to use online monitoring to indicate the water quality of the whole system in a non-circulating system. With the development of GMP and social economy, people pay more attention to the pharmaceutical water systems and have higher and higher risk management awareness. The branched/one way distribution structure has difficulties meeting the risk management and validation requirements for purified water and water for injection, therefore, the design is rarely acceptable for the designer and user, for purified water systems and water for injection systems which require microbial limit control.

6.2.3 Parallel Distribution Loops from Single Tank

The "parallel distribution loops from single tank" is a distribution system composed of multiple distribution loops and a single storage tank. As illustrated in Fig 6.18, which shows a single storage heating system with two separate loops, in which, one loop is for heat circulation, and the other is the instantaneous cooling and reheating systems.

The "parallel distribution loops from single tank" applies to the water supply by a central storage tank for different areas or a large-scale area. Its advantage is a small floor area, easy centralized management and modularized design of multiple distribution loops. The design is most advantageous when the system has many heat points of use and cold points of use simultaneously, or points of use in the whole system are numerous and a single circulation pipeline cannot used.

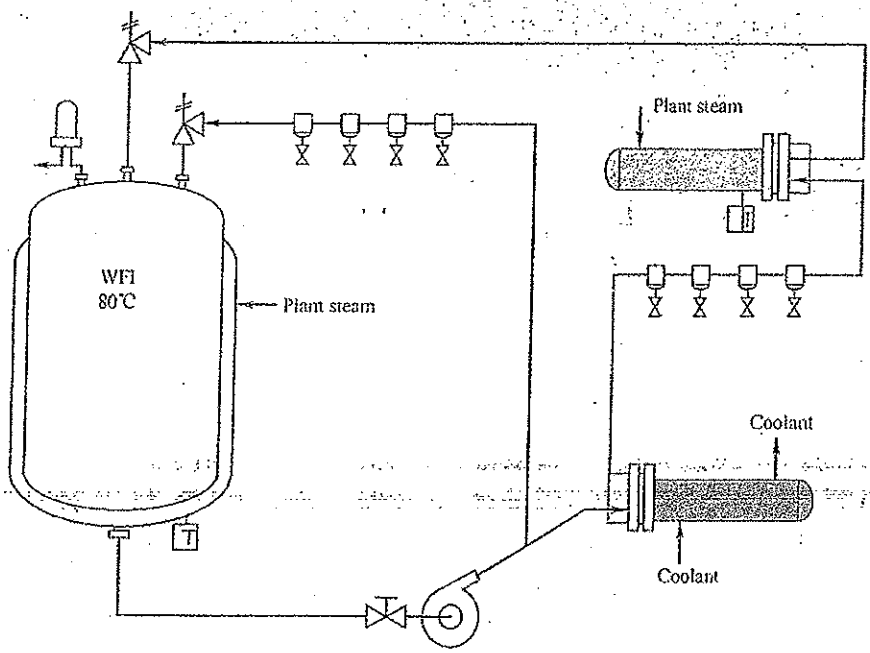


Fig 6.18 Parallel distribution loops from single tank with single pump

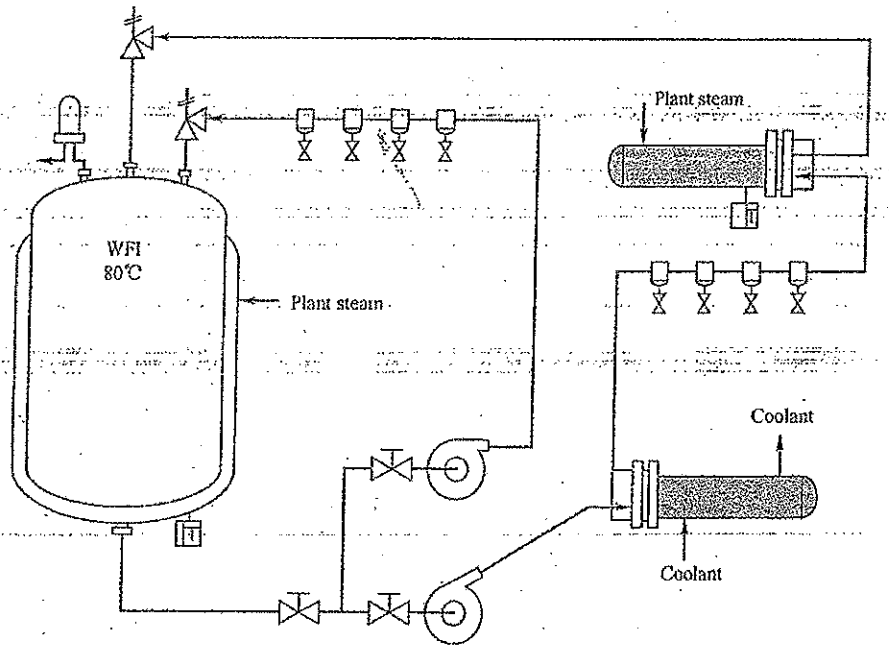


Fig 6.19 Parallel distribution loops from single tank with multiple pumps

Compared with single tank with single loop, the initial investment cost of the system design is relatively low, but when one pipeline set is contaminated, it will result in the whole system being contaminated, meanwhile, the transfer pump is only linked with the flow or pressure signal of one pipeline by frequency conversion, it is difficult for a single pump used with "parallel distribution loops from single tank" to balance the pressure and flow of multiple loops, and it cannot ensure the return water turbulence at the terminal of each branch effectively, the better solution is to install independent transfer pumps for each loop (Fig 6.19).

6.2.4 Heat Storage and Distribution Systems

The "heat storage and distribution system" is mainly used for high temperature water for injection storage and distribution (Fig 6.20). It is the main design alternative for water for injection storage and distribution systems in the pharmaceutical industry. It achieves the system heat storage and distribution by

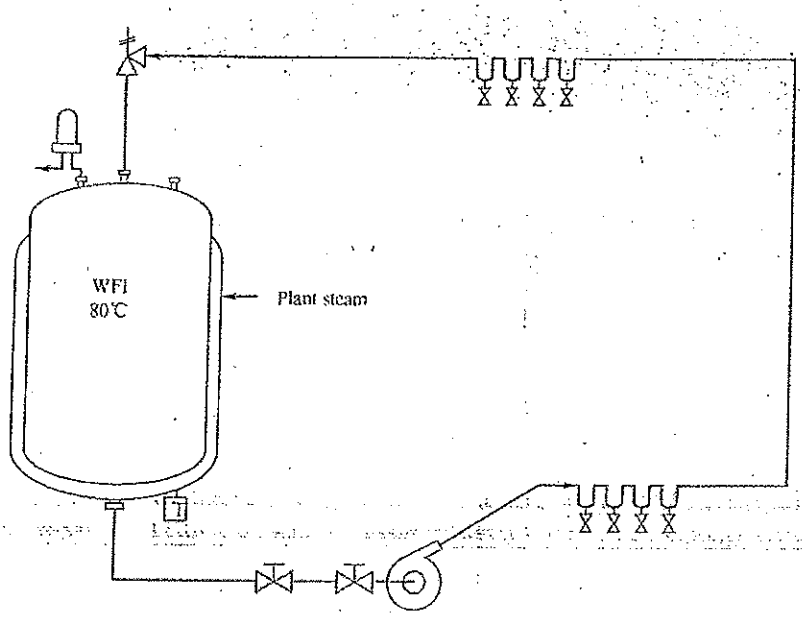


Fig 6.20 Heat storage and distribution system

means of heating with industrial steam in the tank jacket or heating by heat exchanger in the main return pipeline; the system is sterilized periodically by using pure steam sterilization or superheated water sterilization. The circulating water enters into the tank through the spray ball and it reaches the top of the storage tank to ensure the entire top surface is wetted, and the system temperature is uniform. When all points of use require hot water at a temperature exceeding 65 ℃, the advantage of the structure becomes very obvious. For pharmaceutical water systems requiring a high temperature, such as distillation, its system energy consumption requirement is relatively low. Additionally, when the system temperature can be maintained over 65 ℃, the required system sterilization frequency for the storage and distribution pipeline is relatively low, and some systems even require no periodical sterilization. Because the "heat storage and distribution system" itself stays in a continuous pasteurization state, which can control the microbial propagation of the system excellently, the structure has been recommended by the GMP of most countries as the preferred method for water for injection systems, and is widely accepted by regulatory authorities.

For the "heat storage and distribution system", the following conditions should be taken into consideration: protecting the operator from scalding, preventing cavitation occurring in the circulating pump, preventing moisture from collecting in the filter and blocking the filter element, preventing rapid rouge generation, etc. The probability of scalding can be minimized by operating at a lower temperature, conducting appropriate training of the operators, and wearing appropriate protection equipment. The cavitation in the pump can be decreased effectively by operating at lower temperature or installing an inducer. The blocking of filter element can be prevented effectively by installing electrical heating or a steam heating jacket (note: overheating should be avoided, it can damage the filter element). The whole system should have an intelligent and comprehensive design, and adopt the "quality by design" principle. The water for injection circulated at high temperatures above 85 ℃ easily generates serious rouge rapidly; effective system passivation and operation at lower temperature can reduce the risk of rapid generation of rouge.

6.2.5 Ambient or Reduced Temperature Storage and Distribution Systems

The "ambient or reduced temperature storage and distribution system" is usually used when the pharmaceutical water is generated at environment temperature (Fig 6.21). The purified water being generated by a membrane filtration method such as RO/EDI or ultra filtration is the main design feature for purified water storage and distribution systems of this type. An "ambient or reduced temperature storage and distribution system" is not as good as the "heat storage and distribution system" with regard to microbial control, only if the system disinfection is done with a certain frequency and maintained for a sufficient time, good mi-

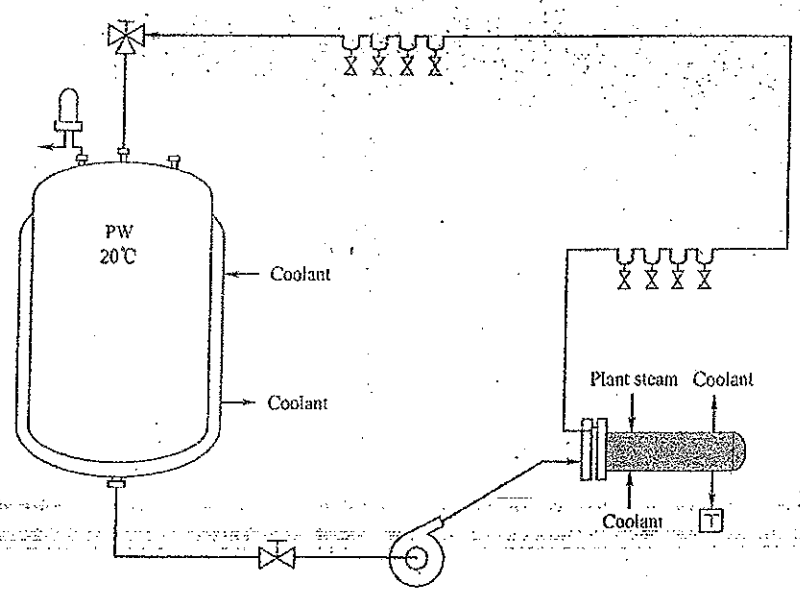


Fig 6.21 Ambient or reduced temperature storage and distribution system

crobial control can be completely achieved. The system operation is safe, energy consumption is low, the investment cost and operation cost are low. Non-metallic construction materials can be considered. Especially for purified water systems, the "ambient or reduced temperature storage and distribution system" can control microorganism better and with easier operation. The structural system has been accepted by GMP of most countries as the preferred method for normal temperature purified water systems, and widely accepted by regulatory authorities. The microorganism proliferation reduction methods for ambient or reduced temperature storage and distribution systems are mainly the following three: maintain a lower water temperature for operation (e.g. 18-22 ℃), install ultraviolet sterilization devices, maintain the ozone disinfection process in the storage tank. The disinfection methods for the "ambient or reduced temperature storage and distribution system" mainly include pasteurization, ozone disinfection and circulating steam disinfection, etc.

6.2.6 Heat Storage, Cooled and Reheated Distribution Systems

When pharmaceutical water is prepared by the high temperature method, it requires strict microbial control measures while having a limited disinfection time, the "heat storage, cooled and reheated distribution system" is a very good choice (Fig 6.22); it pro-

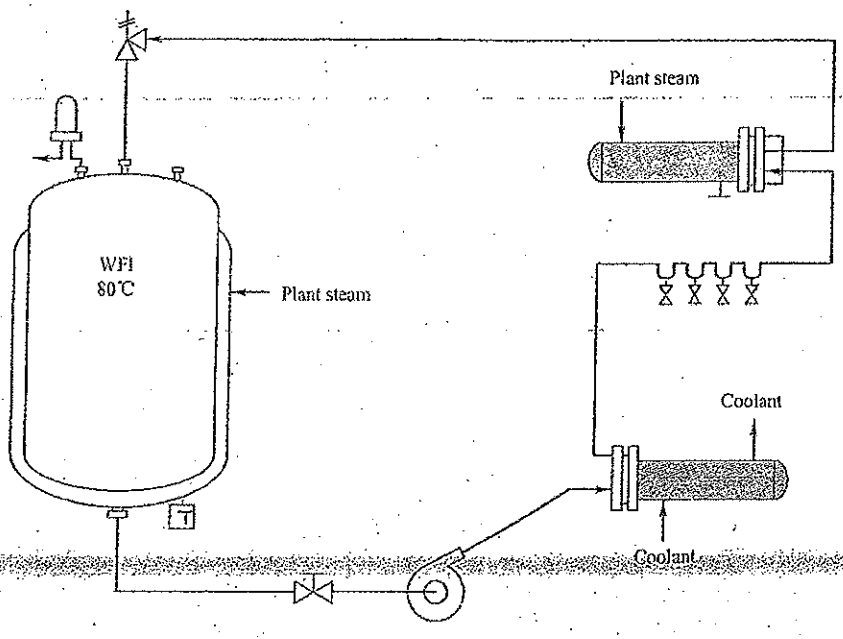


Fig 6.22 Heat storage, cooled and reheated distribution system

vides good microbial prevention measures and facilitates disinfection. If many low temperature points of use with uniform temperature exist in the system, the cost savings are very obvious. The hot water in the storage tank is cooled instantly when passing through the first heat exchanger and flows to the point of use, and is returned to the storage tank after being reheated by the second heat exchanger. The main purpose is to inhibit microbial propagation in the storage systems by means of high temperature storage, and inhibit microbial propagation in the pipeline systems by means of low temperature turbulence circulation while meeting the requirements for water temperature at the point of use. When the enterprise stops production at night, the cooling medium is closed to achieve pasteurization of the return water systems. Meanwhile, pure steam sterilization or superheated water sterilization can be used to conduct overall periodic sterilization for the storage and distribution systems. The main disadvantage of this structure is the very high energy consumption, this is because that regardless of the water being taken from point of use pipeline or not, the circulating water will be cooled and reheated instantly.

6.2.7 Heat Storage, Cooled Bypass Circulating Distribution System

A biological product is characterized by non-heat resistance and easy microbiological contamination during the production processes. It has strict quality risk control requirements during the production process. Due to the production post processing requirements, a biological product workshop has many points of use of normal temperature water for injection, its use temperature is mostly at 20-25 ℃, for example, rinsing water in the appliance cleaning room, water for medium preparation, water for buffer preparation, water for freeze-dried preparations/injections, purification and ultra filtration rinsing water and some other production process water. When the pharmaceutical water is prepared by the high temperature method, the system has many low temperature points of use with uniform temperature, and energy consumption is a critical factor, the "heat storage, cooled bypass circulating distribution system" (Fig 6.23) can be adopted. It is characterized by low system investment cost, low operation and energy consumption, continuously dynamic operation, etc. and is able to control the risk of microbial propagation in the whole system effectively. Its greatest advantage is reducing the energy waste. It suitable for normal temperature water for injection storage and distribution systems for biological products.

The hot water in the storage tank of a "heat storage, cooled bypass circulating distribution system" flows to each point of use after being cooled instantly by a heat exchanger, and returns to the inlet of the transfer pump using a by-pass pipeline. Heating the system storage is done by heating with industrial steam in the tank jacket or heating with a heat exchanger in the main return pipeline. When the point of use needs water, the cooling water in heat exchanger is released, and the main circulation system in a state of low temperature circulation, a large quantity of return water under the control of the proportioning valve enters into the transfer pump directly through the by-pass

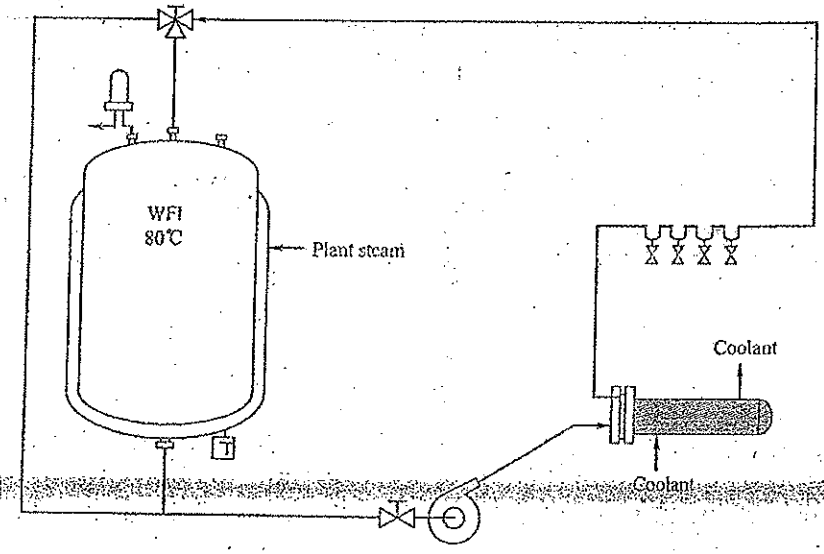


Fig 6.23 Heat storage, cooled bypass circulating distribution system

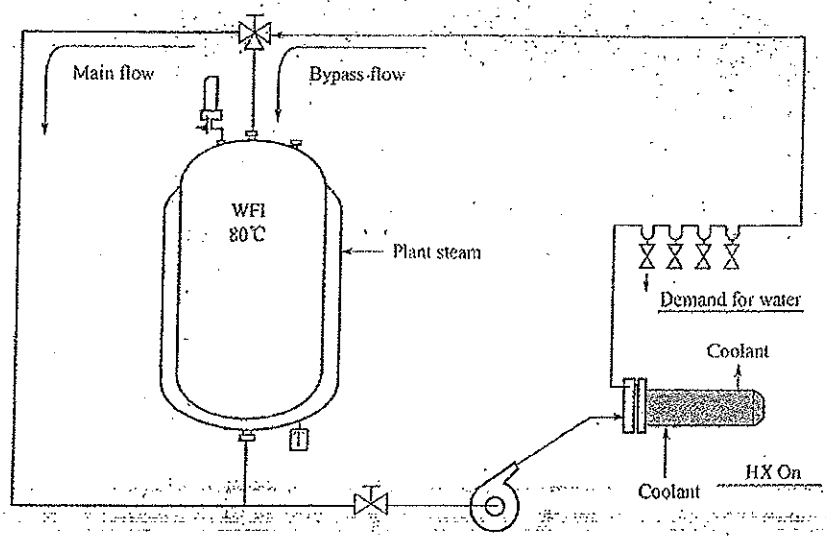


Fig 6.24 Production mode of "heat storage, cooled bypass circulating distribution system".

pipeline, and a little return water enters into the storage tank through the spray ball (Fig 6.24). Its main principle is to inhibit microbial propagation in the storage systems by means of high temperature storage, and inhibit microbial propagation in the pipeline systems by means of low temperature turbulence circulation and meet the requirements of water temperature at the point of use.

To ensure the system has a better microbiological inhibiting effect, the system will prevent cooling by the heat exchanger periodically after the completion of workshop production (e.g. off duty after production of each day) to maintain a periodical heat disinfection state of the circulating pipeline (Fig 6.25). When the point of use does not need water, the cooling water in heat exchanger is not circulating, a large amount of return water under the control of the proportioning valve enters into the storage tank through the spray ball, and a little return water enters into the transfer pump directly through the by-pass pipeline, to ensure the hot water passes through the whole system and stays in the state of pasteurization.

Fig 6.26 illustrates the "heat storage, cooled bypass circulating distribution system" in a biological monoclonal antibody workshop, operating under FDA cGMP validation standards. The high temperature water for injection in the project is used for the CIP workstation, washing machine and GMP cleaning agent. The normal temperature water for injection is used for appliance cleaning, medium preparation, buffer preparation, freeze-dried preparations preparation, purification and ultra filtration rinsing, and disinfectant preparation. After the completion of the workshop production, the "heat storage and normal

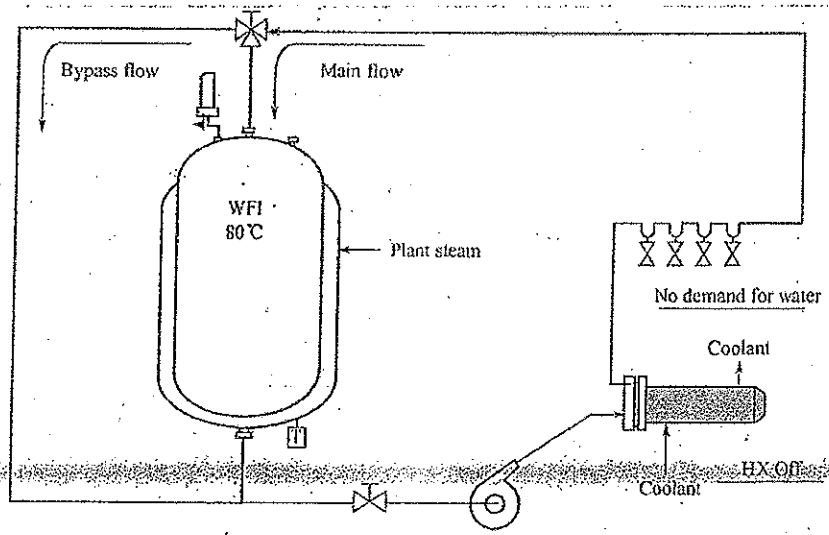


Fig 6.25 Disinfection mode of "heat storage, cooled bypass circulating distribution system"

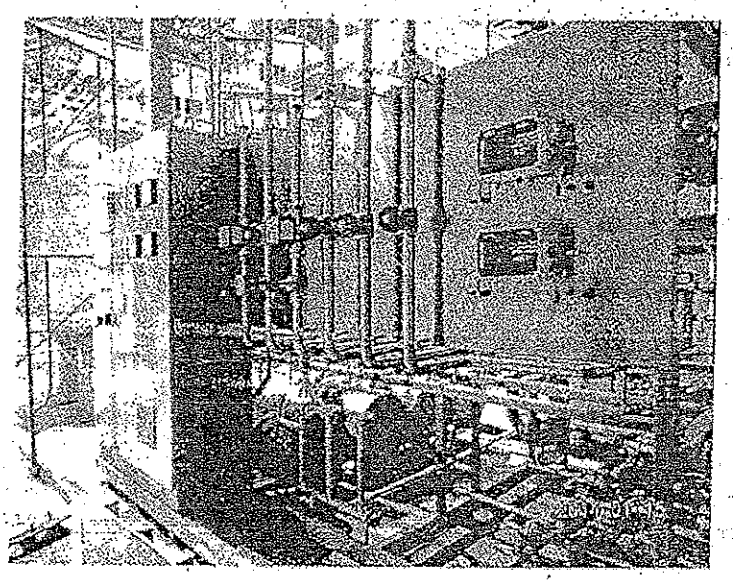


Fig 6.26 Case of "heat storage, cooled bypass circulating distribution system"

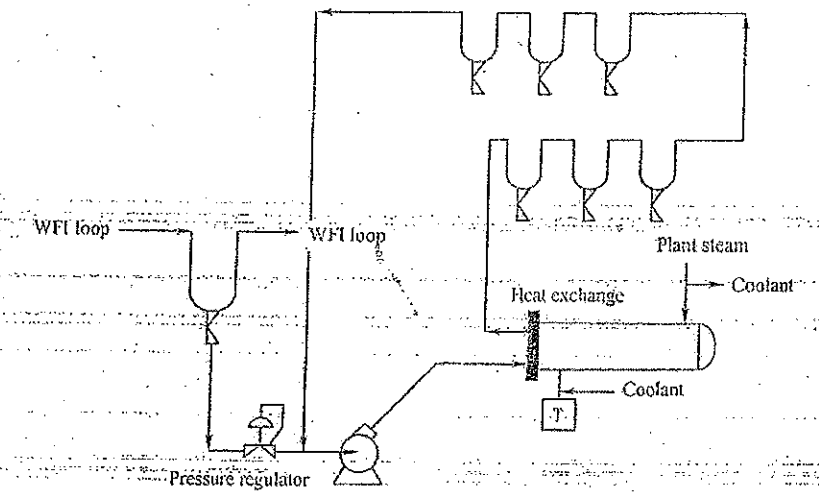


Fig 6.27 Tankless ambient distribution system

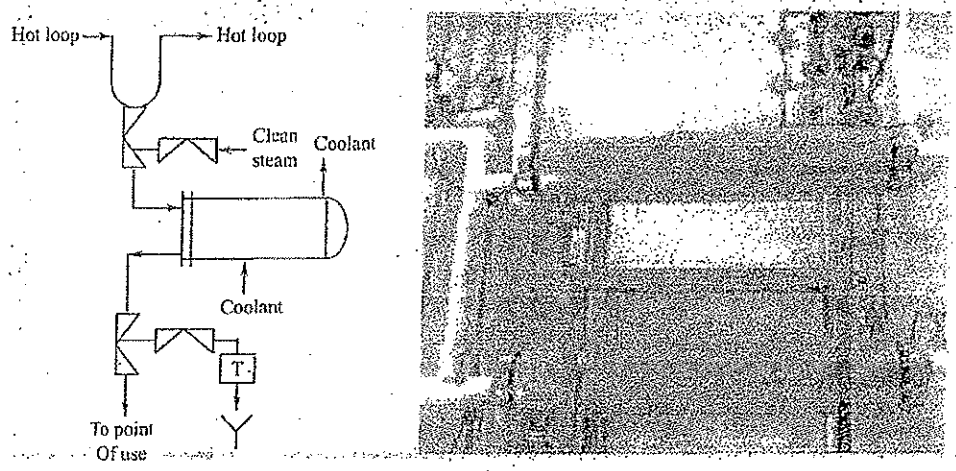
temperature distribution system" is switched to "heat storage and distribution system" automatically. It handles both the normal temperature water demand and energy consumption effectively, with very obvious microbial control effect.

Another design alternative for instances when the whole pipeline operates at low temperature is the "tankless ambient distribution system" (Fig 6.27). Although it has no storage capacity, this design is an effective solution when the enterprise investment budget is limited, and the space of the water generation room is restricted. The main circulating pipeline at the upstream of the system must be operated at lower pressure, furthermore, the microbial contamination occurred in the main circulating pipeline will result in contamination of the whole system. Therefore, the "tankless ambient distribution system" is required to have a more reliable automatic control and improved maintenance and operation measures.

6.2.8 Point of Use Heat Exchange System

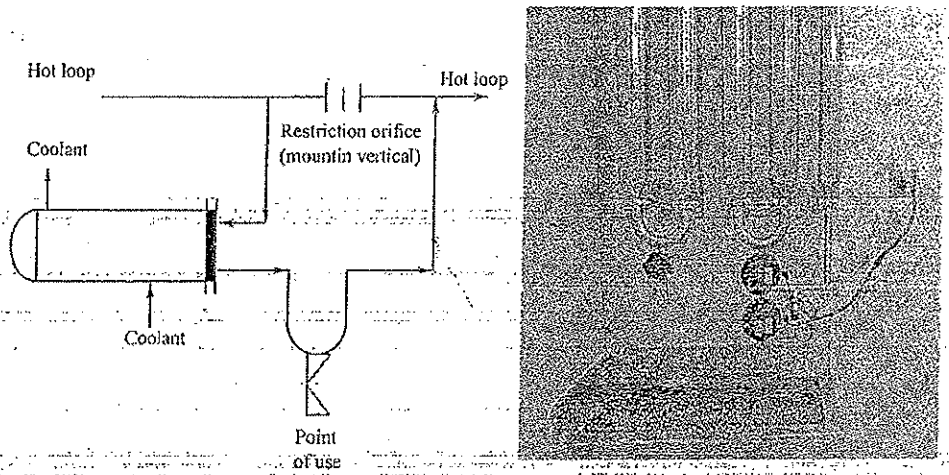
As required by the production process, some water for injection points of use need to be cooled, e.g., water for solution preparation, cleaning and other production processes, etc. When a hot water point of use is present in the same circulating loop with a low temperature point of use, and there are a lesser number of low temperature points of use, the use of the "single point heat exchange system" is a good choice. The commonly used design of the single point cooling mainly includes "single point cooled system behind point of use" and "sub loop cooled system".

"Single point cooled system behind point of use" refers to installing a heat exchanger at the back of point



(a) (b)

Fig 6.28 Single point cooled system behind point of use



(a) (b)

Fig 6.29 Sub loop single point cooled system

of use to achieve a single cooling function (Fig 6.28). The system uses a double-plate tube heat exchanger for instantaneous cooling; to prevent microbial contamination, pure steam can be used to sterilize the exchanger and the downstream pipeline intermittently. The main advantage of the design method is having a small risk of contamination of the pharmaceutical water main system, and the system interface is very clear, it is mainly used for cooling water for injection for the point of use of equipment such as solution preparation tanks and washing machines. The heat exchanger is positioned behind the valve of the point of use; it is usually installed in clean rooms, it has higher requirements for cleanliness and installation space in a clean room.

The "sub loop cooled system" achieves the single point cooling function by means of a branch pipeline (Fig 6.29). In the design, the heat exchanger is installed parallel with the main pipeline. When the point of use has no water demand, the system is sterilized by pure steam or superheated water synchronously with the main circulating system. The greatest advantage of the design method is to achieve full automatic control for the cold point of use, and minimize the effect on the temperature fluctuation of the main pipeline. A double-plate tube heat exchanger is usually installed in a technical mezzanine, its requirements for cleanliness and installation space in clean room less than those for installing a heat exchanger at the back of point of use. It is especially applicable to water for injection cooling for an open point of use such as appliance cleaning. A solution preparation cold point of use with higher automation can also use this design; it

was accepted by most enterprises by virtue of being a beautiful design mode and the possibility of automatic control. It should be noted that the number of cold points of use in the branch pipeline of the sub loop cooled system be not too big in order to reduce the risk of microbial contamination, and avoid the system contamination risk caused by a too long branch pipeline and too long retention time of the cold water.

The "sub loop cooled system" should have a restriction orifice or diaphragm valve installed in the main pipeline and create a certain backpressure to ensure the branch pipeline has sufficient turbulence. Attention should be payed to the effect of the cooling water on the service life of the heat-exchanger at the water for injection cold points of use in the sub loop cooled system design. When the heat exchanger at the cold point of use stops cooling, some cooling water is retained in the shell side of the heat exchanger, if the cooling water is purged and drained from the heat exchanger, a small quantity of cooling water residue in the shell is combined with air, that may result in corrosion of external the side of heat exchange tube, so as to affect the service life and safety of the heat-exchanger. Therefore, it is recommended by FDA *Guide to Inspections of High Purity Water System* that there is no need to drain the cooling water in the shell when the heat exchanger is not working.

The "tube-in-tube cooling module" (Fig 6.30) is

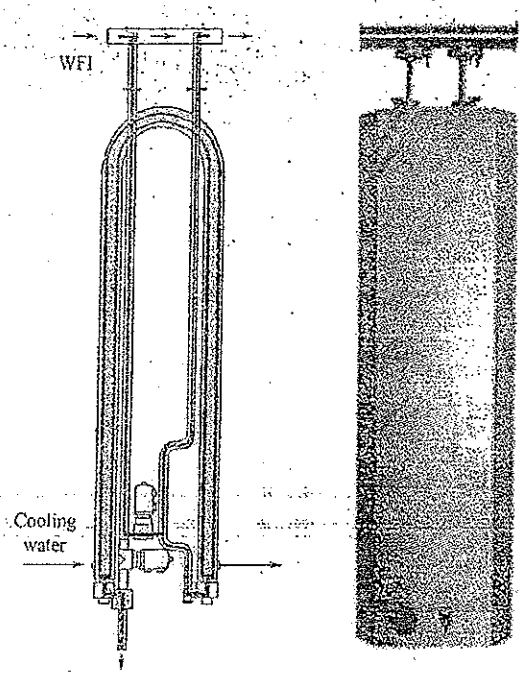


Fig 6.30 Tube-in-tube heat exchanger

a modular design of the sub loop cooled system. The cooled system uses a pitot tube to achieve backpressure in the main pipeline; its design is compact, with easy installation, operation and maintenance. It is especially suitable for cooling simple open water for injection points of use such as a pool.

Chapter 7

Pharmaceutical Steam Systems

Pharmaceutical steam is the most widely used heating agent in the pharmaceutical industry; it participates in the whole production process, including raw material production, separation and purification, finished product preparation, etc. At the same time, the pharmaceutical steam is a good sterilization agent; it has a very strong sterilizing effect and few impurities; it is mainly used in the sterilization of pharmaceutical equipment and systems. The pharmaceutical steam is used in the heating, humidification and sterilization processes during drug production.

7.1 Overview

Steam refers in particular to water vapor, which is widely used in many applications, such as heating, humidification, power generation and drying (Fig 7.1). Steam is classified into saturated steam and superheated steam according to its pressure and temperature. Positive pressure steam has the pressure between 0.1-5 MPa, and the temperature at 110-250 ℃. It is one of the most representative applications of steam in the industry, and widely used for heating and humidification of heat exchangers, steam boxes and other equipment.

When the liquid is evaporated in a limited closed space, some liquid molecules will escape into the space above the liquid level, and become steam molecules. Because steam molecules are in disordered thermal motion, they collide with each other as well as the container wall and liquid surface. When they collide with the liquid surface, some steam molecules are attracted by liquid molecules, return to the liquid and become liquid molecules. When starting evaporation, the number of molecules entering into the space above the liquid surface is larger than that of molecules returned to the liquid, the density of steam molecules in the space above the liquid surface increases continuously accompanying the evaporation, therefore, the number of molecules returning to the liquid is also increased. When the number of molecules entering into the space is equivalent to the number of molecules returning to the liquid, the evaporation and condensation are in the state of dynamic equilibrium. The evaporation and con-

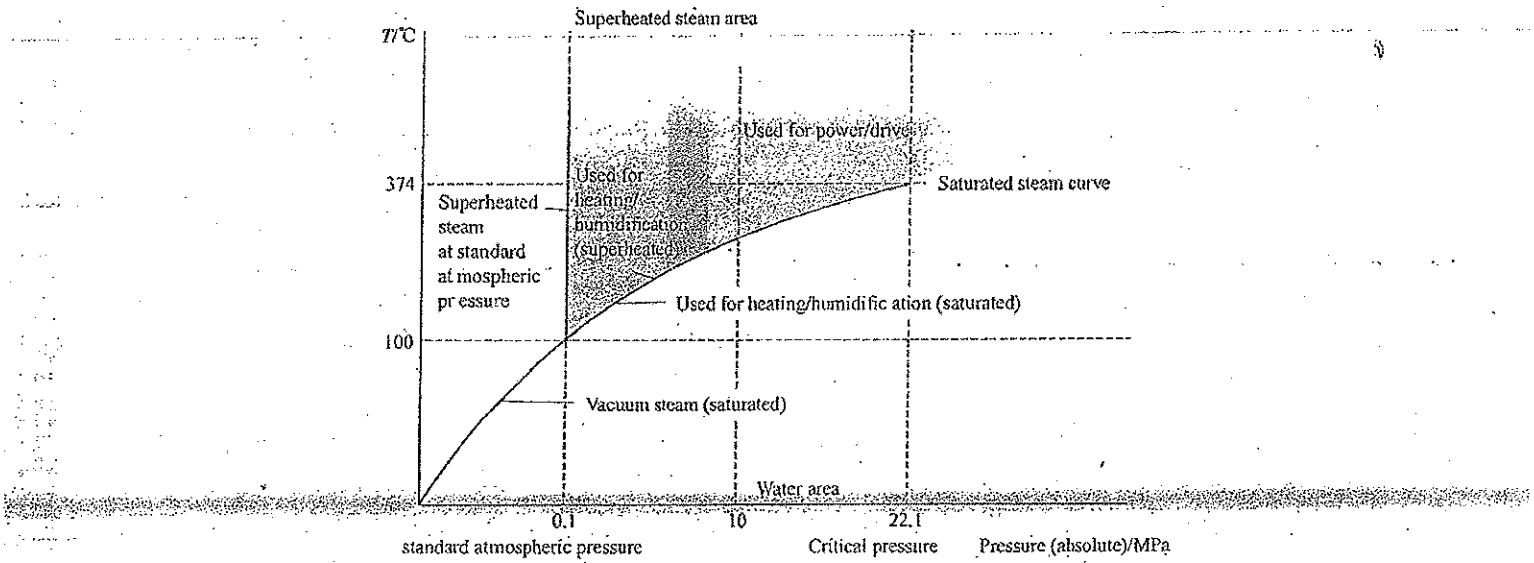


Fig 7.1 Classification of steam

densation are still occurring, but the density of steam molecules in the space above the liquid surface is not increased any more, this is called a saturated state.

The liquid of a saturated state is called saturated liquid, its corresponding steam is called saturated steam, initially, it is wet saturated steam, and it becomes dry saturated steam when the moisture in the steam is completely evaporated. The temperature of the steam is not increased during the whole process from unsaturation, wet saturation to dry saturation. The raw material for saturated steam is water, which is safe, clean and has low cost, especially at the temperature of 100 ℃ and above; it has many advantages, which makes an excellent heat source. Its main feature is the achievement of a rapid and uniform heating process due to the latent heat of vaporization; this can effectively improve the product quality and production efficiency. The pressure and temperature are in a state of dynamic equilibrium, the temperature control can be accurately achieved by controlling the pressure. The heat transfer coefficient is high, and the required heat exchange area is relatively small, which can reduce equipment requirements at the preliminary phase.

Superheated steam is formed by rising the temperature of the dry saturated steam, which continues to be heated, exceeding the saturation temperature. Superheated steam has its special advantages, and is widely used in thermal power generation, food cooking, and sludge drying industry at present. When the equipment is driven by steam, and superheated steam is supplied and exhausted, condensate water cannot be generated. In this way, equipment hazards caused by carbonic acid corrosion can be avoided effectively. The heat efficiency and operational capacity can be enhanced effectively when the degree of superheating reaches infinite specific volume, even vacuum for low pressure steam. Moreover, the theoretical heat efficiency of a steam turbine is related to the enthalpy value of its outlet and inlet, therefore, the increase of the pressure of superheated steam means the increase of the enthalpy value at the inlet of the steam turbine, thus effectively improving the heat efficiency. Using superheated steam for cooking has outstanding advantages, the processed food undergoes uniform heating, fast heating, better taste, and it can prevent losing vitamins. Superheated steam technology can also be used to clean and sterilize conveyor belts, heat food materials, pulverize and deodorize food residues in food processing facilities. The superheated steam drying method implies the superheated steam to be in contact with the materials to be dried, for moisture removal. It is a drying method developed in recent years; compared with traditional hot air drying, this drying technology uses water vapor as the drying agent; the exhaust gas of the drying machine is steam, the latent heat of the steam can by recovered by condensation, and reused.

Superheated steam must be cooled to saturation temperature before condensed to release its latent heat of vaporization, compared with the enthalpy of evaporation of saturated steam, the quantity of heat released by superheated steam when it is cooled to saturation temperature is very small. The main disadvantage of heating by superheated steam is having a low heat transfer coefficient, low production efficiency, and the necessity of a larger heat transfer area; the steam temperature cannot be regulated by controlling the pressure; higher transfer speed should be ensured, otherwise, heat will be lost from the system resulting in a temperature drop; the temperature may be very high, which requires the use of expensive equipment, therefore, it needs higher initial investment. Consequently, superheated steam is rarely used in the heat transfer processes for pharmaceutical industry, and saturated steam is a more suitable choice for the heat source in heat exchange and sterilization processes, compared to superheated steam.

7.1.1 Classification of Pharmaceutical Steam

Steam is an important utility in pharmaceutical enterprises; it is mainly used as the heat source for the generation of pharmaceutical water, temperature control of process equipment, sterilization of sterile process equipment, utensils and terminal products sterilization, etc. Steam can be divided into plant steam (black steam), process steam and pure steam (clean steam).

Plant steam is mainly used to heat process equipment which has no direct contact with products; it is a non-direct impact system. Plant steam can be subdivided into common plant steam and no chemical added steam. Common plant steam is steam generated using softened municipal water, it is a non-direct impact system, used to heat process equipment which has no direct contact with products; usually, only corrosion prevention of the system is considered. No

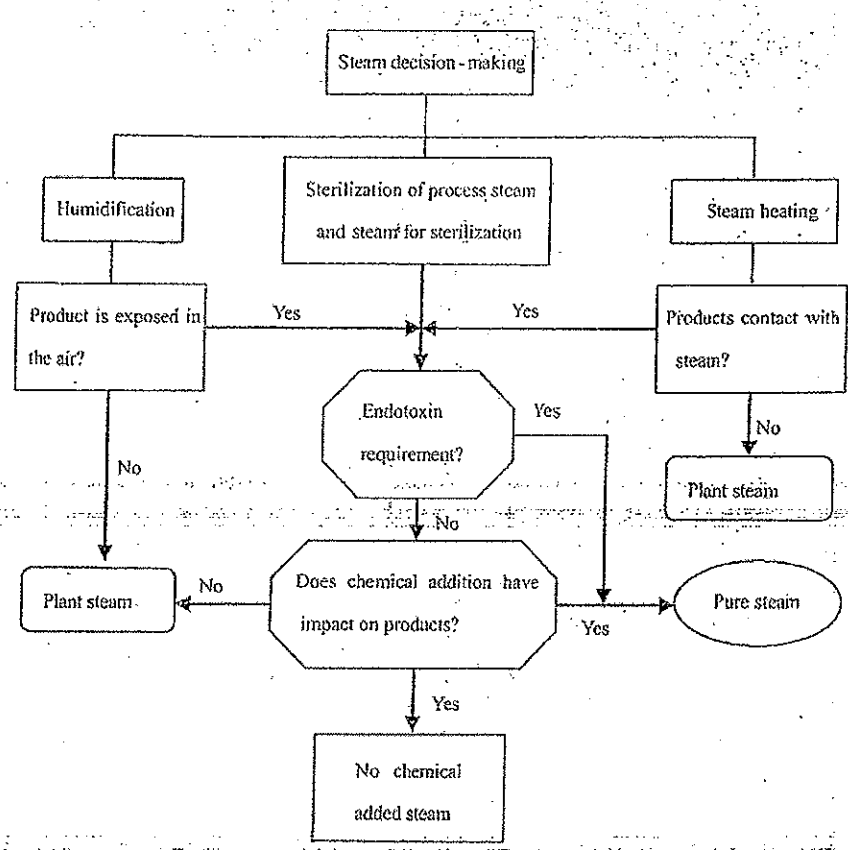


Fig 7.2 Pharmaceutical steam decision-making tree

chemical added steam is steam generated using purified, municipal water with added flocculent, it is a non-direct impact system, mainly used to humidify air, heat and sterilize process equipment having indirect contact with products, inactivate waste materials and waste fluids, etc. No chemical added steam should not contain volatile compounds such as amines and hydrazines.

Process steam is a direct impact system, it is mainly used for heating and sterilizing terminal sterilization products. Its condensate should meet the municipal drinking water standard at least.

Pure steam is a direct impact system, it is generated by distillation; its condensate should meet the requirements of water for injection. If pure steam is used in a moist heat sterilization process, it should meet the requirements of EN 285 and HTM 2010 applicable to non-condensable gas, degree of superheat and dryness. Pure steam is generated from raw water, which should be treated and meet the requirements of drinking water at least. Many enterprises use purified water or water for injection to generate pure steam. Pure steam contains no volatile additives, so it will not be contaminated by impurities such as amines or hydrazines. It is very important to prevent the contamination of injection products.

Which specification is adopted for steam during the design of a steam system can be referred to the decision-making tree recommended by ISPE, as illustrated in Fig 7.2.

7.1.2 Applications of Pharmaceutical Steam

In the pharmaceutical industry, the main functions of steam include heating, sterilization and humidification, etc. When steam is used for indirect humidification (e.g., injecting steam in HVAC air flow before filtration of final air), theoretically, it is not required that the steam is more pure than ambient air; plant steam can be used. When considering the humidification process, the impact of potential volatile impurities on the final drug products should be assessed, e.g., amines or hydrazines impurities. This is very important for critical process points, such as sterile filling and dosing. If it has been found that the diluted water vapor can seriously contaminate drugs, cleaner steam is required to be used, therefore, some enterprises usually use pure steam to conduct air-conditioning humidification for critical process points.

Table 7.1 Application of pharmaceutical steam

Use	Type
Applied to intestinal and parenteral preparations, steam has direct contact with products	Pure steam, generated by pure steam generator
Critical steps in the production process of APIs; steam has direct contact with APIs	Pure steam, generated by pure steam generator
Non-critical steps in the production process of APIs; the added impurities will be removed in the subsequent processes	Pure steam, no chemical added steam is also acceptable.
Sanitation and sterilization of pharmaceutical water systems.	It is usually pure steam, it is acceptable to conduct sufficient rinse after using no chemical added steam
Used for humidification of critical HVAC systems for preparations production; steam has direct contact with drug products. Chemical additives may have adverse effect on drug products	Pure steam, generated by pure steam generator
Used for humidification of non-critical HVAC systems, and drug products are not exposed in the environment directly	Pure steam, no chemical added steam or plant steam
Used for humidification of clean room in which critical process is performed	Pure steam, generated by pure steam generator
As heating source of non-critical posts or double-tube plate heat exchanger	No chemical added steam or plant steam

The purity requirement for steam is determined by the product, but it is impractical to produce the specific steam for each case. Taking engineering management, initial investment and quality risk into consideration, some enterprises will select pure steam with higher specifications to substitute no chemical added steam or process steam. Usually steam with one or two degrees of purity is generated and distributed in the manufacturing process. As a general rule, even if the condensate water of the pure steam may not be required to meet the requirements of water for injection specific to a given application, it is necessary to assess the design and operation of the distribution systems of the evaporator if the condensate water does not comply with those requirements.

Plant steam and pure steam are most commonly used by pharmaceutical enterprises for the production of sterile products. Plant steam is usually used to humidify HVAC systems in non-critical points, heat tank jackets and heat exchangers, sterilize non-product-contact equipment, etc. Pure steam is usually used to sterilize products in sterilizers, sterilize in place pharmaceutical equipment or systems, humidify HVAC systems in critical process points, etc. Table 7.1 lists the typical applications of pharmaceutical steam, general requirements of the pharmaceutical industry and acceptable generation methods.

7.2 Regulations and Pharmaceutical Steam

There isn't a lot of guidance for the pharmaceutical industry regarding the technical specifications, installation requirements and quality assurance of the pharmaceutical steam. The regulatory guidelines for steam generation and purity are usually consistent with those of water for injection, but other special requirements for steam quality must be added, including non-condensable gas, degree of superheat and dryness. UK standards EN 285, HTM 2010 and other international standards provide the indicators for the purity and quality of pure steam applicable to bioprocess technology and pharmaceutical industry. These guidelines include the requirements for material technical specification, size/tolerance, surface treatment, material connection and quality assurance.

7.2.1 United States Pharmacopeia

The *United States Pharmacopeia* specifies guidelines for the generation, quality requirements and use of pure steam; it outlines detailed requirements for the tests of raw water, added substances and properties of condensate water. *United States Pharmacopeia* also stipulates that the user should determine the dryness level and content of non-condensable gas for pure steam

based on the specific use. It stipulates that when pure steam is used in parenteral preparations or other applications which have requirements for pyrogen control, its endotoxin content must comply with the index of water for injection. The large volume parenteral solutions cGMP published in 1976 stipulated that if the raw water of steam generated by a boiler is in contact with components, the drug itself or drug contact surfaces, volatile additives such as amines or hydrazines should not be contained in the raw water.

7.2.2 European Guide

A continuous supply of dry and saturated pure steam is necessary to ensure effective sterilization. The water entrained in the steam will reduce the heat transfer, and the sterilization effect of superheated steam is not better than that of saturated steam. If non-condensable gas is present in the steam, it will act as a thermal insulation of the heat exchange surface, which will make some sterilizers unable to reach the conditions required for sterilization and negatively affect the sterilization effect.

In the HTM 2010 and EN 285 standards, the following additional requirements are stipulated for pure steam used in sterilization equipment:

- the volume of non-condensable gas in 100ml saturated steam should not exceed 3.5ml (equivalent to 3.5% *V/V*)
- the dryness value shall be not lower than 0.95 when sterilizing metal carriers, and the dryness value should be not lower than 0.9 when sterilizing non-metal carriers;
- superheated temperature should not exceed 25 ℃ when the pressure of pure steam is reduced to atmospheric pressure.

7.2.3 Chinese Guide

The *Chinese GMP Inspection Guide* (2010 *edition*) stipulates the requirements for pure steam as follows:

Pure steam is usually steam generated by a pure steam generator or the first stage evaporator of a multi-effect water distiller; when using purified water as raw water, the condensate water of pure steam should meet the requirements of water for injection. Softened water, deionized water and purified water can be the raw water of a pure steam generator; it is transferred to the point of use at certain pressure after evaporation and separation (removal of contaminants such as particles and bacterial endotoxins).

Pure steam can be used in moist heat sterilization and other processes, such as sterilization of equipment and pipelines; its condensate has direct contact with the surface of equipment or products, or materials used for analyzing the properties of products. Pure steam is also used to humidify air in clean facilities; relevant materials are exposed to air of corresponding cleanliness grade in these areas.

7.2.4 Industry Guide

The *ASME BPE Standard* specifies the requirements for the design and construction of pure steam generators and distribution systems. It provides guidance for pure steam systems in the bioprocess technology and pharmaceutical industry. The similar guides in Europe and Asia are respectively the DIN standard and JIS-G standard, which include material technical specifications, size/tolerance, surface treatment, material connection and quality assurance.

The ISPE guide has detailed introductions for steam sterilization and sanitation (refer to section 3.2.15.5) and pure steam (refer to section 6.3.2) used in *Aseptic Manufacturing Facilities*.

a. Steam sterilization and sanitation. When the equipment located in an aseptic area is sterilized using sterilization in place system, the pure steam is piped in the clean room, and the remaining steam and condensate water are drained through pipes. For maintenance and operation convenience, when draining the steam condensate water out of the clean room, the pure steam trap and its components should be installed out of the clean area and as far away as possible. When necessary, materials suitable for surface sanitation should be used, and the thermal insulation materials or similar components installed in the clean room should have no particle shedding.

b. Pure steam. Pure steam used for sterile products should not contain any boiler additives and other impurities, a controllable water source should be used to generate the pure steam, while the condensate water of pure steam should comply with the standard of water for injection. The design principle of a pure steam system requires the elimination of the potential for microbial growth in condensate water to the maximum extent. The pure steam used in the process of sterilization should minimize superheating when entering the high pressure container. The methods for controlling

the content of non-condensable gas by an ideal pure steam generator mainly include the raw water preheat method or the system air exhaust method. When pure steam is used to sterilize equipment or system components coming in direct contact with products, the content of non-condensable gas, dryness and degree of superheat should be tested periodically, and controlled within the range stipulated by HTM 2010 and EN 285.

7.3 Pure Steam Systems

Pharmaceutical steam used by pharmaceutical manufacturing enterprises is mainly plant steam and pure steam. Pure steam is a clean utility system coming in direct contact with products during the pharmaceutical production process, which is emphasized in the book. From the perspective of function, the pure steam systems are mainly composed of the generation unit and distribution unit. The generation unit mainly includes a pure steam generator; its major function is to distill and "purify" raw water to pure steam conforming to pharmacopeia requirements in a continuous and stable way. The distribution systems mainly include a distribution pipeline and points of use; its major function is to transfer pure steam to the required process points at a certain flow rate to meet the requirements on flow, pressure and temperature, and maintain the quality of pure steam conforming to pharmacopeia and GMP requirements.

7.3.1 Pure Steam Generator

The production equipment using pure steam available on the market usually use plant steam as the heat source, and uses the heat exchanger and evaporation column for heat exchange as well as for generating steam and conducting effective steam-liquid separation to obtain pure steam. The heat exchanger, including the vaporization column, using plant steam as the heat source, are recommended to use a double-tube plate structure; such structure design can prevent pure steam from contamination by the heating media. At present, the major pure steam generation methods include boiling evaporation and falling film evaporation (Table 7.2).

The working principle of a boiling evaporation steam generator is as follows: Raw water enters into the separator and tube pass of the evaporator through a feed pump; the liquid level is controlled by a liquid level sensor connected with PLC. Plant steam enters the shell pass of the evaporator to heat and evaporate raw water in the tube pass, converting raw water to steam entraining a few small liquid drops. The small liquid drops are separated from steam by gravity at low speed and the high stroke of separator, and returned to raw water for re-evaporation; concentrated water is drained continuously from the bottom of equipment. Steam enters the top of the separator through a specially designed clean screen mesh device, and pure steam enters each point of use in the distribution systems through an output pipe (Fig 7.3). Pure steam is sampled and tested in place before use, and transferred to the point of use within the required pressure value range. A boiling evaporation steam generator can be viewed as essentially a traditional evaporation boiler. The adjustment of plant steam keeps the pressure of pure steam at the value set by a program according to the requirements of the production process; it is stably maintained at the pressure value set by the user. During the evaporation of raw water, the replenishment of feed water is controlled by liquid level to make it maintain at a normal level. Intermittent draining can be set in the program for concentrated water.

Table 7.2 Comparison of boiling evaporation and falling film evaporation

Item	Boiling evaporation	Falling film evaporation
Major heat exchange position	Heat exchanger	Tube column
Steam response speed	Slower	Superheated water circulation response speed is very fast
Steam-liquid separation	Natural settling of wire mesh demister by gravity	Natural settling by gravity; Reverse the direction of steam-liquid motion for 180°; Spiral separation (By using the difference of centrifugal force)
Residual liquid draining	Continuous draining	Continuous draining
Endotoxin removal ability	Better	Excellent

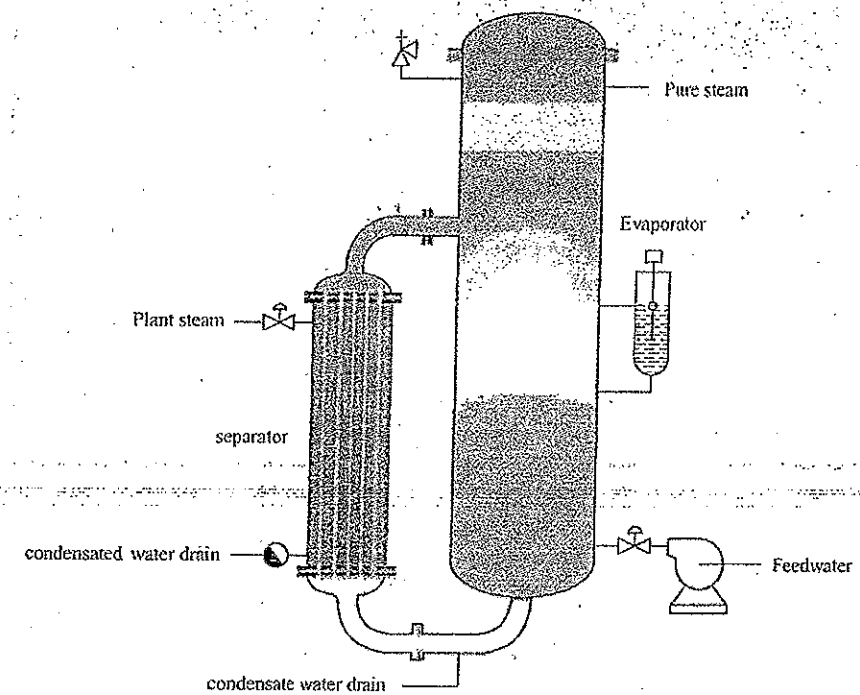


Fig 7.3 Boiling evaporation steam generator

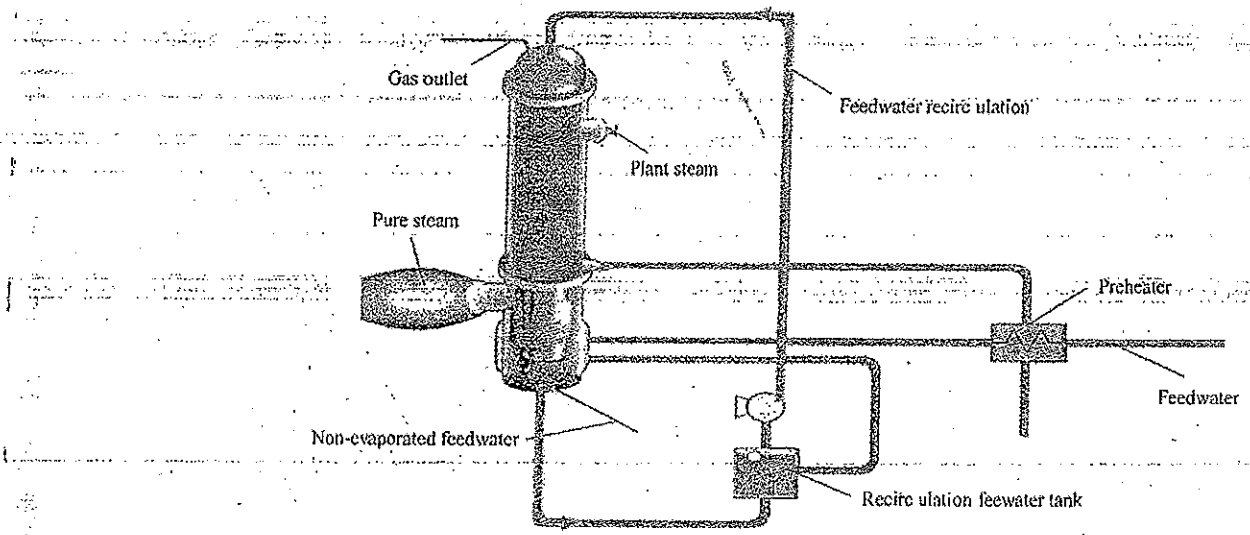


Fig 7.4 Falling film evaporation steam generator

A falling film evaporation steam generator usually adopts an evaporation column similar to the first stage evaporation column of a multi-effect water distiller. Its main principle (Fig 7.4) is that raw water enters into a buffer tank and superheated water circulating pump after being heated by plant steam at the first stage preheater, and then enters the top of the evaporator through the circulating pump, and enters into the evaporation tube nest with uniform distribution due to a distribution plate device; it forms a thin film shaped water flow. Heat is exchanged with the plant steam, the liquid film in the tube nest is evaporated to steam very fast, steam continues to climb spirally and exits at a pure steam outlet as pure steam, through a steam-water separation device, while residual liquid entraining pyrogen is drained continuously at the bottom of column. A small amount of pure steam is cooled and collected by a condensate sampler to judge whether the pure steam is in compliance with the requirements of the online test of conductivity.

The condensate of pure steam used for moist heat sterilization must comply with the specifications of

water for injection stipulated in the pharmacopoeia, endotoxin content being a very important indicator. The principle of removing endotoxin in a pure steam generator is based on the non-volatility of endotoxin. The higher the efficiency of steam-water separation, the purer and more stable the steam generated by the equipment. If the steam entrains liquid droplets, then the endotoxin attached in the liquid droplets will contaminate the pure steam. The separation of steam from entrained moisture is very important in the design of a steam generator. The pharmacopeia requires that the endotoxin in water for injection shall be lower than 0.25 EU/ml, a pure steam generator can reduce the endotoxin in raw water by 3-4 lg value. The endotoxin content in condensate water of pure steam generated with a three-level separation design can be lower than 0.01 EU/ml. It can perfectly prevent the medication risk of sterile injections caused by contamination with endotoxin in pure steam.

7.3.2 Pure Steam Distribution System

The pure steam will be transferred to each point of use by a pure steam distribution pipeline. Pure steam is mainly used for sterilization in place of moist heat sterilizers and dosing systems, and to humidify the HVAC system in critical points. All components a in pure steam distribution system should be able to be completely drained. Because the operating temperature of pure steam system is very high, a reasonably designed pure steam pipeline will have a self sterilization function; the risk of microbial contamination is relatively small, therefore; pure steam generator and distribution pipeline systems can use mechanical polishing $Ra < 0.8$ μm as the final surface finish. Certainly, if the enterprise selects materials of electrochemical polishing for construction, the welding and passivation quality of the pure steam systems will be further guaranteed. In order to restrict the pressure drop, and prolong the pipe lifetime, the flow rate of a pure steam distribution pipeline is usually designed not to exceed 37 m/s, and the flow rate of a point of use pipeline is usually designed as 20-30 m/s. The connection of the pipe fittings should be automatic argon arc welding, sanitary high pressure clamp or flange. Tri-clamp connection should be preferred for the instruments, while for the instruments located behind the diaphragm valve in the discharge pipe, an appropriate threaded connection can be selected, due to the fact that the discharge pipe is maintained at high temperature.

When pure steam is used ina moist heat sterilization process, the quality of condensate water should meet the relevant requirements of water for injection. The endotoxin content in pure steam used in sterile parenteral preparations or under other special conditions must be controlled. Similarly to water for injection systems, the pure steam pipeline systems can be made of 316L stainless steel. The presence of condensate water in a distribution system is one of the potential risks of microbial contamination occurring in the pure steam systems. If pure steam entrains condensate water, the endotoxin dissolved in the condensate water will be likely to be present in the finished products.

The design of a pure steam point of use usually includes a conveniently operated isolating valve and oriented steam trap. The supply pipe for the point of use valve is usually designed to be a branch from the top main pipe to the condensate water steam trap. Fig 7.5 shows the design principle of a pure steam point of use as recommended by *ASME BPE Standard*. The design principle can ensure that the condensate water in each point of use of the pure steam is timely drained thus reducing the risk of microbial and endotoxin contamination effectively.

Ball valves, diaphragm valves and steam traps are widely used in pure steam systems (Fig 7.6). Sanitary ball valves can be widely used in sterile gas systems, such as pure steam systems, sterile nitrogen systems, sterile compressed air systems, etc. The sanitary ball valve is made of SS316L, with a tri-clamp connection, and three-pan design to facilitate maintenance and disassembly. It shall be noted that a ball valve is prohibited to be used in sterile liquid processes due to its structure, because the ponding in the center of the ball valve may easily become a breeding ground for microorganisms and cause microbial contamination of the system when the ball valve is closed. The diaphragm valve designed with a PTFE/EPDM composite diaphragm can resist high temperatures, above 150 ℃, and can be used repeatedly; therefore, the diaphragm valve with double diaphragms is also widely used in high temperature systems such as pure steam systems. The thermostatic steam trap is the ideal steam trap for pure steam systems. To ensure the safety of the pure steam system, the steam trap should be made of SS316L and with a tri-clamp connection.

Similarly to a pharmaceutical water system, a

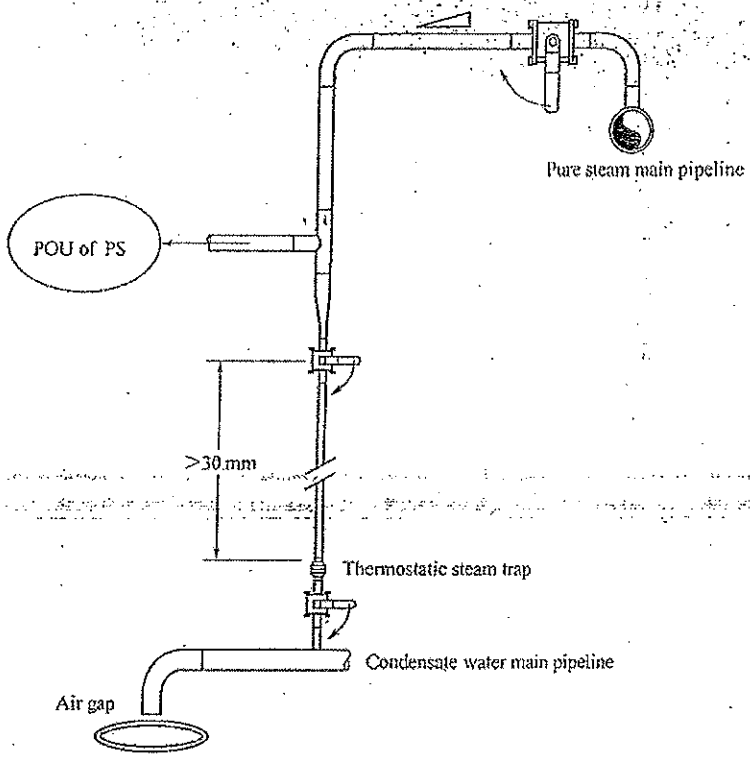
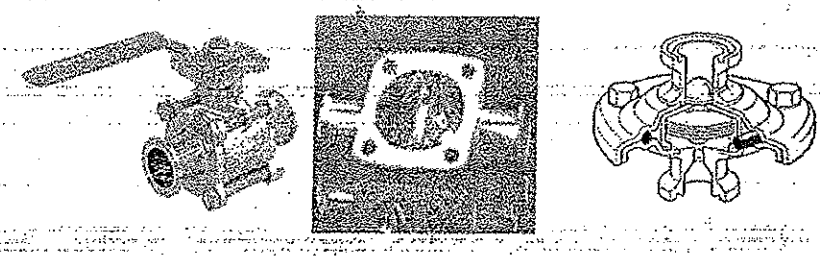


Fig 7.5 Schematic diagram of pure steam point of use



(a) Sanitary ball valve (b) Diaphragm valve (c) Thermostatic steam trap

Fig 7.6 Pure steam valves

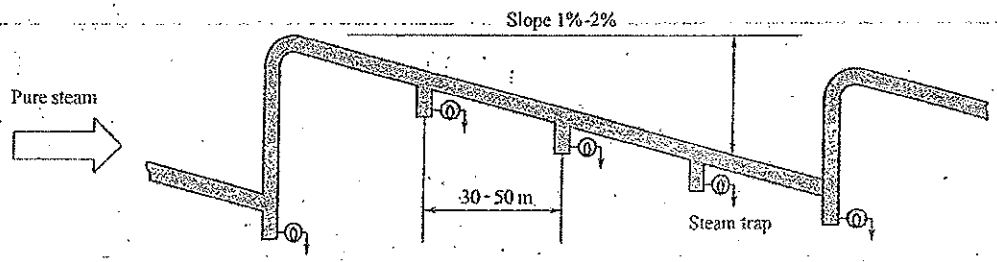


Fig 7.7 Installation of pure steam pipeline

pure steam distribution systems design should use track welding, and passivation is required after installation. The slope of a distribution pipe should not be designed to go against the steam flow direction, to prevent steam entraining water and gathering condensate water. The pure steam distribution systems should have a device that completely exhausts air, and a thermostatic draining device should be installed at the bottom of the vertical ascension pipes every 30-50 m. At any other lowest point in the system a thermostatic steam trap should be installed (Fig 7.7).

An air break is also called air gap. It is recommended by *ASME BPE Standard* that an air break (Fig 7.8) is used in the equipment or system terminal

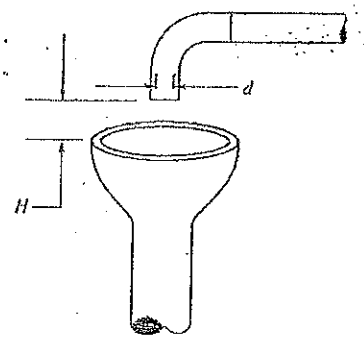


Fig 7.8 Air break

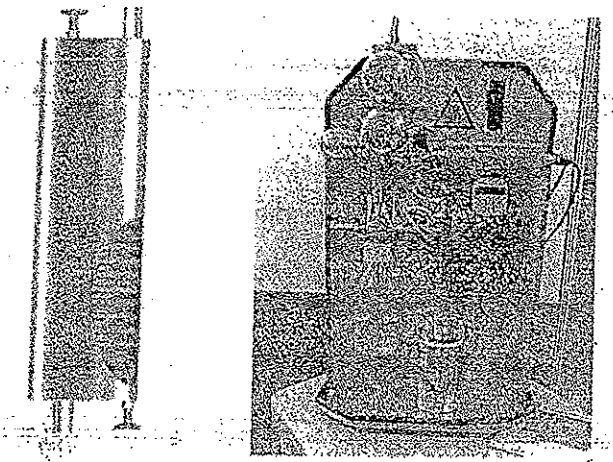


Fig 7.9 Pure steam "purity" samplers

so that reverse contamination can be avoided effectively. Because the draining systems may result in a reverse flow of condensate water or waste water, due to back-pressure, causing contamination of the pure steam systems. Here when $d \geqslant 12.7$ mm, $H = 2d$, and when $d < 12.7$ mm, $H = 25$ mm.

7.3.3 Pure Steam Sampling

Pure steam sampling mainly includes pure steam "purity" sampling and pure steam "quality" sampling.

If the conductivity of the pure steam is measured for the gas phase, it will result in the reading being lower than the expected value, therefore, it is a must to cool the pure steam first, and then measure the conductivity of the condensate water. Pure steam should not contaminate the drug products, if endotoxin and pyrogen are required to be tested from samples, the sampler, pipe and valve should have a sanitary construction. During the phase of operational qualification, each point of use should be monitored by sampling for "purity of condensate water". The sampling position is usually done at the outlet of the pure steam generaror, of the distribution pipeline, and at each point of use. A permanent online sampler can be installed at the outlet of the pure steam generator or the farthest point of the distribution systems. For example, pharmaceutical enterprises usually install an online sampler equipped with a conductivity monitoring and alarm device at the outlet of the pure steam generator. Sampling at the pure steam point of use is usually done using a portable sampler or an integrated sampling module (Fig 7.9). Its main features are flexibility, convenience, and ease of sampling.

High efficiency moist heat sterilization should use dry saturated steam with the lowest degree of superheat. The pure steam used for sterilizing core process equipment or systems such as a moist heat sterilizer

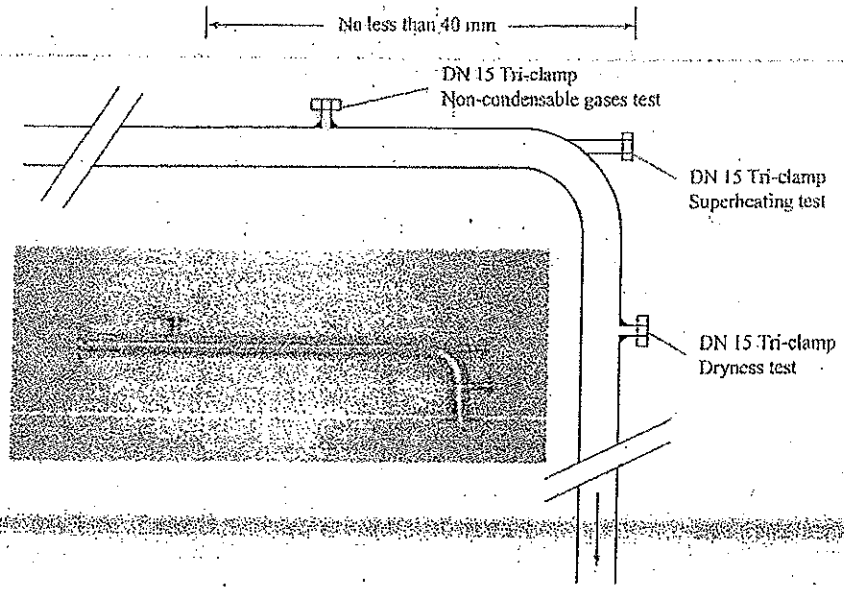


Fig 7.10 Pure steam "quality" sampler

should be tested for the content of non-condensable gas, dryness and degree of superheat, that must be in the controllable range. Pure steam "quality" sampling can be used to confirm the dryness, degree of superheat and content of non-condensable gas, which can be determined by using a steam calorimeter to measure the dryness or saturation of steam. The steam calorimeter is mainly used to measure the proportion of steam in a steam-water mixture. Britain standard EN 285 provides detailed guidance for steam quality testing. Fig 7.10 is a typical pure steam sampling pipe, which is set with three sampling ports for sampling and analyzing the content of non-condensable gas, dryness and degree of superheat of pure steam respectively.

Chapter 8

Sanitation and Sterilization Technology

8.1 Overview

Sanitation and sterilization are two methods for rapidly reducing bioburden in the pharmaceutical water systems. Sanitation refers to killing or eliminating pathogenic microorganisms in media with physical or chemical methods to make them harmless. It usually refers to killing the propagules of pathogenic microorganisms, but not to eliminating the spores, therefore, sanitation is not thorough enough, and cannot substitute sterilization. Sterilization is killing all viable microorganisms with chemical agents or physical methods, including all bacterial propagules, spores, molds and viruses to reach complete sterility. The pharmaceutical industry takes the one per million microbial contamination rate as the relative standard of "sterility" for sterilized products. A different expression of the same standard is 10^{-6} (i.e. the sterility assurance value of the product is 6) survival rate of microorganisms in the steam sterilized products. This chapter not only introduces the application of the sanitation and sterilization technologies in pharmaceutical water systems, but also describes other pharmacopeia accepted sanitation or sterilization technologies to facilitate the reader's understanding of the basic principles and applications of sanitation and sterilization technologies in the pharmaceutical industry more comprehensively.

EU GMP regulates the design, installation and maintenance of water treatment facilities and its distribution systems should ensure that the supply water meets the appropriate specifications. A water system should not exceed its designed capacity during operation. Microbial growth should be prevented during the generation, storage and distribution of water for injection, e.g. thermal insulation circulation at above 70 °C.

The section 6 in Chapter 5, *Equipment*, of the *Chinese GMP* (2010 *Revision*) provides regulation on pharmaceutical water as follows:

Article 99 *the generation, storage and distribution of purified water and water for injection should be able to prevent microbial propagation. Purified water can use circulation, and water for injection can use thermal insulation circulation at above 70 ℃.*

Article 101 *purified water and water for injection pipelines should be cleaned and sanitized according to operation procedures, and relevant records should be kept. When microbial contamination of pharmaceutical water is found to reach the alert or action limit, this should be handled according to operation procedures.*

Under normal operating conditions, the microbiological indicator in the pharmaceutical water systems will increase as time goes on, and microbial contamination is the most commonly and easily occurred contamination in pharmaceutical water systems. It is regulated in the pharmacopeia; the microbial limit for purified water is 100 CFU/ml, for high purity water is 10 CFU/100ml, and for water for injection is 10 CFU/100ml. The pharmaceutical raw water does not have the same requirements as sterile water, but necessary bacteriostasis procedures are essential. As for the sterile pharmaceutical water such as sterilized water for injection, the pharmacopeia stipulates that it must comply with the requirements of sterile products. The sanitation/sterilization technology is the most common and important technology for controlling the microbiological indicator of the pharmaceutical water systems, therefore, pharmaceutical enterprises should adopt appropriate microbial inhibition procedures and sanitize or sterilize the system periodically, to ensure the microbiological indictor in the purified water systems or the water for injection systems meet the limit requirements of pharmacopeia and production quality.

Sanitizers are generally divided into physical sanitizers and chemical sanitizers. Ultraviolet sanitation may have a localized application, and filtration sterilization

Table 8.1 Sanitation and sterilization measures

Type	Purified water system	Water for injection system
Microbial inhibition measures during normal operation	Ozone sanitation Ultraviolet sanitation Low temperature storage(about 20 ℃)	Storage above 70 ℃ Low temperature storage(below 20 ℃)
Periodical sterilization &-sanitation measures	Hydrogen peroxide sanitation Pasteurization sanitation Ozone sanitation Circulated steam sanitation	Pure steam sterilization Superheated water sterilization

may temporarily come into play. In pharmaceutical water systems, pasteurization and superheated water sterilization or pure steam sterilization are regarded as more conventional physical sanitizing methods. Ozone, hydrogen peroxide, hypochloric acid, etc. are commonly used chemical sanitizers. Table 8.1 lists the commonly used sanitation and sterilization measures in pharmaceutical water systems.

8.2 Regulatory Requirements for Sterilization

8.2.1 Pharmacopeia

The Annex Ⅻ, *Sterilization Methods*, in the *Chinese Pharmacopoeia* (2015 *edition*) stipulates that sterile drug means that no viable microorganisms are present in the drug product. The commonly used sterilization methods are moist heat sterilization, dry heat sterilization, radiation sterilization, gas sterilization and filtration sterilization. One or combined sterilization methods can be used according to the characteristics of the products to be sterilized. Terminal sterilization should be selected as much as possible if it is feasible for the product. If not, filtration sterilization or an aseptic production process can be selected to meet the requirements of sterility assurance. If possible, the non-terminal sterilized products should be subject to complementary sterilization (e.g. circulated steam sanitation).

Although the sterilization effect can be evaluated by monitoring some parameters in the sterilization process during the validation of sterilization procedures, the biological indicator is the most intuitive index for evaluating the effectiveness of a sterilization procedure. A biological indicator is a special viable microbial product, which can be used to verify the performance of sterilization equipment, validate the sterilization procedure, and monitor the sterilization effect in the production process, etc. The biological indicator used in the sterilization validation is generally bacterial spore.

a. Moist heat sterilization. the most commonly used biological indicator in moist heat sterilization is spores of bacillus stearothermophilus, such as NCTC 10007, NCIMB 8157 and ATCC 7953. Its D value is 1.5-3.0 min, the number of viable spores is 5×10^5-5×10^6 per slice (or bottle), which shall be killed completely at 121 ℃ for 19 min. Moreover, the spores of clostridium sporogenes such as NCTC 8594, NCIMB 8053 and ATCC 795 can also be used, and the D value is 0.4-0.8 min.

b. Dry heat sterilization. the most commonly used biological indicator in dry heat sterilization is spores of bacillus subtilis, such as NCIMB 8058 and ATCC 9372. Its D value is more than 1.5 min, the number of viable spores is 5×10^5-5×10^6 per slice. The escherichia coli endotoxin is used in the depyrogenation validation, with added amount not less than 1000 EU of bacterial endotoxins.

c. Radiation sterilization. the most commonly used biological indicator in radiation sterilization is spores of bacillus pumilus, such as NCTC 10327, NCIM 10692 and ATCC 27142. The number of viable spores is 5×10^5-5×10^6 per slice. It is placed in the condition of radiation dose of 25 kGy, and the D value is 3 kGy. However, it shall be noted that the microorganism laden in the sterilized product may show stronger radioresistance than spores of bacillus pumilus. Therefore, spores of bacillus pumilus can be used to monitor the sterilization process but not used to establish the sterilization radiation dose.

d. Gas sterilization. the most commonly used biological indicator in ethylene oxide sterilization is spores of bacillus subtilis such as NCTC 10073 and ATCC 9372, while the most commonly used biological indicator in vaporized hydrogen peroxide sterilization is spores of bacillus stearothermophilus, such as NCTC 10007, NCIM 8157 and ATCC 7953. The number of viable spores is 5×10^5-5×10^6 per slice. The D value of bacillus subtilis spore is more than 2.5 min in ethylene oxide sterilization, it should be killed when steri-

lized in 600 mg/L of ethylene oxide, at relative humidity of 60%, temperature of 54 ℃ for 60 min.

e. Filtration sterilization. the most commonly used biological indicator in filtration sterilization is *Pseudomonas diminuta* (such as ATCC 19146), which is used in a filter with the pore filter membrane pore size of 0.22 μm. *Serratia marcescens* (ATCC 14756) is used in the filter with the filter membrane pore size of 0.45 μm.

8.2.2 GMP

The pharmaceutical water systems are the most critical clean utility systems of the drug production process. The system has direct contact with the finished products; it is a direct impact system. The pharmaceutical water systems should comply with the relevant principles of validation, except for the following GEP relevant regulations. The specific requirements for equipment sanitation and sterilization in the Chinese GMP can refer to relevant articles in the *Good Manufacturing Practice* (2010 *Revision*) as follows:

Article 71 The design, model selection, installation, renovation and maintenance of equipment should comply with the intended use. The risk of contamination, cross contamination, mix-up and error should be reduced to the maximum. The design should be convenient for operation, cleaning, maintenance and sanitation or sterilization when necessary.

The Annex 1, *Sterile Drugs*, in the *Good Manufacturing Practice* (2010 *Revision*) stipulates:

Article 4 Sterile drugs can be classified into two types: a product manufactured with terminal sterilization process is a terminal sterilization product, while a product manufactured with part or the whole process adopting a sterile production process is a non-terminal sterilization product.

Article 57 The time interval from solution preparation to sterilization (or filtration sterilization) should be shortened as much as possible, and a corresponding control standard for the time interval should be established, according to the product properties and storage conditions.

Article 58 The monitoring standard for the microbial contamination level before sterilization should be determined on the basis of the effect of the adopted sterilization method, and monitored periodically. The pyrogen or bacterial endotoxin levels should be monitored when necessary.

Article 59 The packaging material, container, equipment and other articles used in aseptic production should be sterilized and entered into the aseptic production area through a double door sterilizer or some other procedure should be used in order to avoid introducing contamination.

Article 61 Sterile drugs should use a heating method for terminal sterilization as much as possible; the survival probability of microorganism (i.e. sterility assurance level, SAL) in terminal sterilized products should be not more than 10^{-6}. If moist heat sterilization is adopted for sterilization, the standard sterilization time F_0 value should be more than 8 min, usually. The circulated steam treatment is not part of the terminal sterilization. For thermolabile products, an alternative method of aseptic production operation or filtration sterilization can be adopted.

Article 62 Moist heat, dry heat, ion radiation, ethylene oxide or filtration sterilization methods can be used for sterilization. Each sterilization method has its specific scope of application, and the sterilization process should be in line with the registration requirements, and should be subject to validation.

Article 63 Any sterilization process must be validated as to its suitability for the products or articles, and its sterilization effect, using physical test methods and biological indicators, before being put into use.

Article 64 The effectiveness of the sterilization process should be revalidated periodically (at least once a year). The equipment should be revalidated after major changes. A revalidation record should be kept.

Article 65 All articles to be sterilized must be processed as per the stipulated requirements to obtain a good sterilization effect. The design of the sterilization process should comply with the sterilization requirements.

Article 66 Validation should be conducted to verify the loading pattern of products and articles to be sterilized in the sterilization equipment chamber.

Article 67 The biological indicator should be stored and used as required by the supplier, and its quality should be verified by positive control tests. Strict management measures should be taken to prevent microbial contamination resulted from the use of the biological indicator.

Article 68 A method for distinguishing sterilized products from the products to be sterilized should be available. Each vehicle (tray or other loading equipment) of products or materials should be labeled, and the product name, batch number and whether it has been sterilized should be clearly indicated. This can be determined using a moist heat sterilization index strip when necessary.

Article 69 Each sterilization operation should have a sterilization record which is one of the requirements of the product release.

Article 70 Heat sterilization includes moist heat sterilization and dry heat sterilization, which should comply with the following requirements.

a. The locations of the temperature probe used for monitoring or recording and that used for controlling during the validation and production process should be determined as per validation requirements. The time-temperature curve of the sterilization process should be recorded for each sterilization. If an automatic control and monitoring system is used, it should be validated and compliance with the requirements of the critical process must be ensured. The automatic control and monitoring system should be able to record the failures occurred during the system and process operation, and it must be monitored by operators. The reading on the independent temperature display should be periodically compared with the spectrum obtained from the sterilization process.

b. The chemical or biological indicator can be used to monitor the sterilization process, but it cannot substitute the physical test.

c. The temperature rise time required by each loading pattern should be monitored, and the sterilization time should be calculated once all sterilized products or articles have reached the set sterilization temperature.

d. Measures should be taken to prevent the sterilized products or articles from being contaminated during the cooling process. Unless it can prove that any leaked products or articles are rejected during the production process, any cooling media (liquid or gas) having contact with products or articles should be sterilized.

Article 71 *Moist heat sterilization should comply with the following requirements:*

a. The parameters monitored for the moist heat sterilization process should include sterilization time, temperature or pressure. For a sterilizer with a drain port installed at the bottom of the chamber, the temperature data obtained from the whole sterilization process for the point should be measured and recorded when necessary. If the sterilization process includes vacuum operation, the chamber should be periodically tested for leaks.

b. The articles to be sterilized, except the sealed products, should be packed with appropriate materials, and the materials used and packaging method should facilitate air exhaustion, steam penetration and prevent contamination after sterilization. All parts of the sterilized articles should be in contact with the sterilization media completely and within stipulated temperature and time ranges.

Article 72 *Dry heat sterilization shall comply with following requirements.*

a. The air in the sterilization chamber should be circulated and kept at positive pressure during dry heat sterilization and non-sterile air must be prevented from entering. The air entering into the chamber should be filtered by a HEPA filter, which should be subjected to an integrity test.

b. When dry heat sterilization is used for depyrogenation, its validation should include a bacterial endotoxin challenge test.

The temperature, time and differential pressure in and out of the chamber during dry heat sterilization should be recorded.

Article 73 *Radiation sterilization should comply with the following requirements:*

a. Radiation sterilization can be used when it has been proven it has no adverse effect on product quality. Radiation sterilization should comply with relevant requirements of the Chinese Pharmacopoeia and registration.

b. The radiation sterilization process should be validated. The validation protocol should include the radiation dose, radiation time, packaging materials and loading pattern; the impact of packaging density on the sterilization effect should be assessed.

c. A dose indicator should be used to determine the radiation dose during radiation sterilization.

d. A biological indicator can be used as an additional monitoring method.

e. Measures should be taken to prevent the radiated articles from mixing with non irradiated articles. A radiation indicating plate which changes color after radiation exposure should be placed on each package.

f. The total radiation dose standard should be reached after a stipulated time.

g. Records should be kept for radiation sterilization.

Article 74 *Ethylene oxide sterilization should comply with the following requirements:*

a. Ethylene oxide sterilization should comply with the relevant requirements of the Chinese Pharmacopoeia and registration.

b. The sterilization process validation should prove ethylene oxide will not have detrimental effects on the product. The provisions set for air exhausting and length of time specific to different products or materials should ensure all residual gas and reaction products are reduced to a set acceptable limit.

c. Measures should be taken to prevent microorganism from being concealed in crystal or dry protein, and ensure the sterilization gas has direct contact with microorganisms. The impact of the properties and quantity of the packaging material of the articles to be sterilized on the sterilization effect should be verified.

d. The sterilizing gas should be piped to the articles to be sterilized as soon as possible after it reaches the temperature and humidity stipulated for the sterilization process to ensure the sterilization effect.

e. A certain number of biological indicators should be placed in different locations for each sterilization to monitor the sterilization effect. The monitoring result should be incorporated into the corresponding batch record.

f. The record of each sterilization should include the time of completion for the whole sterilization process, pressure, temperature and humidity in the chamber during the sterilization process, concentration and total consumed quantity of ethylene oxide. The pressure and temperature of the whole sterilization process should be recorded, and the sterilization curve should be incorporated into the corresponding batch record.

g. The sterilized articles should be kept in a controlled ventilation environment to reduce the residual gas and reaction products to the stipulated limit.

Article 75 The filtration sterilization of a non-terminal sterilization product should comply with following requirements:

a. If terminal sterilization is possible for the product, filtration sterilization should not be used to substitute for the terminal sterilization process. If the drug product cannot be sterilized in the final packaging container, the drug liquid can be filtered into a pre-sterilized container with a 0.22 μm (smaller or equivalent filtering efficiency) sterilizing filter. The heat treatment method can be used to make up for the deficiencies of filtration sterilization, because a sterilizing filter cannot remove a virus or mycoplasma completely

b. Measures should be taken to reduce risk when using filtration sterilization. It is better to install a second sterilizing filter and filter the drug liquid again; the final sterilizing filter should be as close possible to the filling point.

c. After the sterilizing filter is used, appropriate methods must be adopted to immediately check and record its integrity. The commonly used methods include the bubble point test, diffusion flow and pressure test.

d. The filtration sterilization process should be validated, the time required for filtering a certain amount of drug liquid and the pressure at both sides of the filter should be determined during validation. Any significant deviation from the normal time or pressure should be recorded and investigated, and the investigation result should be included in the batch record.

e. A time limit for the use of a sterilizing filter with a specification and model should be validated, and usually it should be not more than one working day.

8.3 Basic Principle of Sterilization

The microbial contamination of the pharmaceutical water systems are divided into exogenous microbial contamination and endogenous microbial contamination, and several factors to be usually considered in the design of the pharmaceutical water systems are time, temperature, dead leg and slope. Raw water is the main exogenous source of microbial contamination in the pharmaceutical water systems, its quality must comply with the specifications of potable water at least, and other potential exogenous microbial contamination sources include dirty air sucked back in water distribution pipeline systems due to negative pressure, the damage to the filter membrane of the vent filter in the water tank, suck-back formed in the contaminated drain outlet, etc. Attention should be paid in the design and maintenance of a pharmaceutical water system to reducing exogenous microbial contamination to the maximum.

Unit operation may be the main cause of endogenous microbial contamination. The microorganisms in raw water may be adsorbed on the operation surface of the internal wall of the tank and pipeline, filter membrane and other units, which induces the generation of a biological film. Some microorganisms use the biological film as an adaptive reaction in order to survive in a low nutrition environment. The routine heat sterilization methods have no effect on already formed biological film; the microorganisms in the biological film shed off and enter in other areas of the pharmaceutical water systems, which may generate a bacterial colony downstream. The microorganisms may attach to the microspore filter membrane, which is the main contamination source of the subsequent filtration sterilization process. The pharmaceutical water systems are the system requiring microbial propagation inhibition, microorganisms may form bacterial colonies on the pipe wall, valve and other areas, and proliferate to form a biological film, thus, a biological film becomes constant microbial contamination source.

Microorganism (Fig 8.1) is a general term for tiny organisms which cannot be seen with the naked eye. It includes prokaryotic bacteria, actinomycetes, mycoplasma, rickettsia, chlamydia and cyanobacteria (it is called cyanophyta or blue-green algae), eukaryotic fungi (yeast and mold), protozoa and microscopic algae, and non-cell viruses, viroids, prions, etc.

The microorganisms in a pharmaceutical water system are usually gram-negative bacteria and thermophilic bacteria, and endotoxin is the metabolite released by them, therefore, the control of the bioburden

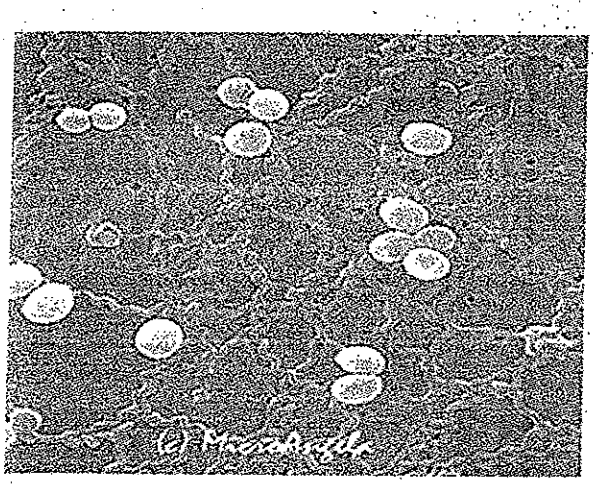


Fig 8.1 Microorganisms

in the pharmaceutical water systems are helpful for controlling the bacterial endotoxin indicator of the product. A biological film (Fig 8.2) is the viscous substances formed by mutual coherence of microorganisms and attached to the pipe surface. It is a combination of complex and diversified living microorganisms and dead microbial aggregates, including polysaccharide-protein compounds, adsorbed organisms and carried particles. The formation of a biological film is the result of a long-term microbial contamination and propagation, it is difficult to be removed using routine heating, mechanical or chemical treatment methods once it is formed.

8.3.1 Effect of Time

The development trend of the bioburden in the pharmaceutical water systems can be indirectly reflected by the "bacterial growth curve" (Fig 8.3). It involves inoculating a few unicellular microbial pure species into a certain volume of liquid medium, incubate in appropriate conditions and determine the quantity of cells by sampling at set time intervals; then take the lg of the number of the bacterial cells as the vertical coordinate, and incubation time as horizontal coordinate to draw a curve as illustrated in the figure. The "bacterial growth curve" is mainly composed of a lag phase, logarithmic phase, stationary phase and decline phase.

The lag phase is also called adjustment phase, the bacteria have a transient adaptive process to the new environment after being inoculated into the medium, while the ones not adapting to it will die after inoculation. The curve is flat and stable because the bacterial propagation is very limited in the phase. The duration of the lag phase varies with the bacterial species, inoculated bacteria amount, cell age and nutrient substances, and the lag phase duration is usually 1-4h. The bacterial volume is increased, and the metabolism is active enough during the lag phase to store sufficient enzyme, energy and intermediate metabolite for bacterial division, proliferation and synthesis.

The logarithmic phase is also called exponential growth phase; the total number of viable bacteria in this phase rises extremely fast. The bacteria are increased rapidly with stable geometrical progression, which can last for several hours to several days based on the incubation conditions and bacterial generations. The bacterial morphology, staining and biological activity are all very typical, and very sensitive to external environmental factors; therefore, this phase is best for studying bacterial characteristics, and it is optimal to assess the antibiotic action on bacteria in this phase.

The total number of bacterial colony at the stationary phase is stable, but the change in the bacterial colony's vigor is significant. The bacterial propagation

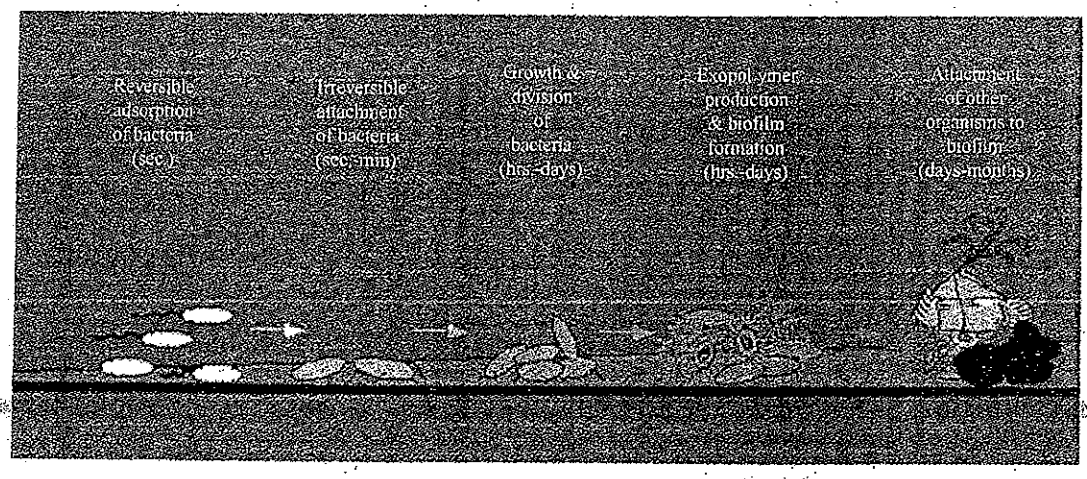


Fig 8.2 Formation mechanism of a biological film

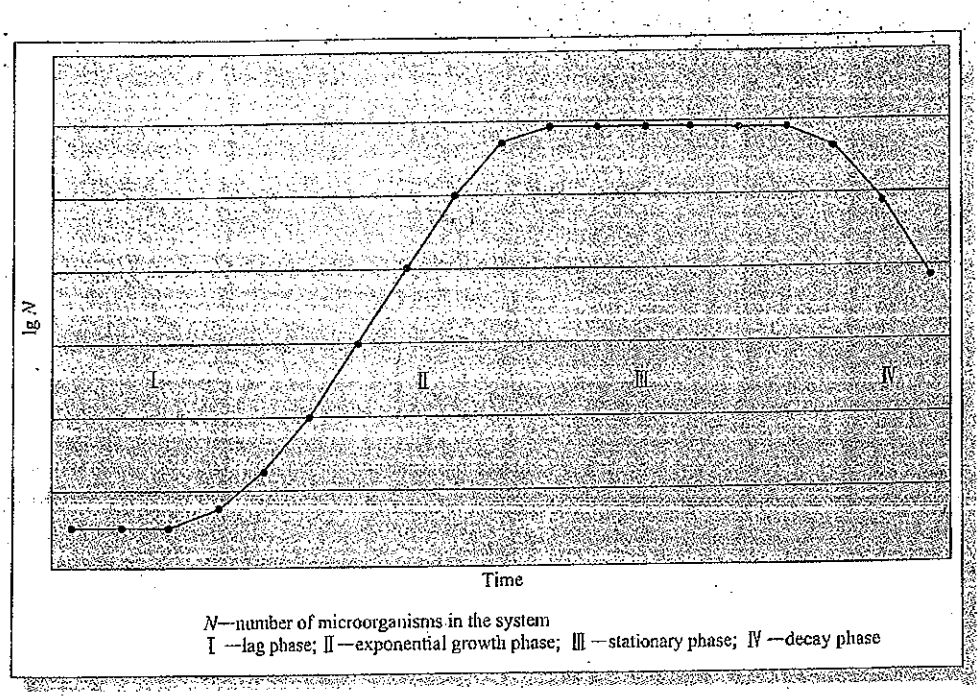


Fig 8.3 Bacterial growth curve

speed is dropping gradually and the relative bacterial death count is gradually increasing due to the impact of adverse factors such as nutrient substances depletion, toxic products (e.g. organic acid, H_2O_2, etc.) accumulation, pH decrease in the medium. The bacterial propagation and death count at the stationary phase become more balanced, and bacterial morphology, staining and biological activity may change, and generate corresponding metabolites such as exotoxins, endotoxins, antibiotics and spores.

Accompanying the development of the stationary phase, bacterial propagation becomes slower and slower, the number of dead bacteria is obviously increased and the decay phase starts. The number of viable bacteria has an inverse relationship with the incubation time, the bacteria get longer and swelling or deformity appear, and even thallus autolysis, it becomes difficult to recognize the shape, physiological metabolism activities approach stagnation, therefore, it is difficult to identify the bacteria on an old culture.

Good understanding of the bacterial growth rhythm in the pharmaceutical water systems helps the enterprise determine the sanitation or sterilization schedule of the pharmaceutical water systems in a reasonable manner. The enterprise can conduct scientific analysis specific to each pharmaceutical water system and understand its change patterns, and, in combination with statistical methods, provide the scientific basis for realizing the "process quality control". The enterprise can reasonably determine the sanitation or sterilization schedule taking into consideration the microbial level of the system, by means of risk assessment. For example, water for injection, as an important raw material for the aseptic preparation process system, has direct contact with sterile products, and its bioburden control is very critical. The water for injection systems adopting high temperature circulation of above 70 ℃ is at the state of pasteurization for a long term, its microbial inhibition effect is usually better; therefore, it is appropriate that some pharmaceutical enterprises set the sterilization schedule of water for injection at half a year, or even one year by performing strict PQ.

8.3.2 Effect of Temperature

High temperature has an obvious lethal effect on microorganisms; different types of microorganisms have different resistance to high temperature. When the environmental temperature exceeds the maximum temperature range of microbial growth, microorganisms easily die. The higher the exceeding temperature or the longer the sterilization time in the condition of high temperature, the quicker the microbiological death. Temperature is an important factor influencing microbial propagation. Vegetative microorganisms will stop growing at above 60 ℃, most pathogenic bacteria will stop growing at above 50-60 ℃, most thermophilic

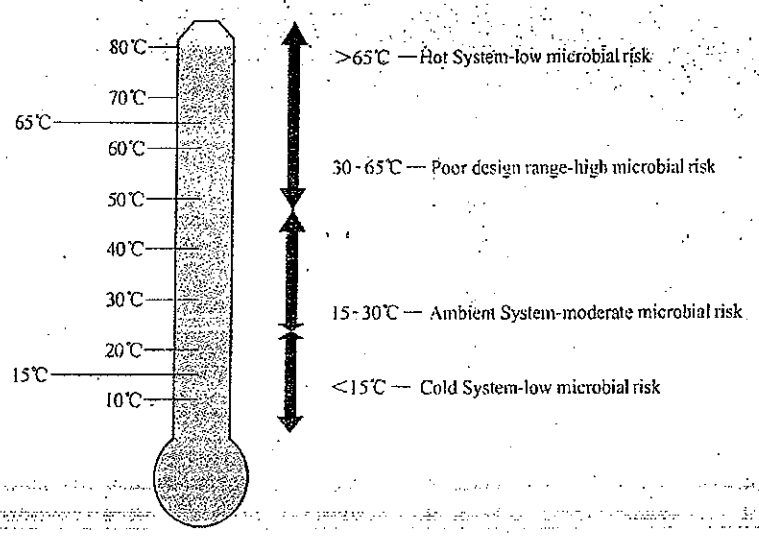


Fig 8.4 The effect of temperature on microorganisms

bacteria will stop growing at 73 ℃, and only spores and some extreme thermophilic bacteria can survive at 80 ℃. Fig 8.4 demonstrates the relationship between microbial propagation and temperature. Microorganism will propagate rapidly and cause contamination of the pharmaceutical water systems at a suitable temperature, e.g., 30-65 ℃.

It is recommended by the GMP that water for injection should be circulated at above 70 ℃, with thermal insulation. The principle is that the water for injection systems always stays at a pasteurization state at above 70 ℃, and its risk of microbial contamination is very low. Moist heat sterilization includes pure steam sterilization and superheated water sterilization. In a pharmaceutical water system, sterilization validation is not a compulsory requirement, but moist heat sterilization technology has been promoted and widely used by many pharmaceutical enterprises. It can make all proteins in the microbial cell solidify which results in bacterial death, effectively reduce bioburden and ensure the aseptic conditions for the pharmaceutical water systems.

8.3.3 Effect of Dead Leg

The dead leg inspection is an important step in the system installation qualification. Pleace refer to section 2.3.1.

8.3.4 Effect of Slope

The slope inspection is another important step during the installation qualification of the system. Please refer to section 2.3.3.

8.4 Sanitation Technology

Sanitation refers to killing or eliminating pathogenic microorganisms in the media with physical or chemical methods to make them harmless. It usually kills the propagules of pathogenic microorganisms, but doesn't damage the spores. Therefore, sanitation cannot substitute sterilization. The commonly used sanitation methods mainly include pasteurization, ultraviolet sanitation, chemical sanitation, boiling sanitation, circulated steam sanitation and intermittent steam sanitation.

8.4.1 Pasteurization

Pasteurization is also called low temperature sanitation. It is heat treatment method for killing various pathogenic microorganisms. It targets mainly pathogenic microorganisms and other growing bacteria. Pasteurization is a sanitation method invented by the French scientist L. Pasteur to solve the beer souring problem. At the time, the wine-making industry in France was facing a headache, which is beer was going sour after it was made, and couldn't be drunk at all, and this souring phenomenon is occurred frequently. Pasteur was invited to study this problem, and after a long-term observation, he found that the main culprit in making the beer sour is lactobacillus, and simple boiling can kill it. Pasteur attempted to use different temperatures to kill lactobacillus, without damaging the beer itself. Finally, Pasteur's research result was to heat the beer for half an hour at 50-60 ℃, which can kill the lactobacillus in the beer, but not boiling it.

This method saved the wine-making industry in France. later, pasteurization was widely applied in many fields such as beer, food and drug industries.

The working principle of pasteurization: within a certain temperature range, the lower the temperature, the slower the bacterial reproduction; the higher the temperature, the faster the bacterial reproduction, but if the temperature is too high, bacteria will die. Different bacteria have different optimal growth temperatures, and heat-resisting and cold-resisting ability. Vegetative microorganisms will stop growing at above 60 ℃, most pathogenic bacteria will stop growing at above 50-60 ℃, most thermophilic bacteria will stop growing at 73 ℃, and only spores and some extreme thermophilic bacteria can survive at 80 ℃. Pasteurization is actually making use of the fact that pathogens do not resist heat, and using treatment at appropriate temperature and thermal insulation to kill it completely. But after pasteurization, some heat-resistant bacteria or bacterial spores still exist; therefore, pasteurization is not a "sterile" treatment process.

The standard work condition of pasteurization is mainly at 61.1-62.8 ℃ for 30 min or at 71.7 ℃ for 15-30 min. At present, the sanitation method has been widely promoted, and its working temperature and time have been extended. As for pharmaceutical water systems, pasteurization has two main functions: ①used for periodic sanitation of the pre-treatment unit such as active carbon in the purified water system, of the RO/EDI unit, and of the storage unit and distribution pipeline; ② used for microbial inhibition during normal operation of the water for injection systems.

The pharmaceutical water systems using pasteurization should be made of stainless steel. The temperature rise of the purified water storage and distribution systems are mainly achieved by heating with plant steam in the tank jacket or heat exchanger in the main return pipeline. The pump will generate heat and require a temperature drop after sanitation, so cooling may be required. The purified water storage and distribution systems should be heated first and then cooled, and its sanitation time is relatively long. The pasteurization of this system is usually done by using hot water circulation at above 80 ℃ for 1-2 h. The purified water systems using this sanitation method have their microbial contamination level usually controlled at lower than 50 CFU/ml. Meanwhile, pasteurization can effectively control endogenous microbial contamination of the system. A water system with good pretreatment capacity can control the bacterial endotoxin at the 5 EU/ml level.

8.4.2 Ultraviolet Sanitation

UV radiation in sufficient dose is an effective sanitation method. UV rays will damage the DNA structure of microorganisms (bacteria, viruses and fungi, etc.), which will prevent the duplication of microorganism (Fig 8.5). The UV light emitted by low voltage ultraviolet lamp is concentrated at 254 nm; this kind of lamp is used as UV sanitation lamp. The UV lamp used for microbial control is usually installed in the generation system for example downstream of the active carbon unit; this position would be suitable for conducting microbial control. Filtration upstream of the UV unit may be helpful in reducing the probability of shielding microorganisms from the UV lamp by particles from the process upstream of the active carbon unit, softener or other media. The principle of ultraviolet sanitation is relatively complex; it is generally considered that it has to do with the nucleic acid which plays a decisive role in phenomena such as biological metabolism, inheritance and variation. All microorganisms contain DNA, while the common characteristic of RNA and DNA is that they have polynucleotide chains connected by phosphodiester according to the principle of purines paired with pyrimidines bases, it has a strong absorptive action of ultraviolet light and reaches the maximum absorption peak at 265 nm. The UV rays with the wavelength at 240-280 nm have sanitation effect, and the sanitation effect varies with the wavelength. UV sterilization has the best effect at 265

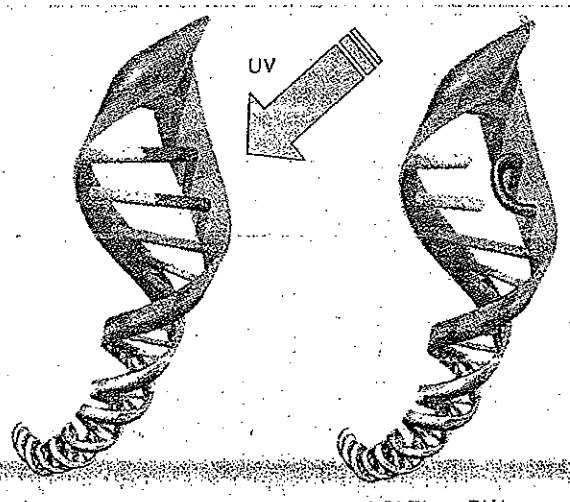


Fig 8.5 The principle of ultraviolet (UV) sanitation

nm; this is because the UV absorption peak of desoxyribonucleic acid (DNA) in bacteria is at 265 nm.

The intensity of UV light, its spectral wavelength and the irradiation time are determining factors of the UV sanitation effect. which is not in a linear relationship with the irradiation dose of the UV rays, i. e. the percentage of killed bacteria is not proportional to the irradiation dose (the UV irradiation dose is the irradiance of the UV rays multiplied by time). Only when the irradiation dose is very low but the number of bacteria is large, the irradiation dose of UV rays is in a linear relationship with the bacterial death rate. When the irradiation dose of the UV rays is increased by a unit dose, it will not kill a certain amount of bacteria, but kill a specific percentage of the living bacteria. If the water has enough contact time with the UV rays and an appropriate flow rate when it passes through the chamber where an UV lamp is installed, 99.9% or more of the microorganisms in the water will be killed. Some bacteria survive from exposure in the chamber; this may be because they attach to non-transparent particles (such as rouge) or are embedded in the center of biological film floccules and are protected from UV irradiation. The UV sanitation device can only kill the irradiated microorganisms, while surviving microorganisms can form a biological film downstream. The online UV sanitation device slows down the development of biological films downstream, and these biological films are formed by microbe cells which are in suspension in the water flowing through the chamber. The UV sanitation is very useful, especially when followed by biological film removal downstream by means of high efficiency filtration methods, and helps reduce the frequency of destructive sanitation.

Another UV sanitation alternative is to use a medium voltage UV lamp, which emits a wider spectral range of 180-400 nm. The medium voltage modulator tube used for sanitation will usually emit UV light below 220 nm. The sterilization effect of the broad spectrum UV light is stronger than that of the low voltage monochromatic spectrum. The UV rays below 220 nm can create very reactive and transient hydroxyl radicals in water molecules. The hydroxyl radical has an instant and rapid reaction with organic molecules that are in contact with it, including the organic molecules on bacterial cells and soluble organic molecules which constitute the TOC in water. When a hydroxyl radical reacts with an organic molecule, it can oxidize the C—C covalent bond to create organic acid and increase the water conductivity. If a deionization device for purification is installed downstream of the 185 nm ultraviolet sanitation device or at other location in the tank and the distribution systems, the organic molecules ions can be removed from the water to reduce the level of TOC. With the continued circulation of water in the 185 nm ultraviolet sanitation device and the deionization device, the level of TOC will be continuously decreased.

The UV radiation affects the generation of biological films by slowing down the growth speed of new bacterial colonies in the system, but it is only effective against airborne microbes. Ultraviolet radiation is not an effective sanitation method for pipelines, for ultraviolet rays cannot irradiate other parts of the pipeline except that in the chamber of ultraviolet equipment, if a UV lamp is used together with routine intermittent sanitation methods such as hot water or chemical sanitation methods, it will be very effective and extend the time interval between sanitations. The ultraviolet sterilizer should be equipped with time accumulation prompt, intensity monitoring and alarm functions, alerting the user to timely replace the ultraviolet tube. When the system is subjected to periodical pasteurization, the design structure of the ultraviolet lamp should meet the requirements for high temperature resistance.

In a pharmaceutical water system, ultraviolet radiation can rapidly and effectively reduce the bioburden in the water and inhibit the speed of microbial propagation, but UV rays cannot kill the microorganisms attached to the distribution pipeline, therefore, it cannot completely substitute for periodic sanitation or sterilization measures such as pasteurization, ozone sanitation or steam sterilization; however, it can reduce the sterilization frequency of the whole distribution system effectively. Therefore, ultraviolet sterilizers are mainly installed in the circulation pipe of RO/EDI, and the storage and distribution pipeline of purified water systems to prevent an excessively fast increase of the microbial indicator in the system, and the periodic sanitation of the system should still be done by using sanitation methods such as pasteurization or ozone sanitation.

8.4.3 Ozone Sanitation

Ozone is a broad-spectrum bactericide. It damages the structure of biological film by oxidization to achieve

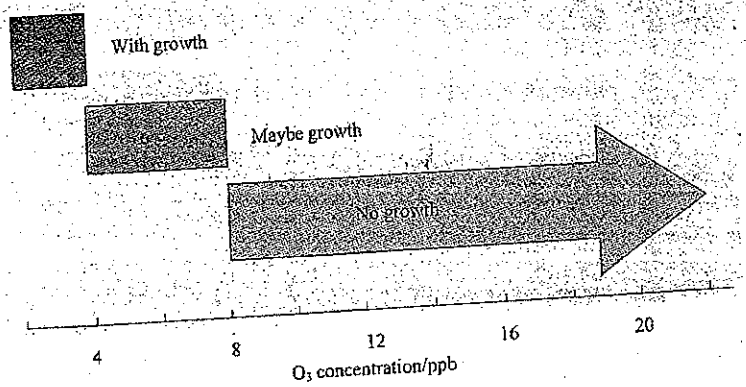


Fig 8.6 Sterilization concentration of ozone

the sterilization effect. It can kill bacterial propagules, spores, viruses and fungi, etc. and destroy the botulinus toxin. The virus inactivation mechanism of ozone has the following steps: first it damages the cytomembrane, causing a obstacle to metabolism, then the ozone continues to penetrate the membrane and damage the lipoprotein and lipopolysaccharide in the membrane changing the permeability of the cell, damage its ribonucleic acid (RNA) or desoxyribonucleic acid (DNA) by oxidization, resulting in cytolysis and death. The half-life period of ozone is only 30-60 min, the sterilization speed of ozone water in high concentration is very fast, and 100 ppb ozone can kill 60,000 microorganisms in 1min. It is indicated by research that microorganisms will stop propagating (Fig 8.6) when the ozone concentration in water exceeds 8 ppb, while the system can effectively kill microorganisms and bacteria when the ozone concentration in water exceeds 50 ppb.

Ozone can kill the microorganism in water and degrade the formed biological film effectively, and the ozone broken down by ultraviolet has no residue at all. At present, ozone sanitation has become the main sanitation measure for normal temperature storage and distribution systems. It is indicated by practice that when the ozone concentration reaches 100-200 ppb, it can ensure that the microbial content in a pharmaceutical water storage and distribution system is not more than 1 CFU/100ml. Compared with pasteurization, ozone sanitation has the advantage of simple operation, no fluctuation of the water temperature, no demand for plant steam, short sanitation time and degradation of biological films, besides that, it can be used with wide choice of pipeline materials. An ozone sanitation system is operated at normal temperature; it can be made of stainless steel or PVDF.

The equipment for generating ozone mainly includes air/oxygen source ozone generators and water electrolysis ozone generators. An air/oxygen source ozone generator mainly takes air or oxygen as the source to generate gaseous ozone; it dissolves the ozone in purified water using a jet device or high pressure pump during the process. A water electrolysis ozone generator (Fig 8.7) takes clean purified water as the starting material for generating ozone, its working principle is to let purified water or high purity water from the pharmaceutical water circulation pipe enter the anode chamber of the reaction unit; it is separated into two components on the contact surface between the anode and an electrochemical stable film. The hydrogen proton enters into the film, it is compressed to hydrogen at the cathode and released into the atmosphere as

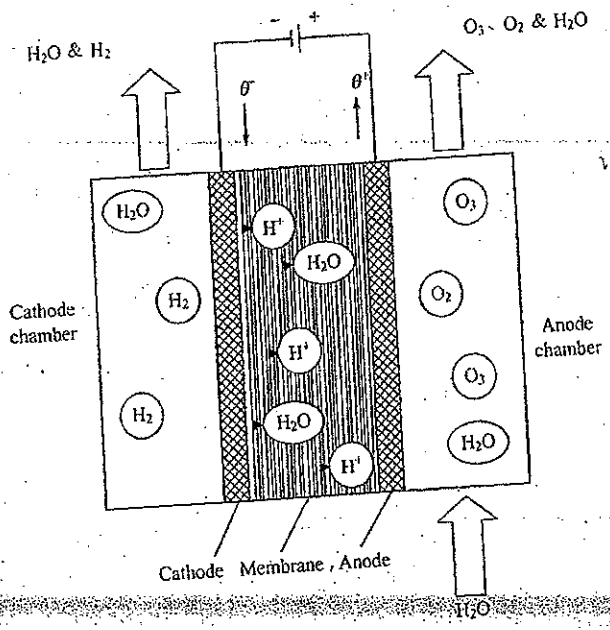


Fig 8.7 Working principle of water electrolysis ozone generator

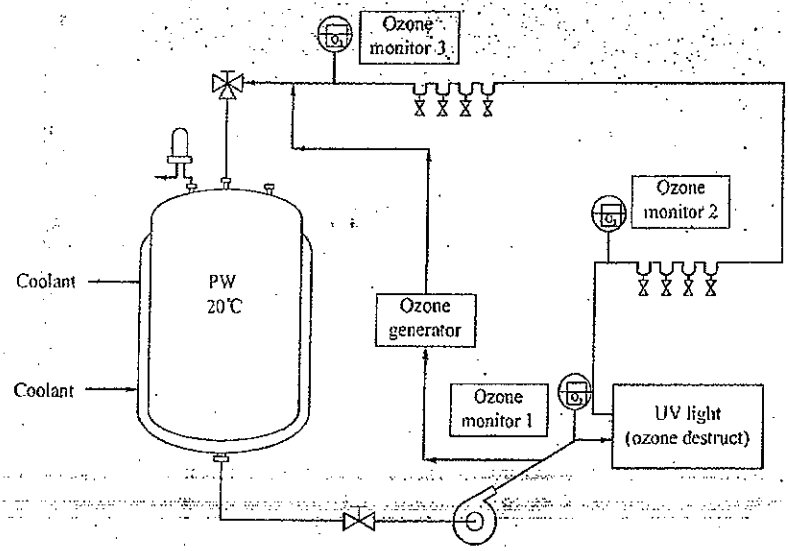


Fig 8.8 Successive ozone sanitation

hydrogen, while the free oxygen at the anode is converted to ozone, and dissolved rapidly in water to obtain water with high ozone concentration, and returned to the pharmaceutical water storage and distribution system. The main advantage of the water electrolysis ozone generator is that it generates ozone using the purified water to be sanitized, eliminating contamination from the exterior of the system effectively.

Water electrolysis ozone sanitation can be divided into two types: successive type and intermittent type. Fig 8.8 shows a typical successive ozone sanitation working principle: the whole system has three online ozone probes to conduct real-time monitoring of the ozone concentration in the storage tank, pipe inlet end and pipe water return end. The water temperature in the system is controlled at about 20 ℃; the outlet of the vent filter breaks down the ozone by means of active carbon adsorption or heating. For successive type ozone sanitation, the ozone concentration is usually less than or equal to 0.1 ppm, because it usually reacts with very sensitive stem cells or small plankton film floccules entered into the distribution system form the final operation unit of the purification system. During normal production, the ozone generator and ultraviolet lamp are both working, and the purified water storage system always stays in an ozone protection state. The point of use pipeline uses ultraviolet lamps with a wavelength of 253.7 nm to completely break down the ozone from the circulation pipe, to ensure no residual ozone is in the purified water when it is used. During periodic sanitation, the ultraviolet lamp is off to maintain the ozone concentration in the water and keep it for a certain time, and then the sanitation is ended.

Figure 8.9 shows the intermittent ozone sanitation working principle: the whole system has one online ozone probe to conduct real-time monitoring of the ozone concentration of the pipe water at the return end. The water temperature in the system is controlled at about 20 ℃. During normal production, the ozone generator and ultraviolet lamp are both off, when conducting periodic sanitation, the ozone generator is turned on to maintain the ozone concentration in the water for a certain time, after the completion of the sanitation, a ultraviolet lamp with the wavelength of 253.7 nm removes the ozone form the circulation pipe to ensure no residual ozone is left in the purified water when it is used. When ozone is used as an intermittent sanitizer, it requires being at ever-increasing concentrations, because the ozone needs to destroy biological films coated by EPS, and its penetration is very poor. The biological film can be degraded by ozone sanitation if ozone can penetrate into it, which happens only when the EPS outer layer, endotoxin and bacterial cell are decomposed. If the biological film has enough growth time and becomes thick enough, then it is very difficult for the ozone to destroy it; if the application is not repeated for a long time, only a thin biological film can be completely destroyed by ozone, therefore, ozone sanitation must be performed periodically, so that the structure of biological film coated by any EPS will stay at its early phase.

The distribution layout of a water electrolysis sanitation system is mainly composed of a water electrolysis ozone generator, ultraviolet lamp, transfer pump with

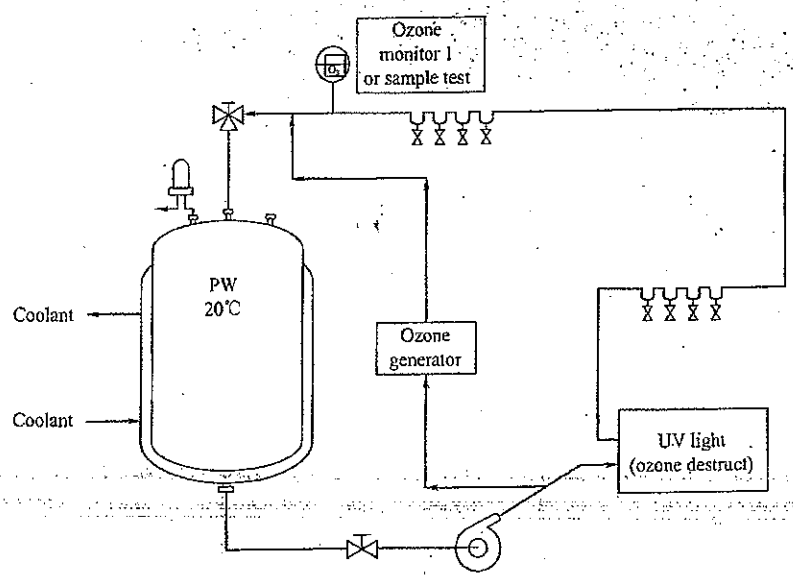


Fig 8.9 Intermittent ozone sanitation

frequency converting control, heat exchanger and its cooling regulation device, sampling valve, diaphragm valve, pipe fitting, temperature sensor, pressure transducer, ozone sensor, conductivity sensor, TOC online monitoring instrument, counterbalance valve and its matched integrated control system. Fig 8.10 shows a typical water electrolysis ozone water distribution module.

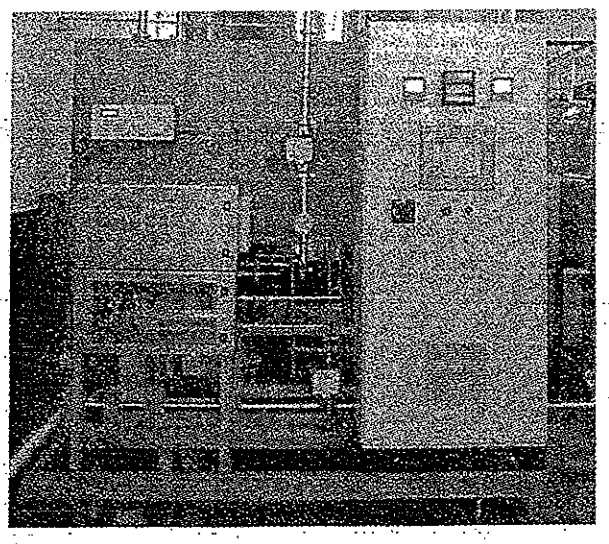


Fig 8.10 Ozone sanitation module

8.4.4 Chemical Sanitation

Chemical sanitizers are able to affect the chemical constitution, physical structure and physiological activity of bacteria, and thus play a role in sanitation or sterilization. The working mechanism of a chemical sanitizer is mainly to promote thallus protein denaturation or solidification, interrupt the bacterial enzyme system and metabolism, damage the bacterial cytomembrane, reduce the cell surface tension and increase its permeability, cause extracellular liquid intravasation and result in bacterial rupture, etc.

Chemical sanitizers can be divided into sterilants and sanitizers. The former can kill all viable microorganisms including spores and viruses, while the latter can kill the propagules of microorganisms, but cannot damage its spores. The commonly used chemical sanitizers include peroxide sanitizers, phenol sanitizers, biguanides and quaternaries sanitizers, alcohol sanitizers, iodine-containing sanitizers, chlorine-containing sanitizers, aldehyde sanitizers and ethylene oxide, etc.

a. Peroxide sanitizers. They include hydrogen peroxide, peracetic acid, chlorine dioxide, ozone, etc. which have strong oxidizing ability, and various microorganisms are very sensitive to them. The advantage of peroxide sanitizers is no residual toxicity on the surface of articles after sanitation, but because the chemical properties of this kind of substances are not stable, usually, they require special handling or have other ingredients added to ensure their stability, for example, the mixture of hydrogen peroxide and peracetic acid can be used for rapid sanitation.

Hydrogen peroxide is a commonly used chemical sanitizer in the pretreatment device for purified water generation. Hydrogen peróxide is a strong sanitizer and is available as concentrated solution. It can be diluted to a solution with maximum sanitation effect at high concentration. The commonly selected concentration is

3% to 5%, it has very good stability, and therefore, if the initial concentration is high enough, it is unnecessary to add chemical substances to maintain a long-term effective concentration. The pH stability of hydrogen peroxide allows it to be combined with strong alkaline substances resulting in a very good sanitizer and biological film remover. It can react with other oxidizing sanitizers to mutually produce a large amount of hydroxyl radicals with high lethality. This mixture has a stronger reaction capacity than any one single sanitizer. Hydrogen peroxide becomes unstable with increasing temperature; therefore, it should only be used below 25 ℃. Hydrogen peroxide is an exogenously added substance, which must be removed from the system after the sanitation circulation. The rinsing effect after sanitation can be verified by a rapid test reagent and test paper, but usually, it is only quantified to 1 ppm. Therefore, in order to avoid the validation risk caused by chemical residue, hydrogen peroxide is mainly used to sanitize the pre-treatment unit of the purified water generator, while the pharmaceutical water storage and distribution system is rarely sanitized by hydrogen peroxide.

b. Phenol sanitizers. They include phenol, methyl phenol, halogenated phenol and derivatives of phenol, e. g. saponated cresol solution or trichloro hydroxydiphinyl ether is phenol sanitizer. At present, phenol derivatives sanitizers are widely used in the foreign pharmaceutical industry. Its major ingredients are *p*-tert-Amylphenol and *o*-phenylphenol. It is indicated by research that the sanitizer should be used alternately in acidic and alkaline conditions to prevent microorganisms from developing resistance.

c. Biguanides and quaternaries sanitizers. These are cationic surfactants active agents, used for sterilization and decontamination. The sterilization effect can be enhanced by dissolving in ethanol. They are usually used for sanitizing non-critical articles and hand skin in hospitals. Because this kind of compound can change the permeability of the bacterial cytomembrane, it is usually compounded with other sanitizers to improve sterilization effect and sterilization speed. Quaternaries sanitizers have been developed almost one hundred years ago. The first generation of quaternaries sanitizers is bromogeramine; the second generation has added alkyl or chlorine substituents to the molecular structure of bromogeramine. The third generation is the mixture of the first and second generations, and the fourth generation is the tetraalkyl ammonium salt solution developed in recent years. The double long-chain alkyl quaternary ammonium salt is the fifth generation of quaternaries sanitizers, its carbon chain has an appropriate length, which not only avoids the insufficiency of the single long-chain alkyl sterilization capacity, but also overcomes the deficiency of the too long carbon chain of double strands and bad water solubility. If synergist is added scientifically, it can synergistically improve the adaptability of double long-chain alkyl quaternary ammonium salt to external conditions such as organic matter, hard water and pH.

d. Alcohol sanitizers. The most commonly used alcohol sanitizers are ethanol and isopropanol, which can solidify protein and cause pathogens to die. Alcohol sanitizers are medium efficiency sanitizers; they can kill bacterial propagules, damage lipophilic viruses such as herpes simplex virus, hepatitis B virus and HIV. The commonly used concentration of ethanol is 75%, and that of isopropanol is 70%. In recent years, many types of compound alcohol sanitizers have been researched and developed at home and abroad, these products are mostly used for sanitation of the hand skin.

e. Iodine-containing sanitizers. They include iodine tincture, iodophor, etc. The commonly used concentration of iodine tincture is 2%, and the applied concentration of iodophor is 0.3%-0.5%. They can halogenate the pathogen protein and cause its death. Iodine-containing sanitizers can kill bacterial propagules, fungi and some viruses. They are usually used for the sanitation of skin and mucous membrane, and for hand skin sanitation in hospitals.

f. Chlorine-containing sanitizers. This mainly refers to the sodium hypochlorite sanitizer which is dissoluble in water and has bactericidal activity; its sanitation effect is usually measured by the available chlorine. The relative molecular weight of sodium hypochlorite is small, it is easily diffused on bacterial surface, penetrates the cytomembrane, enters the thallus, and causes mycoprotein oxidation and bacterial death. Chlorine-containing sanitizers can kill various pathogens, including bacterial propagules, viruses, fungi, etc. They are divided into inorganic chloride (e. g., sodium hypochloride, bleaching powder, bleaching agent, trisodium chlorophosphate, etc.) and organic chloride (e. g., sodium dichloro isocyanurate, trichloroisocyanuric acid, etc.). The inorganic chloride is unstable,

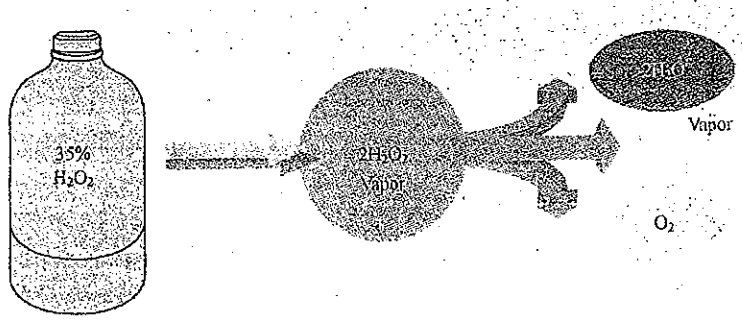


Fig 8.11 Working principle of vaporized hydrogen peroxide

easily affected by light, heat and moisture, losing its effective constituent, while organic chloride is relatively stable. A high concentration chlorine-containing sanitizer has an obvious irritating effect on the respiratory mucosa and skin, and a bleaching effect on articles, it will pollute the environment if used in large amounts. Therefore, appropriate sanitation concentration and action time duration should be selected in accordance with the characteristics of the pathogen. Generally, chlorine-containing sanitizer with effective chloride of 1000 ml/L can be selected when killing viruses, and the action time duration is set at 30 min. Chlorine-containing sanitizers are usually used for sanitation of the environment, material surfaces, tableware, drinking water, sewage, excrement, rubbish, etc. The chloride ion has a strong corrosive effect on stainless steel surfaces; it should be used prudently in the pharmaceutical industry to avoid unnecessary corrosion of the production equipment.

g. Aldehyde sanitizers. They mainly include formaldehyde and glutaraldehyde. These are active alkylating agents, act on amidogen, carboxyl, hydroxyl and sulfydryl in the pathogen protein, damaging the protein molecule and causing its death. Formaldehyde and glutaraldehyde can kill various pathogens. Because they irritate and solidify human skin and mucosa and induce human sensitivity, they cannot be used for sanitizing air and tableware. Pharmaceutical enterprises usually use formaldehyde fumigation for environmental sanitation of clean areas, because it has a carcinogenic effect on humans, some companies at home and abroad have recently replaced formaldehyde fumigation with vaporized hydrogen peroxide (VHP) sanitation.

h. Ethylene oxide It is a high efficiency sanitizer, can kill all viable microorganisms. For ethylene oxide has strong penetrability and no damage to most articles, it is usually used to sanitize valuables such as leathers, plastics, medical devices, books, documents and precise instruments.

i. Vaporized hydrogen peroxide (VHP) has excellent characteristics for killing bacteria and spores, its final decomposition products are oxygen and water with no chemical residues (Fig 8.11), and its sanitation concentration is usually 1-2 ppm (25 ℃). In foreign countries, VHP sanitation is a widely used sanitation method for clean room environments, the sanitation of all clean rooms can be realized by the circulation of HVAC system.

A hydrogen peroxide generator is a special device for generating vaporized hydrogen peroxide (Fig 8.12). It can be used to conduct biological sanitation of closed spaces and internal apparatus surfaces in the system, and sanitize packed devices. It has been widely accepted and promoted by the pharmaceutical industry.

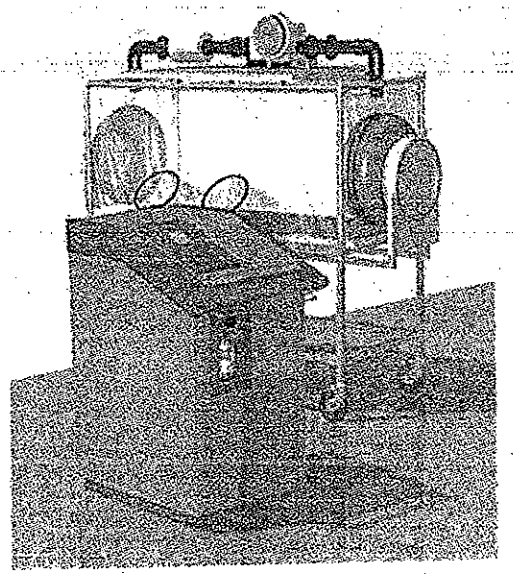


Fig 8.12 VHP generator

8.4.5 Boiling Sanitation

Boiling sanitation refers to placing articles in boiling water. At normal pressure, common bacterial propagule

can be killed by boiling at 100 ℃ for 5 min, but boiling cannot kill all viable microorganisms such as spores, therefore, this method is not a sanitation method accepted by pharmacopoeias. During sanitation, the time duration should be calculated after the water starts boiling, 2% sodium carbonate is added to raise the temperature of boiling water to 105 ℃ making use of the property of the raised boiling point of the solution, to accelerate microbial death. Usually, the items such as syringes, injection needles, scissors and tweezers are boiled for 10-15 min to achieve the sanitation effect.

8.4.6 Steam Sanitation

Steam sanitation includes circulated steam sanitation and intermittent steam sanitation. The major characteristic is the use of high pressure steam as the heat source to sanitize the whole system with circulation. It is different from pure steam sanitation; steam sanitation is normal pressure sanitation, it requires opening the valve of the vent filter during sanitation, and allows to open the drain valve at the low or end point directly for draining the condensate water is required.

Circulated steam sanitation is a sanitizing method that uses water vapor at 100 ℃ for 15-30 min at standard atmospheric pressure. It can kill most pathogenic microorganisms, but can't kill spores or non-pathogenic microorganism with stronger resistance thoroughly, therefore, it is not a sanitation method accepted by pharmacopoeias. Circulated steam sanitation is mainly used for sanitizing articles that become unstable during high temperature sterilization. During sanitation, the package of articles should not be too large or tight as to affect the penetrability of steam. It is regulated by the *Chinese Pharmacopoeia* that circulated steam sanitation can be used as a complementary sterilization measure for non-terminal sterilization of sterile articles. It is usually used for bioburden control of the purified water storage and distribution systems.

The intermittent steam sanitation is a sanitizing method that uses water vapor at 100 ℃ for 30 min in repeatedly. Its operation method is similar to that of the circulated steam sanitation, but it should be repeated for more than 3 times. At each interval of sanitation, the articles to be sanitized shall be put into an incubator at 37 ℃ and kept overnight. The purpose is to make spores grow into propagules. Inrermittent steam sanitation is mainly used to sanitize sugar-containing media or milk media which do not resist high temperature. If the articles to be sanitized do not resist a 100 ℃ temperature, it can be cooled to 75-80 ℃, the heating time is extended to 30-60 min, and the number of repetitions is increased.

8.5 Sterilization Technology

Sterilization is a process that kills all viable microorganisms using chemical agents or physical methods, including all bacterial propagules, spores, molds and viruses, to reach total sterility. The pharmacopoeia accepted sterilization methods include the moist heat sterilization method (pure steam sterilization and superheated water sterilization), dry heat sterilization, radiation sterilization, gas sterilization and filtration sterilization.

8.5.1 Moist Heat Sterilization

Moist heat sterilization is a method of heat sterilization, generalized moist heat sterilization uses saturated steam or superheated water for sterilization, and e.g., pure steam sterilization and superheated water sterilization are both moist heat sterilization methods. The accepted pharmacopoeia moist heat sterilization refers in particular to the method in which the articles are placed in a sterilizer and the protein and nucleic acid in the microbial thallus are deformed due to the high pressure of the saturated steam and superheated water spray, which kills the microorganisms. This method has strong sterilization ability, it is the most effective, and widely used heat sterilization method. Drugs, containers, media, gowning, stoppers and other articles which incur no changes or damage in high temperature and humid conditions can be sterilized with this method. The *Chinese Pharmacopoeia* (2015) stipulates "*moist heat sterilization is usually done at* 121 ℃ *for* 15 *min*, 121 ℃ *for* 30 *min or* 116 ℃ *or* 40 *min*, *or other temperature and time parameters*, *but no matter what sterilization temperature and time parameters are used*, *it must be demonstrated that the adopted sterilization process and monitoring measures can ensure that the SAL of sterilized articles is* $\leqslant 10^{-6}$ *during the routine operation process*". Circulated steam cannot kill bacterial spores effectively, but it can be used as auxiliary sterilization method for non-heat-resisting sterile products.

At the same temperature, the effect of the moist heat sterilization is better than that of the dry heat sterilization, the reasons are ① the temperature required for protein solidification is dependent on the water content, the higher the water content, the lower the temperature required for solidification. ② A large amount of latent heat is released in the moist heat sterilization process to increase the humidity rapidly, therefore, the temperature required by moist heat sterilization is lower than that required by dry heat sterilization, and the time required for moist heat sterilization is shorter than that required for dry heat sterilization at the same temperature. ③ The penetrating power of moist heat is higher than that of dry heat, which affects the depth to which the articles reach the sterilization temperature; therefore, the effect of the moist heat sterilization is better than that of the dry heat sterilization.

In the pharmaceutical industry, common moist heat sterilizers include vacuum steam sterilizers, steam-air mixture sterilizers and superheated water sterilizers, etc.

A pulse vacuum steam sterilizer is also called a moist heat sterilizer or pre-vacuum sterilizer. It is the most widely used high pressure steam sterilizer in drug production, and usually composed of a sterilization chamber, sealing door, control system, pipeline system, etc. and it is connected to a compressed air system, steam/pure steam system, vacuum pump, etc. The air is removed from the chamber by the vacuum pump or other system before the start of the sterilization phase, and then saturated steam is piped in. It is vacuumized and steam is piped in to completely replace the air, repeatedly, for sterilization. A pulse vacuum steam sterilizer is equipped with a vacuum system and an air filtering system, its sterilization procedure is computer-controlled. The removal of cold air in the chamber is relatively thorough. It is characterized by a short sterilization cycle and high efficiency. The pulse vacuum steam sterilizer has less strict requirements for the packaging and placement of articles, and the articles are not easily damaged by oxidization under vacuum. It is usually used to sterilize loads with porous/hard articles from which air is difficult to be removed, and can contain or carry air, such as flexible pipes, components of filters and filling machines.

A steam-air mixture (SAM) sterilizer is equipped with a sterilization chamber, centrifugal fan, heat exchanger and shelf, connected to a compressed air system, steam/pure steam system, vacuum pump, etc. When the steam enters the sterilizer, the fan will mix the steam with air in the sterilizer and circulate it to sterilize the product and air together. Air is added to the steam to produce a pressure which is higher than the pressure of the saturated steam at a certain temperature. Compared with saturated steam sterilization, the heat transfer rate of steam-air mixture sterilizer is lower; a fan is usually used to circulate the steam-air mixture. The sterilization pressure in the container and temperature dynamics of the sterilizer are the functions of the container type (such as rigid or nonrigid), filling volume, size of the head space and chamber temperature. After the steam-air mixture is sterilized, the product can be cooled by various methods. A frequently employed method is to use cooling water in the jacket or coil of the sterilizer, and keep cool air in circulation. Some steam-air mixture sterilizers are cooled by spraying cooling water above the product.

A high pressure superheated water spraying sterilizer is also called water bath sterilizer. It uses superheated circulating water as sterilization heat carrier to perform the sterilization operation by superheated water spraying. During the whole operation process, superheated water is used in a relatively closed circulating system. The equipment has a series of advantages such as high heat availability, uniform temperature and wide temperature regulating range; it can prevent secondary contamination effectively during the operation process.

A high pressure superheated water spraying sterilizer is equipped with a hot water storage tank, heat exchange unit, circulating fan, circulating pump, rotatory device, etc. During sterilization, the products are fixed in the tray, sterilizing water begins to enter the sterilization chamber, which is heated using the heat exchanger cycle heating, direct heating by steam, and then sprayed, and sterilized. After the completion of sterilization, the sterilizer can recover the sterilizing water, and some processes can dry the products by piping sterile air, circulation heating and dehydrating. This sterilization procedure by superheated water circulation uses pressurized air to keep the pressure required by the product safety; its heating and cooling rates are easily controlled, and is applicable to the sterilization of soft pouches. A high pressure superheated water spraying sterilizer can be widely used in the terminal

sterilization of large-volume parenteral solutions and small-volume parenteral solutions packed in glass bottles, ampoules, plastic bottles and IV bags in pharmaceutical industry.

Although the pharmacopoeia accepted moist heat sterilization method is mainly applicable to the sterilization of preparations, raw materials, excipients, medical devices, etc. which must be performed in a sterilizer, in the pharmaceutical water systems, in order to control the bioburden of the system, pure steam sterilization and superheated water sterilization have been widely used, e.g., periodic sterilization of the water for injection systems.

a. Pure steam sterilization. It is a method that uses high temperature and high pressure steam for sterilization. It is a moist heat sterilization method. The penetrating power of pure steam is very strong, protein and protoplasm colloid are easily denaturated and solidified under moist heat conditions, the enzyme system is easily damaged, steam enters into the cell and condenses to water, which can release potential heat and raise the temperature and increase the sterilization ability.

Pure steam sterilization procedures are mainly divided into four phases (Fig 8.13). ① air exhaust: pure steam is piped to replace non-condensable gas in the tank; ② heating: the vent filter is closed, pure steam continues to be piped and heats the system from 90 ℃ to 121 ℃; ③sterilization: the temperature is maintained at 121 ℃ for 30 min, timing must begin only after the tank temperature, pipeline temperature and vent filter sterilization temperature have reached 121 ℃; ④ cooling: the pure steam valve is closed, and cooling takes place at a predetermined rate using a natural cooling method or a compressed air cooling method.

The pure steam sterilization's advantages are short cycle time, latent heat of vaporization and use of a simple system. Pure steam itself has no residue, no contamination to the environment, no damage to product surface, easy control and reproducibility. It is widely used in the sterilization process of purified water systems and water for injection systems. Pure steam sterilization can kill all microorganisms, including bacterial spores, fungi spores or hypopus and other high temperature resistant species. The temperature of the steam for sterilization is risen with the increase of steam pressure, if the steam pressure is increased, the sterilization time can be significantly shortened. At present, sterilization at 121 ℃ for 30 min is usually used as sterilization parameters for the pharmaceutical water systems or the pure steam of the pharmaceutical water systems.

b. Superheated water sterilization is another typical moist heat sterilization method. Its principle is to use high temperature and high pressure superheated water for sterilization, which can kill all microorganisms, including bacterial propagules, fungi, protozoa, algae, viruses and bacterial spores with stronger resistance. It is similar to pure steam sterilization, superheated water sterilization may cause changes of the membrane structure, enzyme passivation and protein solidification, causing cell death. Superheated water sterilization is widely used in the pharmaceutical industry; it is applied to the water for injection storage and distribution systems sterilization, the sterilization production process of sterilized water for injection, and the terminal sterilization process of large/small volume parenteral solutions.

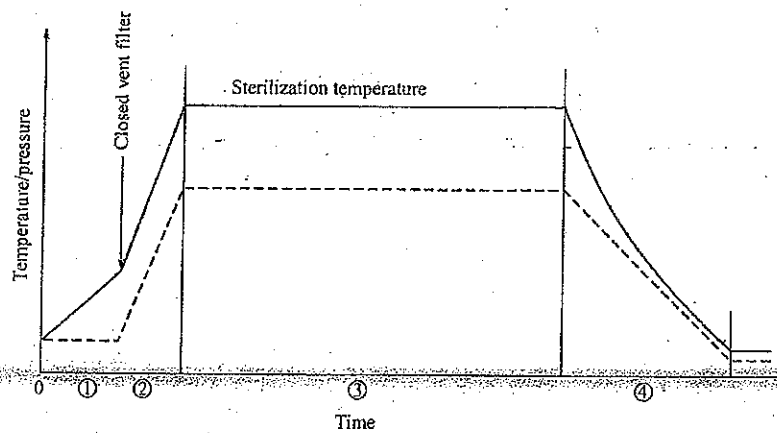


Fig 8.13 Performance graph of pure steam sterilization

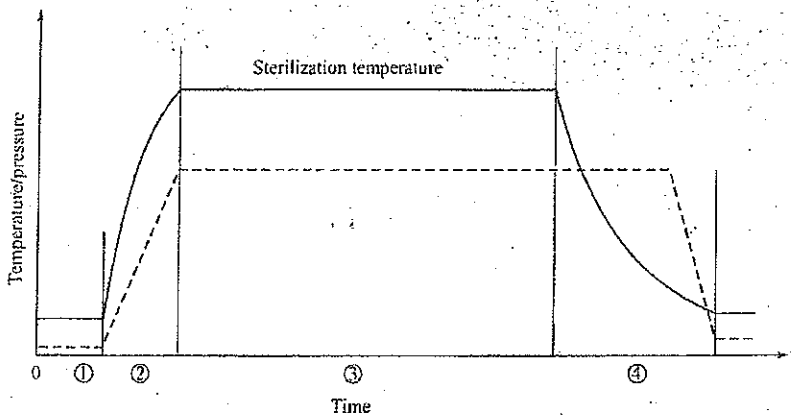


Fig 8.14 Performance graph of superheated water sterilization

Superheated water sterilization procedures are mainly divided into four phases (Fig 8.14): ①water injection: a certain volume of water for injection is injected in the tank, generally, it is 30%-40% of the tank's liquid level; ②heating: the circulation system is started, and the water for injection in the tank is heated from 80 ℃ to 121 ℃ using a double-plate tube heat exchanger or a steam jacket; ③ sterilization: 121 ℃ is maintained for 30 min, timing must start only after the tank temperature, pipeline temperature and vent filter sterilization temperature have reached 121 ℃; ④cooling: the water cooling control procedure starts, water for injection is circulated and cooled to a set temperature at a predetermined rate. At present, 121 ℃ and 30 min are usually used as superheated water sterilization parameters.

Compared with pure steam sterilization, superheated water sterilization has the following advantages: ①Plant steam is used as the heat source, not requiring additional pure steam generation; ②During the sterilization process, it is not required to consider the drainage of condensate water at the lowest point, the high pressure superheated water is circulated to pass through the whole system, with no sterilization dead leg caused by the absence of timely drainage of the condensate water; ③During the superheated water sterilization, the gas phase in the container is high pressure saturated pure steam, which can perform reverse sterilization in place of the vent filter in the water for injection storage tank effectively. However, pure steam sterilization uses the latent heat of vaporization for sterilization; its penetrating power is very strong, when superheated water sterilization is not sufficient, pure steam sterilization is a good remedial measure.

During the production of sterile drugs, any equipment having contact with products involved in production and cleaned should be subjected to timely sterilization. From the perspective of whether the sterilized articles require transfer, the sterilization methods in pharmaceutical industry can be classified as sterilization out of place and sterilization in place. Sterilization out of place is a method used to sterilize articles that must be dismantled or transferred to receive effective sterilization. Sterilization in place (SIP) is a method to sterilize equipment or systems in place without disassembly or with little disassembly. The modern biopharmaceutical water system usually adopts sterilization in place to achieve complete sterilization of the system. The Article 25 in Annex 3 *Biological Products* of the *Chinese GMP* (2010 *Revision*) stipulates that the pipeline systems, valves and vent filters should allow convenient cleaning and sterilization. It is preferred to use clean in place and sterilization in place systems. It should be possible for the valve of a closed container (such as fermentation tank) to be sterilized by steam.

Compared with traditional sterilization out of place, the advantage of sterilization in place is very obvious when considering microbial contamination control, validation, safety and production efficiency. The working principle of a sterilization in place system is to open the pure steam gulp valve automatically as per a set procedure to achieve automatic sterilization in place by setting the parameters such as temperature and time. The temperature test points are usually the tank, vent filter, pipe end or lowest point, etc. The system can conduct curve monitoring and print records for the critical parameters such as time and temperature of each sterilization procedure. The sterilization end point of the system is assessed by the PLC automatically.

The main features of sterilization in place include

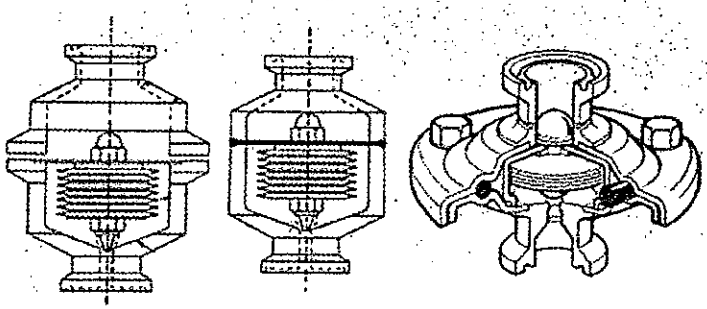


Fig 8.15 Thermostatic steam trap

the following:

- The system does not require disassembly, it is safe and energy saving.
- The sterilization end point is assessed automatically to save pure steam.
- The reproducibility of sterilization results is good and cross contamination between batches is effectively avoided.
- It is automatically operated in order to save labor, reduce misoperation, rationalize the production plan, and improve product quality and production efficiency.
- The set parameters in the procedure can be adjusted to facilitate the execution of performance qualification and optimization of operating cost.
- It is in full compliance with GMP requirements to achieve the validation of the sterilization process.

In the pharmaceutical water systems, pure steam sterilization is the preferred method of sterilization in place. The pharmaceutical water systems should have the vent filter closed when conducting pure steam sterilization, and a steam trap installed at the lowest point of the system to make sure condensate water at all low points are timely drained. The thermostatic steam trap is the ideal steam trap for pure steam sterilization (Fig 8.15). It is made of 316L stainless steel, and has a tri-clamp connection to ensure the sterility of the sterilization in place system effectively.

Air will form a "protective film" on the surface of articles to be sterilized to impede saturated steam from contacting the surface of articles, therefore, it is a must to exhaust non-condensable gas in the container during the pure steam sterilization, otherwise the sterilization effect will be significantly reduced. For example, moist heat sterilizers will remove the non-condensable gas in the chamber using pulse vacuum before sterilization. For the convenience of the validation of the sterilization process, it is possible to install temperature sensors or thermometers in key equipment or components (e.g., tank, vent filter, drug liquid filter) for monitoring. Timing cannot be started until the temperature at the coldest point of the system reaches the sterilization temperature. The temperature sensor is usually installed before the steam trap. If possible, the distance between the block valve and steam trap for sterilization in place should be kept at more than 1000 mm, and the distance between the steam trap and temperature sensor should be kept at more than 600 mm to avoid that the condensate water that is drained affects the temperature monitoring (Fig 8.16). To save installation space, a specially designed draining device can be used to ensure timely drainage of condensate water.

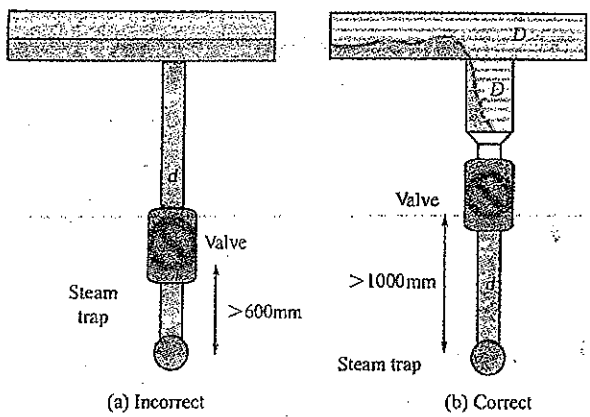


Fig.8.16 Installation of temperature sensor

Any fluid process system adopting pure steam sterilization should ensure 100% drainability so that the condensate water can be drained timely be means of gravity during the sterilization process. The "full gravity drainage" can be validated by slope inspection in installation qualification. Most of the pharmaceutical water systems use pure steam to conduct system SIP, the design and installation of the whole system should

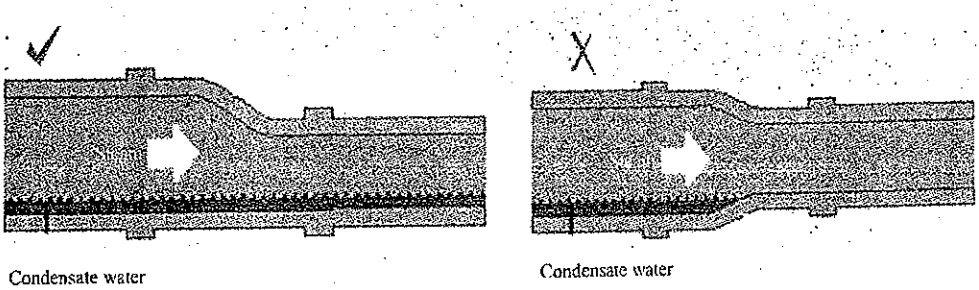


Fig 8. 17 Installation of reducing nipple in horizontal pipeline

follow the principle of "full gravity drainage". The *ASME BPE Standard* is taken as an example, the slope of the transfer pipe of the purified water and water for injection systems should be not less than 1%, that of the sterile process gas systems and pure steam system should be not less than 2%. The installation of a reducing nipple may be chosen in the pharmaceutical water system, to ensure the drainability of the system, for a vertical pipeline, a concentric or eccentric reducing nipple can be installed, while for a horizontal pipeline, a concentric reducing nipple will impede the condensate water from being drained out, therefore, an eccentric reducing nipple must be installed in the pipeline (Fig 8. 17).

The system temperature should be above 121 ℃ and at positive pressure during the pure steam sterilization. The pressure in different containers or pipelines may be different due to the different temperature conduction of different components as well as system design and installation. Fig 8. 18 shows two containers or pipelines sharing a steam trap, if they are sterilized at the same time, it is possible for sterilization failure to occur because of the different sterilization pressures, therefore, when all components of the pharmaceutical water systems are undergoing pure steam sterilization at the same time, at the bottom of each container or at the end of each section of pipeline a steam trap should be installed to ensure the thorough sterilization of the system; otherwise, the sterilization should be conducted at different times.

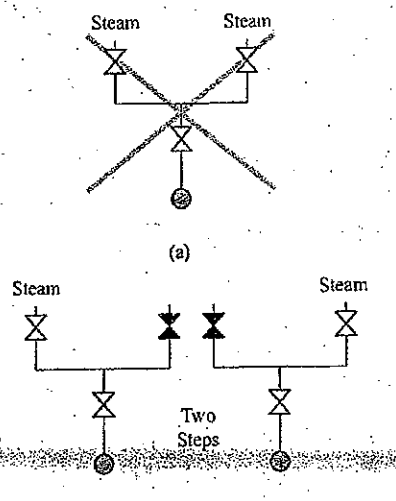


Fig 8. 18 Design of steam traps

8. 5. 2 Dry Heat Sterilization

Dry heat sterilization is another heat sterilization method; it is a technology used to sterilize in dry conditions; it includes flame sterilization and dry heat air sterilization. Flame sterilization uses direct exposure to the flame, the sterilization is rapid, reliable and simple, and applicable when sterilizing articles and utensils made of flame resisting materials (such as metal, glass, porcelain, etc.), but not applicable to sterilize drug products. Dry heat air sterilization uses high temperature dry hot air. This method is applicable when sterilizing high temperature resistant glass and metal wares as well as grease which is not penetrated by moist heat gas (e. g., oily ointment matrix, oil for injection, etc.) and high temperature resistant powdered chemicals.

Bacterial propagules can be killed at 80-100 ℃ for 1h in dry conditions. Spores can be killed after being heated to 160-170 ℃ for 2 h. In dry heat conditions, the heat resistance of microorganisms is stronger due to the less heat penetrating power, it must be sterilized at high temperature for a long time; therefore, dry heat sterilization requires higher temperature and a longer time than that required by moist heat sterilization.

The pharmacopoeia accepted dry heat sterilization is a method for killing microorganisms or removing pyrogens using dry heat air by placing the articles in equipment such as dry heat sterilizers and depyrogenation tunnels. It is applicable to sterilization of articles which resist high temperature but not suitable to be sterilized by moist heat sterilization, such as glass wares, metal containers, fiber products, solid reagents, liquid par-

affin. The conditions for dry heat sterilization are usually 160-170 ℃ for more than 120 min, 170-180 ℃ for over 60 min or 250 ℃ for over 45 min, or it may use other temperature and time parameters, but no matter what sterilization temperature and time parameters are used, it must be demonstrated that the sterilization process and monitoring measures can ensure the SAL of the sterilized articles is $\leqslant 10^{-6}$ during the routine operation process. Overexposure to dry heat is used when the determination of contaminating microorganisms is not done before sterilization. The *Chinese Pharmacopoeia* (2015) regulates that dry heat sterilization at 250 ℃ for 45 min can remove pyrogens in the packaging container or filling utensils for sterile products, meanwhile, it should be demonstrated that the sterilization conditions can reduce at least 3 lg units for endotoxins.

The articles to be sterilized should have an appropriate loading pattern when dry heat sterilization is adopted. They should not be arranged too closely to ensure the effectiveness and uniformity of sterilization. For dry heat sterilization it should be verified that the temperature distribution in the sterilizer complies with set standards and the position of coldest point defined, etc. The commonly used biological indicator is spores of bacillus subtills. The bacterial endotoxin sterilization validation test is used to prove the effectiveness of the depyrogenation process. It is usually consists of adding not less than 1,000 units of bacterial endotoxin to the articles to be depyrogenated, and demonstrate that the depyrogenation process can reduce 3 lg units at least for endotoxin. The bacterial endotoxin used in the bacterial endotoxin inactivation validation test is usually escherichia coli endotoxin.

In pharmaceutical industry, commonly used dry heat sterilization equipment includes dry heat sterilizers and tunnel sterilizers. The dry heat sterilizer is a widely applied sterilization equipment in sterile drug manufacturing enterprises; it uses the principle of dry heat air sterilization. It is mainly used for glass wares, metal containers, porcelain utensils and other articles which can resist high temperature. A tunnel sterilizer is also called a depyrogenation tunnel; it is a type of oven, which conducts drying using hot air circulation in a long cabinet or far infrared drying. The tunnel sterilizer is an important part of the production line of larger volume parenteral solutions, squirt cuts and powder for injections. It is can be used for the drying, continuous sterilization and depyrogenation of glass containers such as glass bottles, ampoules, and vials of each specification. A depyrogenation tunnel is a type of continuous drying equipment, which can dry uninterruptedly to improve the production efficiency.

8.5.3 Radiation Sterilization

Radiation sterilization is a method used to kill microorganisms by exposing the articles to γ rays from a radioactive source or an electron beam accelerator's ionizing radiation. The most frequently used method is radiation sterilization using ^{60}Co-γ rays. Medical devices, containers, production auxiliaries, raw materials and finished products not damaged by radiation can be sterilized by this method. The SAL of sterile articles sterilized by using radiation sterilization should be $\leqslant 10^{-6}$.

The parameter controlled for γ ray radiation sterilization is manly the radiation dose (means the absorbed dose of the sterilized articles). The establishment of the dose should consider the adaptability of articles to be sterilized, the maximum quantity of microorganisms that may be contaminating the items, and the strongest radiation resistance. The used dose should be validated in advance to prove that it has no impact on the safety, efficacy and stability of articles to be sterilized. The commonly used absorbed dose for radiation sterilization is 25 kGy. A low radiation dose should be used as far as possible for the finished products, raw materials and some medical devices during sterilization. Before sterilization, the level of microbial contamination and strength of radiation resistance of articles to be sterilized should be determined to evaluate the sterility assurance level of the sterilized articles obtained from the sterilization process. The preset dose should be reviewed periodically to validate its effectiveness.

During sterilization, appropriate chemical or physical methods should be used to monitor the radiation dose absorbed by the sterilized articles to fully justify it is at the stipulated limit. If a dosimeter which is irradiated together with the articles to be sterilized is used, it should be placed in the stipulated position. The dosimeter should be calibrated with a standard source for the first installation, and recalibrated periodically. The frequently used biological indicator for Co-γ ray radiation sterilization is spores of bacillus pumilus.

8.5.4 Gas Sterilization

Gas sterilization is a method used to kill microor-

ganisms with gas generated by a chemical sanitizer. The commonly used chemical sanitizers include ethylene oxide, vaporized hydrogen peroxide, formaldehyde, ozone, etc. This method is applicable to sterilize articles which are stable in the gas. The operator should be aware of the combustibility, explosibility, teratogenity and residual toxicity of sterilization gas when gas sterilization is adopted. A frequently used gas with this method is ethylene oxide; it is usually used by mixing with 80%-90% inert gas, and performed in a hyperbaric pressure chamber filled with sterilization gas. This method can be applied to sterilize articles such as medical devices and plastic products which cannot use high pressure sterilization. The articles containing chloride or adsorbing ethylene oxide cannot use this method for sterilization.

When ethylene oxide is used for sterilization, the temperature and humidity in the sterilization cabinet, sterilization gas concentration and sterilization time are important factors affecting the sterilization effect. The following sterilization conditions can be used: Temperature, 54 ℃ ± 10 ℃; Relative humidity, 60% ± 10%; Sterilization pressure, 800, 000 Pa; Sterilization time, 90 min.

Sterilization conditions should be validated. When sterilizing, the sterilization chamber should be vacuumized, and then steam piped to make the chamber reach the set value of balanced temperature and humidity, filtered and preheated ethylene oxide gas is piped. During sterilization, the chamber temperature, humidity, pressure, ethylene oxide concentration and sterilization time should be strictly monitored, and the sterilization effect should be monitored by biological indicators when necessary. The control of the sterilization procedure has a certain degree of difficulty, and the whole sterilization process should be conducted under the supervision of qualified personnel. After sterilization, the gas should be replaced by fresh air, residual ethylene oxide and other volatile residues dispersed, and the ethylene oxide residue and reaction products in the sterilized articles should be monitored to demonstrate they does not exceed the stipulated concentration and avoid toxicity.

When using ethylene oxide for sterilization, a leak test should be conducted to confirm the leakproofness of the sterilization chamber. The impact of packaging materials and arrangement of articles in the sterilization chamber on sterilization gas diffusion and penetration should also be taken into consideration during the verification of the sterilization procedure. The biological indicator usually uses spores of bacillus subtilis.

8.5.5 Filtration Sterilization

Filtration sterilization is a method of removing microorganisms in a gas or liquid using the principle of bacteria cannot pass through compact porous filter materials. It is usually used to sterilize gas, heat-labile drug liquids or raw materials. A sterilizing filter has a microfiltration membrane with uniform pore size distribution as filter material; it is divided into hydrophilic and hydrophobic microfiltration membranes. The material of the filter membrane is determined by the characteristics of the articles to be filtered and the filtering purpose. The sterilizing filter membrane used in drug production has usually a pore size of not more than 0.22 μm. The definition of pore size of the filter is based on the retainment of microorganisms by the filter, not the distribution coefficient of average pore size. Therefore, the filter used for final sterilization must use sterilizing filter proved by a retaining test. The adsorption by the filter should not affect drug quality, have no fiber shedding, and filters containing asbestos should not be used. The user of the filter should know the properties and quantity of precipitates from filtration and evaluate the toxicity effect. The filter and filter membrane should be cleaned before use, and sterilized with high pressure steam or sterilized in place. The filter should be cleaned first, and then the filter element replaced or the filter should be replaced directly before changing brands and batches.

The sterility assurance during the filtering process is related to the initial bioburden of the filtering liquid and log reduction value (LRV) of the filter. LRV is the common log value of the ratio of microbial population before and after filtration of the filtered liquid in stipulated conditions, i. e.

$$LRV = \lg N_0 - \lg N \qquad (8.1)$$

In which, N_0 is microbial population before sterilization; N is microbial population after sterilization.

LRV is used to express the sterilizing filtration efficiency of the filter. For a filter with pore size of 0.22 μm, it is required that the LRV of effective filtration area per 1 cm^2 should be not less than 7. Therefore, the total contamination level of the filtered products during the sterilizing filtration sterilizing should be con-

trolled at the stipulated limit. To ensure the filtration sterilization effect, it is possible to connect filters from two sterilizing levels in series for filtration, or re-filtering before filling. It should be noted that, the microbial contamination level of the feed liquid before the sterilizing filtration should be not more than 10 CFU/100ml, and the bioburden of the feed liquid can be reduced by using of prefiltration.

During filtration sterilization, critical parameters of the filter cannot usually be monitored (the pore size of the filter membrane and its distribution, the integrity and LRV of the filter membrane) during the whole process, therefore, a filter integrity test should be performed before and after each filtration sterilization, i.e. bubble test, pressure maintaining test or gas diffusion flow test, to verify the effectiveness and integrity of filter membrane in the sterilizing filter. The compliance with the test standard is concluded from relevant bacterial retaining test data. The service intervals of the sterilizing filter should be validated, generally not more than one working day.

The commonly used biological indicator for filtration sterilization is pseudomonas diminuta. A product which cannot reach sterility through filtration sterilization should be strictly monitored for the cleanliness of its production environment, and the filtering operation should be conducted under aseptic conditions. Relevant equipment, containers, stoppers and other articles should be sterilized with appropriate methods and protected from recontamination.

Sterile water for injection is prepared from water for injection according to the production process of injections. It is a colorless clear liquid, with no odor and taste, and a type of product water included in the pharmacopoeia. The preparation process of the sterile water for injection should be sterilized by moist heat sterilization, and filtration sterilization is an effective supplement.

Chapter 9

Rouge Formation

Metal corrosion is the degeneration of metal materials caused by environment, the direct result of metal corrosion is the shortening of the service life of engineering materials and loss of performance. Metal corrosion represents a threat to environment safety, the metallic corrosion products or the leakage of chemical substances caused by corrosion may cause serious pollution to water resources, atmosphere and soil, even disastrous accidents. In the pharmaceutical industry, rouge (Fig 9.1), as the main type of direct metal corrosion can cause damage to components, such as leakage of pipelines, red foreign matters on membranes, blockage of filtration elements caused by absorption of rouge, etc.

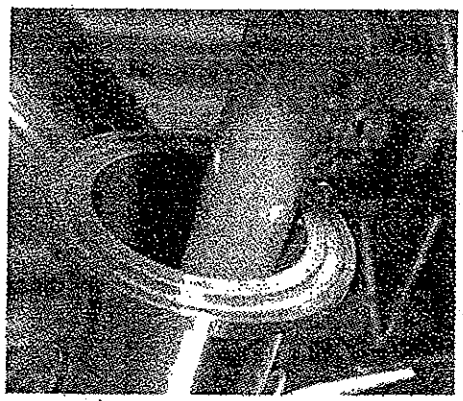


Fig 9.1 Rouge (see the color pages behind)

9.1 Regulatory Viewpoint

Rouge belongs to the category of particulate contamination, the concept of rouge is described in the ISPE *Baseline-Water and Steam System* (*Second Edition*) as follows: There is no specific definition for rouging, and rouge may be confused with localized corrosion (e.g., pitting corrosion) as similarly colored products are generated. Rouge in stainless steel systems utilized in the biopharmaceutical/life science industry, is a general term used to describe a variety of discolorations on the product contact surfaces, caused by variations in hydration agents and the formation of metallic (primarily iron) oxides and/or hydroxides from either external sources, or from alteration of the chromium rich "passive" layer.

The Chinese Good Manufacturing Practice (2010 *Revision*) states with regard to purified water and water for injection systems:

Article 101 *The pipeline for purified water and water for injection should be cleaned and disinfected according to related operating procedures with documented records. When the quantity of microorganisms in the pharmaceutical water reaches the alert and action limits, actions should be taken according to related operating procedures.*

The purpose of periodic cleaning is to remove the microorganisms and rouge attached to the system surface; the cost of the surface treatment is a direct loss. In addition, rouge, as an important source of particulate contamination in drug products, may cause that the products or water quality to be out of the internal standards of the corporation, which results in deviations of test results, problems with handling and operations, even the rejection of one or several batches products and unnecessary production halts. The loss caused by specific halts may be different according to the different value of the products of each enterprise. Corrosion may also cause the leakage of containers/pipelines, which results in the outflow of drug products. Once heavy rouge formed in water distillers and pure steam generators which are used as the generation equipment of water for injection and pure steam with the principle of heat exchange, the energy consumption cost of the enterprise will be significantly increased due to the thermal conductivity coefficient of the iron oxide being far below that of the alloy.

It is clearly specified in Article 99 of the *Chinese Good Manufacturing Practice* (2010 *Revision*) that water for injection should thermally circulate at above

70 ℃. The purpose of circulating at high temperature is to prevent the growth of microorganisms. And the *Chinese Drug Products GMP Guideline-Facility and Equipment* also clearly specifies that the circulating temperature of water for injection should be not more than 85 ℃; the main reason is that the formation speed of rouge will be increased rapidly under the action of electrochemical corrosion, pitting corrosion and other mechanisms once the temperature is above 85 ℃. This is also due to the fact that the ion product constant of high temperature water is far above that of normal temperature water.

In the pharmaceutical industry, water for injection and pure steam are widely used in vial washing machines, washing machines, sterilizers, CIP stations, solution preparation tanks for washing or drug liquid formulation; and other equipment in direct contact with the product. For sterile products, water for injection is a critical raw material, and the water for injection systems is in direct contact with the water for injection; how much substance is shedding from the surface of its pipeline will impact the quality of the water for injection, thus resulting in product quality problems occurring. This conclusion has been accepted by the ISPE and the GMP guidelines of many countries. At present, there have been several cases that the visible foreign matter and clarity of product requirements are constantly not met due to rouge.

If the rouging is severe it may reach to Class Ⅱ or Class Ⅲ in water for injection generation, storage and distribution systems; and then the rouge will be brought downstream and may contaminate the product. In most situations, a terminal aseptic filter will be considered during design; the filter elements are normally made of Polytetrafluoroethylene (PTFE), polypropylene (PP) or polyvinylidene fluoride (PVDF), which have a very strong electrostatic adsorption force to rouge particles, and will cause "gradual blocking" of the filter element, it could lead to damage of the filter element and impact on product quality.

In the manufacturing of sterile products, the mechanisms and control measures of microbial contamination have been studied widely by the pharmaceutical industry. For pharmaceutical water systems, both microbial contamination and particulate contamination are critical risk control points during the manufacturing of drug products, so rouge should be recognized by the pharmaceutical enterprises as one potential source of particulate contamination.

The *Chinese Good Manufacturing Practice* (2010 *Revision*) mentions "risk" about 24 times, so risk control is a matter of great concern during the manufacturing of drug products, for example:

Article 3 *As part of the Quality Management system, this regulation is the basic requirement for the manufacturing management and quality control. The purpose is to maximize the reduction of the risks of contamination, cross contamination, mix-up and error, to ensure that products conforming to the intended use and registrations requirement are consistently produced.*

Article 13 *Quality risk management is a process of assessment, control, communication and review of the quality risk. It can be applied both proactively and retrospectively throughout the life-cycle of the product.*

Article 14 *The evaluation of the quality risk is based on scientific knowledge and experience with the process to ensure the product quality.*

Article 15 *The methods, action, formality employed and documentation formed during the quality risk management process shall adapt to the level of risk.*

Article 71 *Equipment should be designed, selected, installed, renovated and maintained to suit its intended purpose, and maximally prevent the risk of contamination, cross-contamination, mix-up and errors; also should be easily operated, cleaned, maintained and allow disinfection and sterilization when necessary.*

Article 138 *Manufacturers should confirm the required qualification and validation activities to determine that the critical steps of specific operations are effectively controlled. A risk assessment approach should be used to determine the scope and extent of qualification and validation.*

The US FDA has no specific written requirement on rouging, its existence, or presence in high purity water, steam, and process systems. Their criterion is to meet established standards of quality for those systems. The 21 CFR (Code of Federal Regulations) Chapter I, Part 211, Subpart D-*Equipment*, Section 211.67-*Equipment cleaning and maintenance* reads: "*Equipment and utensils should be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements.*"

The *Adulterated Drugs and Devices Federal Food Drug & Cosmetic Act*-31 December 2004 Amendment, Section 501 (a) (2) (B) reads: "*A drug or device*

should be deemed to be adulterated if … the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

Rouge consists of iron oxide, but iron is not a heavy metal, so the *US Pharmacopeia* neither identifies rouge as a contaminant nor proposes alert and action limits or methods for detecting rouge product streams; the USP usually does not address design or material criteria directly, but rather indirectly by defining limits for the components that ultimately will enter the human body.

The scope of the *US Pharmacopeia* covers the quality of the water that is used, not the system that generates it, and rouging is a matter that relates to material selection for the system; conversely, design criteria are intended to minimize the risk to the water. The USP requires representative sampling; therefore, we can infer that the sample represents the water quality for the entire system and the water quality between sampling periods; the USP gives only specifications to that quality. Additionally, design criteria are intended to ensure this quality, and to keep the process under control for a longer time (even if the water is non-compendial water). The owner/user should decide if the water quality obtained from a system that shows rouge is still compliant with the USP as well as internal requirements for the process.

The *European Pharmacopeia* monographs do not mention rouging or give guidance in this matter. There is one paper describing the maximum acceptable metal residues arising from the use of catalysts in the synthesis of pharmaceutical substances (*Note for Guidance on Specification Limits for Residues of Metal Catalysts*-EMEA-December 2002). This guideline applies to all dosage forms, but different limits are applied to oral and parenteral routes of administration; it can be applied as a guiding document for risk assessment on heavy metals in products and/or water systems.

Now, pharmaceutical enterprises around the world are paying close attention to rouging, although there are no any mandatory regulations or compendia explicitly making it in routine testing indexes, but pharmaceutical enterprises should periodically focus on the rouge formation and its level in clean fluid process systems on the basis of implementing the FDA quality metrics philosophy, to avoid the occurrence of irreversible quality problems of the finished products.

9.2 Rouge Classification

Rouge is a normal engineering phenomenon in pharmaceutical industrial equipment, and various colors of rouge, such as yellow, red, even black may be found in the pump cavity, pipe wall, spray ball, membrane and other locations. It is divided into three classes Ⅰ, Ⅱ and Ⅲ in industrial standards, like the ISPE *Guidelines-Water and Steam* (*Second Edition*) and the ASME BPE 2014.

9.2.1 The ISPE Classification

The classification of rouge is addressed in the ISPE Guidelines-*Water and Steam* (*Second Edition*), Chapter 10, Section 4, see details below:

- Class Ⅰ-Migratory rouge-consists of various oxides and hydroxides derived from the source metals [iron oxide or ferrous oxide (FeO) being the most prevalent]. It is predominantly orange to red-orange, is particulate in nature, and tends to migrate from its originating point on the original metal surfaces. These deposited particles can be removed from the surface leaving the composition of the stainless steel unchanged.

Class Ⅰ rouge is attached to the surface of the stainless steel (Fig 9.2), and cannot cause constitutive and component damage to the stainless steel, so this class of rouge has lower engineering risk with a short forming time. It is a normal engineering phenomenon, it is not recommended to remove the class Ⅰ rouge and carry out re-passivation frequently from point of view of the input-output ratio.

- Class Ⅱ-*In-situ* oxidation of non-passive surfaces-localized form of active corrosion [iron oxide or ferric oxide-hematite (Fe_2O_3) being the most prevalent]. It occurs in a spectrum of colors (orange, red, blue, purple, grey, and black). It can, most commonly, be the result of chloride or other halide attack on the surface of the stainless steel. Integral with the surface, it appears more frequently on mechanically polished surfaces or where the interaction of metal and flowing product may have compromised the passive layer.

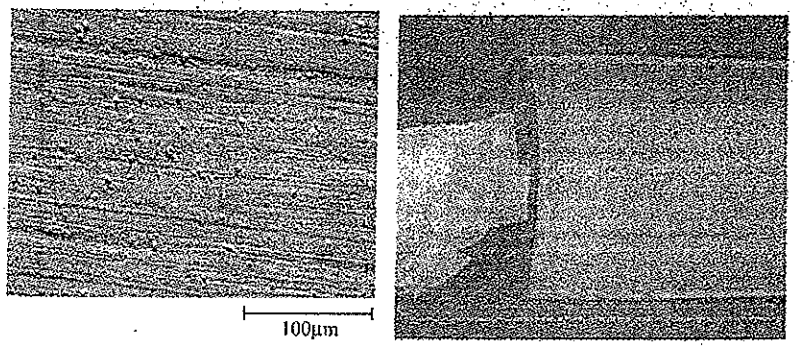


Fig 9.2 Class Ⅰ rouge (see the color pages behind)

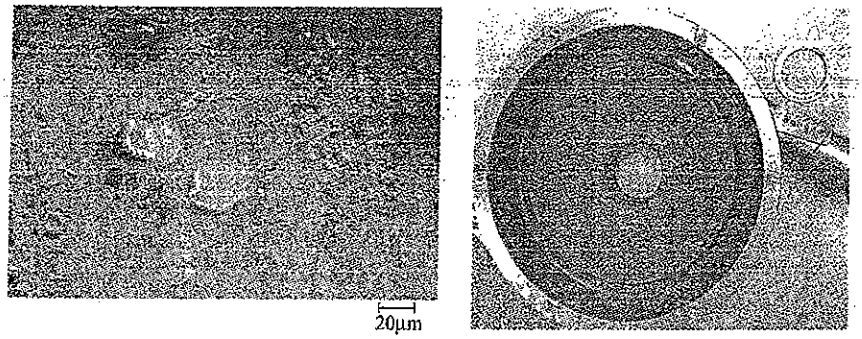


Fig 9.3 Class Ⅱ rouge (see the color pages behind)

Class Ⅱ rouge can damage the surface finish of stainless steel (Fig 9.3), resulting in the risk of microorganism growth. The enterprises are recommended to reduce the risk caused by class Ⅱ rouge through periodic washing and derouging mechanisms.

• Class Ⅲ-Black oxide produced by hot-oxidation—a surface oxidation condition occurring in high temperature environments, such as pure steam systems. As the rouge layer thickens, the system's color transitions from gold to blue and to various shades of black. This surface oxidation initiates as a stable film and is rarely particulate in nature. It is an extremely stable form of magnetite [ferroferric oxide (an oxide containing two atoms or radicals of some other substance), Fe_3O_4].

The hazard of class Ⅲ rouge is mainly focused on the growth of microorganisms (Fig 9.4), because the main component of this type of rouge is magnetite [ferroferric oxide (Fe_3O_4)] which is hard to be removed. Normally, enterprises use hydrofluoric acid or renovation to solve this problem. Comprehensive rouge of class Ⅲ will occur in a system after long term operation, if hydrofluoric acid is used for derouging in this condition, it is more likely to cause leakage considering the very strong corrosivity of the hydrofluoric acid and safety accidents may occur in severe conditions. Another solution is to renovate and upgrade the whole system, but the investment will be very significant. Therefore, it is recommended to remove the rouge during the class Ⅱ stage.

9.2.2 ASME BPE Classification

More detailed classifications can be found in the *ASME BPE Standard*-2014 (Revision of ASME BPE-2014), Non-mandatory Appendix D *Rouge and Stain-*

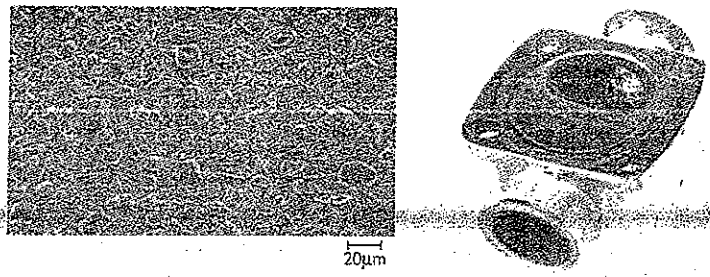


Fig 9.4 Class Ⅲ rouge (see the color pages behind)

less Steel:

Class Ⅰ rouges are weakly attached to the surface and relatively easily removed and dissolved. This rouge is generally hematite or red ferric iron oxide with low levels of other oxides or carbon content. Phosphoric acid is useful to remove light accumulations and can be blended with other acids and compounds including citric, nitric, formic, or other organic acids and surfactants to assist in its derouging effectiveness. Citric acid-based chemistries with additional organic acids are effective at rouge removal. The use of sodium hydrosulfite (i. e., sodium dithionite) is also fast and effective at removal of class Ⅰ rouge.

Class Ⅱ rouge is removed with chemistries that are very similar to the above listed processes with the addition of oxalic acid, which improves the effectiveness in removal of this type of rouge. This rouge consists mostly of hematite or ferric iron oxide with some amount of chromium and nickel oxides as well as small carbon content. All of the above chemistries remove the rouge without damage to the surface finish with the exception of oxalic acid, which may etch the surface depending on conditions and concentration processed. Class Ⅱ rouges are more difficult to remove than class Ⅰ, and may require additional time, even though these processes are often run at slightly higher temperatures and increased concentrations.

Class Ⅲ rouge is much more difficult to remove compared to class Ⅰ and class Ⅱ rouge, both due to its chemical composition difference and its structural difference. These high temperature deposits form magnetite iron oxide with some substitution of chromium, nickel, or silica in the compound structure. Significant amounts of carbon are generally present in these deposits due to reduction of organics present in the water, which sometimes produces the "smut" or black film that may form during derouging. The chemistries used to remove this rouge are very aggressive and will affect the surface finish to some degree. Phosphoric acid-based derouging systems are generally only effective on very light accumulation of the rouge. The strong organic acid blends with formic and oxalic acid are effective on some of these high temperature rouges, and being less aggressive, produce much less potential for etching of the surface finish.

9.3 Metal Corrosion

Metal materials will be damaged in different forms due to the influence of surrounding environment when using, the most common destructive forms are breakage, abrasion, and corrosion. Corrosion is the chemical or electrochemical interaction between a metal and its environment, which results in undesirable changes in the properties of the metal. Rouge is the typical corrosion of metals; hence, the understanding of the cause of metal corrosion is particularly crucial to the understanding of the formation mechanism of rouge.

9.3.1 Classification of Metal Corrosion

There are different classifications of corrosion due to its complicated phenomenon and mechanism, the common used method is to classify corrosion according to its mechanism, form, and environment that produces it.

a. Classification by corrosion mechanism. Corrosion can be classified into chemical corrosion, galvanic corrosion, physical corrosion according to its mechanism, of which galvanic corrosion is the most common, and the most severe hazard to metal.

• Chemical corrosion is damage caused by the chemical reaction of the metal surface with a non-electrolyte directly. There is no electric current occurring during the reaction process, for example, when the steel is heating in air, iron will have a chemical reaction with oxygen in the air and generate loose iron oxide; the corrosion of aluminum in carbon tetrachloride and ethanol; the corrosion of magnesium or titanium in methanol, etc. all those are instances of chemical corrosion. The characteristic of this type of corrosion is that the corrosion products are formed by the direct interaction of non-electrolyte oxidants with the surface atoms of the metal under certain conditions, the electrons are transferred between the metal and oxidant during the corrosion process, that's the reason why there is no electric current. High temperature oxidation of metal is normally considered as chemical oxidation, but because the high temperature can form a semiconductor oxidation film on surface of the metal, the high temperature oxidation is also considered to have an electrochemical mechanism.

• Galvanic corrosion is the damage of electrochemical reaction caused by metal with ion conductive electrolyte in water solution. There is electricity occurring during reaction process. The surface of the corroding metal can be cathode or anode, the anodic reaction is removing electrons from the metal and makes it be-

come positively charged; iron ions enter the medium, this is called an anodic oxidation process. The cathodic reaction is when the oxidizing agent in medium accepts electrons from the anode, also called cathodic reduction reaction. Those two reactions are mutually independent and conducted simultaneously, called a pair of conjugated reactions. A short circuit cell is constituted by cathode and anode on the metal surface, and an electric current occurs during the corrosion process. The corrosion of metal in media like the atmosphere, seawater, salt solutions, tap water, water for injection, etc. is in this category.

• Physical corrosion is the damage caused by the simple physical dissolution of metal in the surrounding medium. The physical dissolution of metal can occur in high temperature melted salts of liquid metal, and dissolved alkali. Physical corrosion is caused by material migration, solid metal is damaged by being dissolved in the liquid medium and migrating into the liquid, therefore no electric current occurs, this is a pure physical process. For example, a steel container is dissolved by melted liquid metal zinc, and damaged by thinning of the container wall.

b. Classification by forms of corrosion. The corrosion can be divided into uniform corrosion and localized corrosion according to damage type of the corrosion.

• Uniform corrosion refers to the damage of the entire or most of the metal surface, also called general corrosion. The results of corrosion are the reduction of material mass and thinning of the material. The potential danger of uniform corrosion is small, because the service life of materials can be calculated if the rate of corrosion is known, for example, steel is dissolved in hydrochloric acid rapidly, and some stainless steel is dissolved in deducing strong acids and organic acids. In most cases, protective corrosion coatings will be applied on the surface of the metal to slow the corrosion.

• Localized corrosion refers to the damage occurring on a narrow area of metal surface. Its potential danger is more severe than that of uniform corrosion, accounts for above 65% of the equipment mechanical corrosion damage. Because most of the localized corrosion is hard to find, it can have a sudden and disastrous impact on the equipment and system; the main forms include:

-Galvanic corrosion, the phenomenon when metals or alloys with two different electrode potentials are in contact and an electrochemical reaction takes place in a certain medium, rapidly damaging the negative potential metal.

-Hole corrosion, also known as pitting corrosion or point corrosion. This is a small and deep cavity occurring on a very specific area of the metal surface, normally, the depth of the cavity is much larger than its diameter, and the equipment may be penetrated in severe cases.

-Crevice corrosion refers to the localized damage phenomenon occurring in small gaps between metal and metal or metal and non-metallic surfaces to which the migration of ionic is limited and concentration cell is formed.

-Intergranular corrosion A localized corrosion phenomenon; the corrosion occurs along the grain boundary of the material to making the loss of binding force between grains when the metal is in certain corrosive media.

-Stress corrosion cracking. The cracking phenomenon that lowers the ultimate strength of materials and occurs locally under the action of tensile stress (including residual stress caused by applied load, thermal stress, cold working, welding, etc.) when the metal is in certain corrosive media.

c. Classification by corrosion environment. The corrosion can be divided into atmospheric corrosion, soil corrosion, seawater corrosion, biological corrosion, high-temperature gas corrosion, irradiation corrosion, corrosion in acids, alkali and salts, fused salt corrosion and corrosion in non-aqueous solutions, etc.

9.3.2 Typical Metal Corrosion

a. General corrosion. The general corrosion refers to the corrosion occurred on the entire surface of the metal, that is the same rate of corrosion on the entire surface of the metal, which results in the overall thinning of metal material. General corrosion is very common; it can be caused by electrochemical corrosion, such as the self-dissolving process of a homogeneous phase (pure metal) or a microscopic composite electrode (uniform alloy) in electrolyte solution, or may be caused by a purely chemical corrosion reaction. Usually, general corrosion refers in particular to the corrosion caused by electrochemical corrosion reactions.

Although general corrosion can cause significant loss of metal, usually it will not cause sudden failure accidents of metal equipment due as it is easily detected.

Especially for uniform general corrosion, the service life of the equipment can be correctly estimated based on the data obtained from several simple tests, thereby, a corrosion allowance will be considered in advance during the engineering design, preventing corrosion damage of the equipment occurring at an early stage. The technical measures used to control general corrosion are simple, like selecting appropriate materials or coatings as well as corrosion inhibitors and electrochemical protection, etc. The evaluation index of the general corrosion resistance of metal can be expressed as weight index, depth index and current density index, etc.

• Weight index of corrosion rate. It is the conversion of the weight variation due to corrosion of a metal into the weight change value of a unit of surface area of the metal per unit of time, see equation 9.1:

$$V_w = \Delta W/(St) \qquad (9.1)$$

In which, V_w is the rate of corrosion expressed with weight, g/(m² · h); ΔW is the weight variation of metal before and after corrosion, g; S is the surface area of the metal, m²; t is the corrosion time, h.

• Depth index of corrosion rate. The reduced thickness of the metal due to corrosion expressed with a length unit, and converted to an equivalent in a time unit, generally expressed as mm/a. this index is very convenient when measuring the corrosion rate of various metals with different densities. Its formula is as follows:

$$V_d = 8.76V_w/\rho \qquad (9.2)$$

In which, V_d is the rate of corrosion expressed with depth, mm/a, V_w is the rate of corrosion expressed with weight, g/(m² · h); ρ is the density of metal, g/cm³. Generally, the three-level criteria in Table 9.1 and ten-level criteria in Table 9.2 are used when the depth of corrosion is used to evaluate the performance of a metal in general corrosion resistance.

Table 9.1 Three-level criteria for corrosion resistance of a metal

Corrosion resistance assessment	Corrosion resistance level	Depth of corrosion /(mm/a)
Anti-corrosion	1	<0.1
Usable	2	0.1-1.0
Not usable	3	>1.0

Table 9.2 Ten-level criteria for corrosion resistance of a metal

Corrosion resistance assessment	Corrosion resistance level	Depth of corrosion /(mm/a)
Full anti-corrosion	1	<0.001
Good anti-corrosion	2	0.001-0.005
	3	0.005-0.01
Anti-corrosion	4	0.01-0.05
	5	0.05-0.1
Slight anti-corrosion	6	0.1-0.5
	7	0.5-1.0
Very limited anti-corrosion	8	1.0-5.0
	9	5.0-10.0
No anti-corrosion	10	>10.0

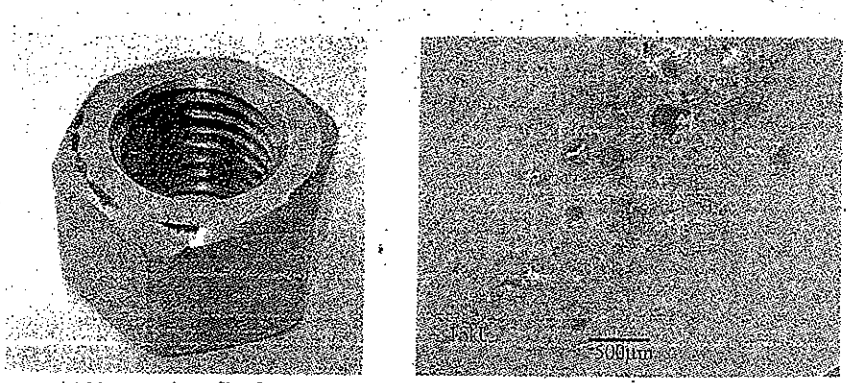
• Current density index and corrosion rate. Use the anodic current density during the electrochemical corrosion of a metal to measure the rate of electrochemical corrosion of the metal. According to Faraday's law, the current density index and weight index can be associated, and expressed in a formula (9.3):

$$i_{corr} = nFV_w/M \qquad (9.3)$$

in which, i_{corr} is rate of corrosion expressed with current density, A/m²; n is number of electrons gained or lost; F is faraday constant (F=96,500 C/mol=26.8 A · h/mol); V_w is the rate of corrosion expressed with weight, g/(m² · h); M is atomic weight.

b. Galvanic corrosion. It is a phenomenon when metals or alloys with two different electrode potentials are in contact and an electrochemical reaction occurs in a certain medium causing the negative potential metal to be rapidly damaged and the positive potential metal to be protected. Galvanic corrosion is very common in engineering; the most common method of cathodic protection with a sacrificial anode is making use of the principle of galvanic corrosion.

The impact factors of galvanic corrosion include materials, area ratio of the cathode and anode, and the medium, etc. When galvanic couple is formed with dissimilar metals, the further they are in the galvanic series, the more severe the tendency of galvanic corrosion; the acceleration effect on corrosion is not obvious when the potential difference between the metals is less than 50 mV and form a galvanic couple; the area ratio of the cathode and anode has an important impact on galvanic corrosion; the larger the area ratio of the cathode and anode, the larger the anodic current density, the larger the rate of metal corrosion; other



(a) Macroscopic profile of a nut (b) Microscopic features of a nut

Fig 9.5 Pitting corrosion of a stainless steel nut

factors are also having an important impact on galvanic corrosion, such as the composition of the medium, temperature, resistance of electrolyte solution, pH of solution, change of environment conditions, etc., they affect not only the rate of corrosion, but the galvanic couple reverse its polarity under different environment conditions.

c. Pitting corrosion. Pitting corrosion is another form of galvanic corrosion and is an extremely localized type leading to the creation of small pits or holes at the surface of the metal. It is a type of corrosion in a very small area at the surface of the metal, and the pinhole corrosion may deeply penetrate the metal; because the diameter of the corrosion hole is small but the depth is large, it also called hole corrosion. Fig 9.5 shows the macroscopic profile and microscopic features of pitting corrosion on a stainless steel nut, in which pit can be seen at a macroscopic level and punctiform pit can be seen at a microscopic level. As one of the most hidden corrosion forms, pitting corrosion will seriously damage the engineering alloy and cause adverse results. Pitting corrosion is normally formed on a passivated alloy. Some alloys/metals, such as stainless steel and Al, Ti, Zr and their alloys are generally all passivated in the industry environment. Although Fe and steel is not passivated under normal conditions, they also are passivated in some environments and suffer pitting corrosion.

Pitting corrosion is the most common failure cause for austenitic stainless steels. This type of corrosion is of great concern because once a pit is initiated there is a strong tendency for it to continue to grow, even though the majority of the surrounding steel is unaltered. The stimulus for this phenomenon is the lack of oxygen around a small area; this area becomes anodic while the area with excess of oxygen becomes cathodic.

Pitting on alloys is the damage on passivation which is caused by special ions at a microscopic level. The occurring of pitting corrosion can be divided into two stages: initiation and growth; there are metastable state pit points with small size and shallow depth during the initiation stage; the corrosion pit during the growth stage is larger with a lace structure at the edge of the pit and deep. When pitting corrosion occurs in a metal, different corrosion pit forms will be formed in different metal types and medium environments, etc. and the profile of the corrosion pit can be affected by chemical composition, microstructure, and impurities of the alloy.

d. Crevice corrosion. Crevice corrosion is different from pitting corrosion; normally occurs on a large area at the surface of a metal, with larger corrosion degree than pitting corrosion. Fig 9.6 shows the crevice corrosion on the weld coating of a heat exchange pipeline of a seawater cooling system. This weld coating protected against pitting corrosion, but crevice corrosion was found below the gasket after six months. Crevice areas where contacting liquid is retained will occur on parts due to inherent design or work environment; the

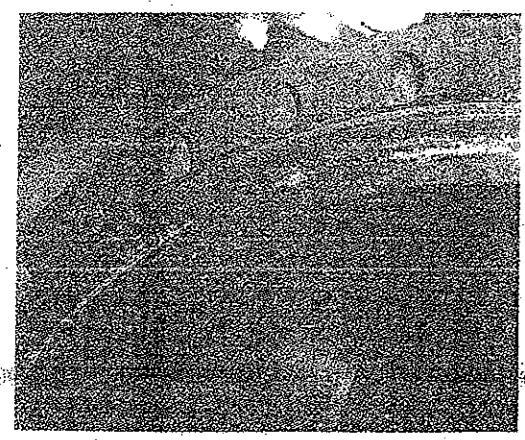


Fig 9.6 Crevice corrosion on a heat exchange tube

failure caused by rapid corrosion due to hindered exchange of substance inside the crevice is called crevice corrosion or under deposit corrosion. Typical crevice corrosion will occur at flanges, gaskets, the end of rotation pipelines, joints of threads, rivets, seal rings, spacers, lap joints, non-full melting weld joints, etc. On the other hand, crevice corrosion occurring in contamination areas is also a concern, although the failure reasons are different, but the principle of crevice corrosion is the same, that's why they are classified as the same type.

Crevice corrosion includes two stages: initiation and development. The oxygen outside the crevice can migrate to the surface of the metal through convection and diffusion, but the migration of oxygen inside the crevice can only be realized through diffusion. Because the solubility of oxygen in water is low, the dissolved oxygen diffused on the surface of the metal is also very low. Therefore, the oxygen inside crevice will be exhausted in a short time, which results in a negative shift of metal corrosion potential, by this time, the anodic polarization reaction of the metal is in the active dissolution area of the anodic polarization curve, which results in the instability of the passivation film at the crevice. Under these circumstances, the metal will be dissolved with very high speed.

Following the aggravation of corrosion, the dissolved metal ions will have a hydrolysis reaction, and will be deposited at the crevice, resulting in an occluded cell being formed and acidity increase, the aggregation of H^+ can break the electric neutrality environment of the occluded system, as a result, more corrosive negative ions migrates into the crevice, to produce acidification and concentration of chloride ions which promotes the further activation of corrosion and prevents the re-passivation of the metal. At this stage, the development of the crevice is similar to the self-catalysis developing process of pitting corrosion. The voltage drop inside and outside the crevice will make the crevice to be in activation state all the time. The above mentioned process reaction formula is as follows:

$$M \longrightarrow M^{n+} + ne^-$$

(accelerated dissolution of anode)

$$M^{n+} + nH_2O \longrightarrow M(OH)_n + nH^+$$

(pH value increased)

$$nH^+ + nCl^- \longrightarrow nHCl$$

(aggregation of chloride ion)

e. Intergranular corrosion is a localized corrosion which can affect the metal along the grain boundary of materials in a corrosive medium; the binding force between grains is lost. It is a form of relatively rapid and localized corrosion associated with a defective microstructure known as carbide precipitation. When austenitic steels have been exposed to high temperatures and allowed to cool at a relatively slow rate, such as occurs after welding, the chromium and carbon in the steel combine to form chromium carbide particles along the grain boundary; the formation of these carbide particles depletes the surrounding metal of chromium and reduces its corrosion resistance, allowing preferential corrosion along the grain boundaries. Steel in this condition is referred to as "sensitized."

The polycrystalline form is the mostly used form of engineering metal materials; at the grain boundary between the single grains many defects and lattice mismatches are present. According to thermodynamics, those defects have higher energy, which results in the boundary of grain being more easily corroded than the interior of the grain; on the other hand, the high energy state of the grain boundaries may cause the segregation of chemical compounds and precipitation of new phase, which can result in a difference of electrode potential, electrochemical reactions at grain boundaries and interior of the grain, and accelerate the corrosion of grain boundaries.

The chemical segregation and phase precipitation are the main factors involved in intergranular corrosion. Of all metal engineering materials, stainless steel is the most widely applied in industry, and the intergranular corrosion is the most common corrosion type in stainless steel. The intergranular corrosion easily occurs when the stainless steel is treated at high temperature; the critical temperature range for intergranular corrosion is related to the type and composition of the stainless steel.

f. Stress Corrosion. It is the delayed cracking or even fracture of materials subjected to a tensile stress in a specific corrosive environment. The corrosion is very limited when the material is not subjected to stress, cracking or fractures may occur in less severe corrosion conditions when the stress exceed a certain critical value; this is referred to as stress corrosion cracking. General corrosion is not likely to occur when stress corrosion occurs on metal structures; the strong capability to oppose uniform corrosion is caused by the passivation film at the surface of the metal or the pro-

tection of an alloy layer, one of the main reasons of stress corrosion cracking is film rupture.

9.4 Rouge Formation

The oxidation reaction is one of the basic chemical reactions in nature, and the rusting of stainless steel is in essence a type of oxidation reaction. Except for very few precious metals, almost all metals in nature will have oxidation reactions. As long as a reducing metal that is easy to be oxidized exists in the metal component, rust will be certainly found after prolonged exposure to an environment containing oxygen.

Rouge is actually a mixture constituted of different iron oxides, the free iron at the surface of stainless steel equipment in a high temperature fluid process system will first have a reaction with hydroxide ions in water, the whole reaction process is very complicated, and the color of rouge will be different if the proportion of specific ingredients is different. Fig 9.7 shows one common mechanism for rouging, although there is some academic controversy involving this mechanism, it can intuitively explain the chemical process of the rouging occurrence.

$2Fe+2H_2O+O_2 \longrightarrow 2Fe(OH)_2\downarrow$ (White, extremely unstable)

$Fe(OH)_2 \longrightarrow FeO\downarrow$ (Black, extremely unstable) $+H_2O$

$2Fe(OH)_2+O_2+H_2O \longrightarrow 2Fe(OH)_3\downarrow$ (Reddish brown, unstable)

$2Fe(OH)_3 \longrightarrow Fe_2O_3\downarrow$ (Reddish brown, better stable) $+3H_2O$

$6FeO+O_2 \longrightarrow 2Fe_3O_4\downarrow$ (Black, most stable)

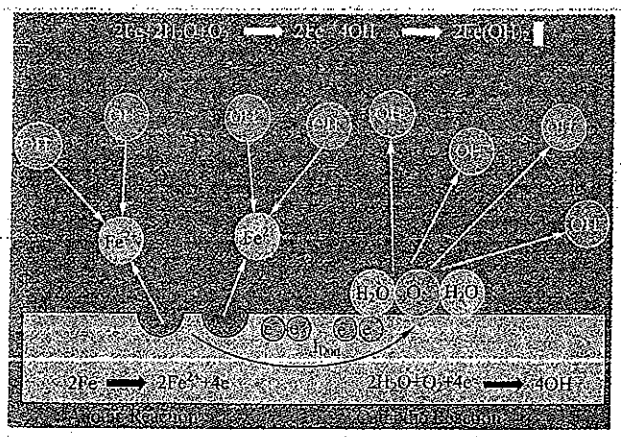


Fig 9.7 The Mechanism of Rouging

The ionic product constant of water (K_w) is the product of hydrogen ions concentration and hydroxide ions concentration, which increases with the rise of temperature. The concentration of hydroxide ions at 80 ℃ is five times the one at 24 ℃; and concentration of hydroxide ions at 90 ℃ is six times the one at 24 ℃. Under normal conditions, a high temperature circulating system for water for injection in pharmaceutical industry will maintain the temperature within the range of 75-85 ℃, this shows that the rouging rate of the water for injection systems which uses heat treatment for sterilization/disinfection will be faster than that of a purified water system which is circulating water at normal temperature.

When the rouge is found in equipment or system, its source needs to be assessed. Using the origin of rouge as the principle, rouge can be classified in endogenous rouge and exogenous rouge. Any stainless steel fluid process system will have some formation of rouge, the key points of a pharmaceutical enterprise in the control of rouging are: completely eradicate exogenous rouge and restrain endogenous rouge. The cause of exogenous rouge is factors outside the system, such as, halide ion environment, migration, or mechanical processing and other quality defects. Those factors need to be addressed during the design, installation, and operation stages and completely eradicated; the cause of endogenous rouge is related to the operation parameters or environment of the system itself.

9.4.1 Exogenous Rouge

Exogenous rouge is the rouging caused by external factors. It is mainly caused by external migration, environment corrosion, mechanical processing defects, improper welding and passivation operation, etc.

a. Upstream migration. The exogenous rouge causes by upstream migration can also be called upstream migration rouge, for example, the diaphragm, gasket or filter element which are mainly made of plastic, like polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), and polyether sulfone (PES), will adsorb a layer of rouge by electrostatic adsorption, but those materials themselves cannot generate rouge, the rust is from external components, therefore, this is exogenous rouge of the diaphragm, gasket or filter element caused by migration. Another example, some yellow, red and black granular substances are often found on the internal surface of the formulation tank in some pharmaceutical enterprises, it can be removed rapidly with manual wiping, but it will reappear after a few

days; although the formulation tank is made of stainless steel, but such rapid rouging is unlikely occurring without damage caused by accelerated external corrosion, hence, we can assume that the rouge is brought by the water for injection distribution systems or pure steam distribution systems, and results in rusting of the formulation tank; for a formulation tank, the visible yellow, red and black granular substances are exogenous rouge caused by migration.

b. Mechanical processing. The exogenous rouge cause by pipe cutting or surface finish can also be called mechanical processing rouge, its main cause is oxidation of pipe cutting powder, the causes are: improper pipe cutting, improper surface finish, and improper welding of stainless steel, etc.

During the pipe processing, the worker must cut the pipe in order to satisfy the requirements for a specific size, but cutting will unavoidably cause powder particles of stainless steel; the powder will be retained in the interior of the system if the treatment after cutting is improper, and a large surface of iron powder will accelerate the oxidation rate, turning the iron scraps into iron oxide. Therefore, during the pipe cutting of a clean fluid system needs the following details need to be paid attention to: a dedicated saw web is recommended for cutting; the cutting must be flat surface without oblique angles; a grinding wheel is not allowed for cutting; the fracture surface of the pipe should be leveled with a dedicated pipe flatting machine; and deburred; the deburring on the internal and external surfaces of a pipe can be removed with a replaceable blade knife; the pipe and fittings can be welded only after being thoroughly cleaned. Various foreign matters on the surface of the pipe, such as oil, dust, soil, paint, grinding scraps, should be removed prior to welding. The clean pipe end face for welding should not be touched with the hand; all tools, utensils, and machines should be protected and stored properly, to prevent the contamination of the environment and meet routine work requirements.

Another type of mechanical processing rouge is the oxidation of powder caused by mechanical polishing. Mechanical polishing is done with a polishing machine, smoothing the surface by the relative grinding and rolling action generated between very fine polishing powders and the grinding surface. It is divided into rough polishing and fine polishing. As with oxidation of pipe cutting powder, the powder needs to be thoroughly cleaned after the completion of mechanical polishing, to prevent the metal granules with large surface area from being oxidized into oxide granules.

The last kind of mechanical processing rouge is brought by welding oxidizing slag; high temperature will damage the original passivation layer on the surface of stainless steel during welding; generally, passivants (such as nitric acid, citric acid or other regulation recommended passivant) will be used for passivation after the completion of the welding of the whole system, to repair the damage surface at position of welding; however, if the relevant standards, like ASME BPE, are not followed strictly during welding, oxidizing slag may be retained, resulting in the shedding of rouge particles and contaminating the whole clean fluid process system.

c. Welding quality. Welding is one of the most common, and important processes in the processing of stainless steel system, the author found in many derouging cases that unacceptable welding quality is the main reason for rouging rapidly occurring in the system.

For the welding of sanitary stainless steel pipes, fittings and other process components, track welding is compulsive, for positions where track welding cannot be conducted, approval of customer or the third-party management company is needed prior to using manual welding. Strict quality control measures must be taken for the welded junction of the manual welding. The quality control of welding is an important factor in deciding whether a pharmaceutical fluid process system can meet the process design requirements or not, therefore, the requirements on the welding equipment, quality of argon, appearance of weld, color of weld, finish degree of weld, slop, deadleg, etc., are very strict. The quality control of the welding needs to be strictly managed by the construction unit, and a representative should be assigned to supervise and inspect the quality of welding.

Defects such as welding blowholes, incomplete-penetration weld and incomplete fusion, solid inclusions, welding deformation and shrinkage, tearing and polishing scratches on the surface, etc., are the common reasons for rouging in system due to welding.

• Welding blowhole. It is an air hole caused by an un-escaped bubble in the molten pool during solidification. There are two main types of welding blowholes, one is formed by gas from outside with limited solubility

(such as hydrogen, nitrogen, etc.); and another is formed by gas generated by metallurgy products in the molten pool; prevention of the generation of blowholes requires control of the sources of gas and the generating conditions of metallurgy products in the molten pool.

• Incomplete-penetration weld and incomplete fusion. incomplete-penetration means that the root of the joint is not fully penetrated or the depth of welding seam is not adequate during welding, its main influencing factors include: welding current is too low, welding speed is too fast, the welding wire is misaligned with the center of welding seam when the wire filling or tungsten electrode is misaligned with the center of the welding seam when non-pulse metal argon-arc welding is used. Incomplete fusion means that the weld pass and base metal are joined without completely melting, because the welding speed is too fast, etc.

• Solid inclusions. it refers to slag inclusion, occluded foreign substances, tungsten inclusion, etc. which are caused by improper pre-treatment of the surface of the welded joint or improper operation during manual argon arc welding. The presence of solid inclusions in the welded joint may bring a series of problems, such as stress concentration, stress corrosion or rough surface of weld, etc., if the cutting pipe orifice is not polished or polishing is improper, etc., this could ultimately lead to the finish of the internal wall failing the requirements of pharmaceutical engineering.

• Welding deformation and shrinkage. the circumferential weld of an austenitic stainless steel pipe should be lengthened by 2-3 mm, to control the problem of welding deformation and shrinkage, because its heat conductivity is only 1/3 of carbon steel with slower heat transfer and larger thermal deformation, and its coefficient of linear expansion is 40% larger than that of carbon steel, all these can increase the thermal expansion when heating and shrinkage when cooling resulting in more noticeable deformation after welding.

• Tearing and polishing surface scratching. Tearing of the surface mainly appears after the completion of the initial assembly of the pipe, the welded joint of a spot welding is torn due to improper operation or no protection of the initial assembled pipe resulting in damage of the surface of the base metal; polishing surface scratching is damage on the surface resulting from the polishing of the clean pipe not following the operating procedures.

The welding process must be protected with 99.99% argon filling at least, to obtain a bright and acceptable weld color. According to the color contrast table in Fig 9.8, a tempering color of above level 3 (including level 3) at least can meet the user requirements, otherwise, it will be considered an unqualified welded junction after the endoscopy inspection and needs to be welded again.

The welding log is the objective evidence of the welding process, which should include the following contents: welding date (year, month, day), description of the two welding materials [including materials category, type, specification (external diameter, wall thickness)], type of welding (automatic track welding or manual welding), welding procedure number of the welding machine; welder signature, the welding machine model and number unified by construction party, information for welding gas (such as type of gas, and purity description), information for forming gas (such as type of gas, and purity description), information for filled inert gas (such as type of gas, and purity description). Printed records of the welding must be attached to the log.

d. Passivation quality. Passivation is a method of making the surface of one active metal or alloy less easily oxidized, the chemical activity of the metal or alloy will be reduced. A passivation layer will be self-generated on the surface of stainless steel under aerobic envi-

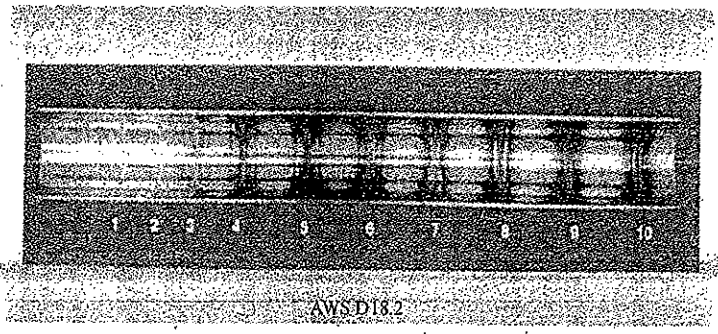


Fig 9.8 Oxidation Identification chart for endoscopy

ronment. Even if a passivation layer will be self-generated on the surface of stainless steel, it will be damaged at welding joint and heat-effected zone due to increasing of the iron content, and reducing of the chromium content during welding, in this case, those locations become risk sources. In addition to this, the cutting and bending of pipes will also produce some contaminants, such as scrap iron, thermal printing, solder, arc damage, etc., which can be removed with acid picking and passivation. Passivation should be done after the completion of welding for stainless steel components, for welded components before electrochemical polishing, and for the components of a new system after the completion of welding.

The passivation film can effectively inhibit the development of corrosion on the surface of stainless steel. The mechanism of passivation can be explained by the film theory: a passivation film which is very thin, compact, has a good covering performance will be generated and attached tightly to the surface of the metal under the action of an oxidant. This film is in an independent phase, and generally a compound of oxygen and metal. It plays a part in separating the metal and corrosion medium completely, and preventing the direct contact of the metal with the corrosive medium; it stops the metal from dissolving and forms a passive state, preventing corrosion damage.

The ratio of chromium to iron (Cr/Fe) is the mole number ratio of chromium to iron on the surface of the passivation film. The ratio of chromium to iron should be increased significantly after the surface passivation of 316L stainless steel, if the passivation process is used properly, the higher the ratio of chromium to iron the better, according to the definition of passivation. The accepted ratio of Cr/Fe should be not less than 1 whatever the detection method used, hence, a Cr/Fe of passivation layer equal to 1 is the critical point between a good passivation layer and a poor passivation layer in engineering, and passivation with Cr/Fe ratio higher than 1.5 is normally regarded as meeting quality requirements. Note that the values may be different when different detection methods are used due to accuracy differences.

The thickness of the passivation film can be measured with the ESCA/XPS method. Generally, a thickness of the passivation film of 1.5 nm is regarded as meeting passivation requirements. Note that a description of the passivation effect is required after the completion of passivation, including a general check, accurate check, electrochemistry and testbed check and chemical analysis test. Under existing conditions, the free iron test method is widely accepted in the passivation industry due to its advantages i.e. portability and accuracy, and used to decide whether element or system has been passivated.

e. Deadleg. The deadleg check is an important step during the installation qualification of a system. The quality risks brought by a too big deadleg in a pharmaceutical fluid process system are: increased product residue in pharmaceutical formulation system which will affect the yield of product; providing a hotbed for the reproduction of microorganisms, which can cause the formation of biological film and out of limits level of microorganisms, an increase in TOC or endotoxins resulting in the final product failing quality requirements; the secondary microorganism contamination caused by insufficient disinfection or sterilization of the system; contamination or cross-contamination caused by improper cleaning of system; rouge risk caused by residual rust staining of the system, etc. the presence of any deadleg in a pharmaceutical fluid process system may cause the microorganisms or particle contamination of the whole system.

The *Chinese GMP* (2010 *Revision*) stipulates that the design, selection, installation, renovation and maintenance of equipment must comply with the intended use, to reduce the risk of contamination, cross-contamination, confusion and mistakes. If the deadleg of pharmaceutical formulation system is too large, it may cause cross-contamination of the product due to improper cleaning of equipment. The cleaning validation module of a deadleg (Fig 2.8) helps conduct a scientific and correct analysis of the correlations between the system deadleg, flow rate and cleaning, and providing evidence of the risks of the deadleg using theoretical data.

In order to reduce the system deadleg, decrease the residue of high value-added drug liquid, prevent cross-contamination and formation of rouge in pharmaceutical fluid process systems, the ideal measures to control deadleg include: sterile transfer slabs, sterile tank bottom valves, GMP valves, multiple-pass in one valves, NA clamping fittings and fast connecting spring sleeve connecting pieces and other system components, pharmaceutical enterprises can make a reasonable selection according to actual conditions.

f. Slope. The slope check is another important step during the installation qualification, the slope of a pharmaceutical formulation system needs to meet the requirements of relevant regulations. Please refer to 2. 3. 3.

g. pH. Electrochemical corrosion is the primary cause and mechanism of corrosion and rouge generated in stainless steel, and the one element of electrochemical corrosion is that the materials will appear in electrolyte solution. Therefore, the electrolysis degree of a fluid is closely related to the corrosion of stainless steel.

The mechanism of corrosion is hydrogen evolution corrosion if the fluid is acidic; numerous tiny batteries form on the surface of stainless steel and with the cathode of made of iron, anode of made of carbon and an electrolyte solution of acidic fluid. The reaction of hydrogen evolution corrosion is:

cathode (iron): iron is oxidized $Fe-2e^- \longrightarrow Fe^{2+}$;

anode (carbon): the H in solution is reduced $2H^+ + 2e^- \longrightarrow H_2\uparrow$;

the overall reaction $Fe+2H^+ \longrightarrow Fe^{2+} + H_2\uparrow$, the final products of hydrogen-type corrosion are soluble iron salt and hydrogen.

The mechanism of corrosion is oxygen absorption corrosion if the fluid is slightly acidic, neutral or alkaline. The mechanism of electrochemical corrosion causing the rusty of stainless steel mentioned above is oxygen absorption corrosion. The reaction of oxygen absorption corrosion is:

cathode (iron): iron is oxidized $2Fe-4e^- \longrightarrow 2Fe^{2+}$;

anode (carbon): the O is reduced $2H_2O+O_2+4e^- \longrightarrow 4OH^-$;

the overall reaction $2Fe+O_2+2H_2O \longrightarrow 2Fe(OH)_2$

the final product of oxygen absorption corrosion is insoluble ferrous hydroxide, this is the earliest product of rouge.

According to the laws of chemical reactions, the reaction will proceed in the positive direction if the reactant concentration is higher. Therefore, the oxygen absorption corrosion or hydrogen evolution corrosion will be accelerated if a substance is added in the pharmaceutical making the electrolysis degree of fluid increased and the pH higher (concentration of hydrogen ion increased) or lower (concentration of hydroxyl ion increased).

h. Halogen ions. The most common halogen ion in pharmaceutical industry is the chloride ion (Cl^-), which can cause rapid and severe corrosion to the passivation layer of stainless steel, the materials selection of the whole storage and distribution piping system should be consistent, such as 316L or 304 stainless steel. The thermal insulation material of the stainless steel pipe should be made of chloride-free materials, to avoid the pitting corrosion formed on the passivation film of austenitic stainless steel by chloride ions (Fig 9. 9).

The mechanism of corrosion of the chloride ion, a halogen ion, of stainless steel is mainly described by the oxide-film theory and adsorption theory. Oxide-film theory is that due to the small ionic radius and strong penetrability, the chloride ion easily penetrates the tiny pores inside the oxidation film and reaches the metal surface, then interacts with the metal to form a soluble compound, and changes the structure of the oxidation film; metal corrosion is generated. The adsorption theory is that the primary cause of oxidation film damage by the chloride ion is its strong capacity to be adsorbed by the metal, the chloride ion will be pref-

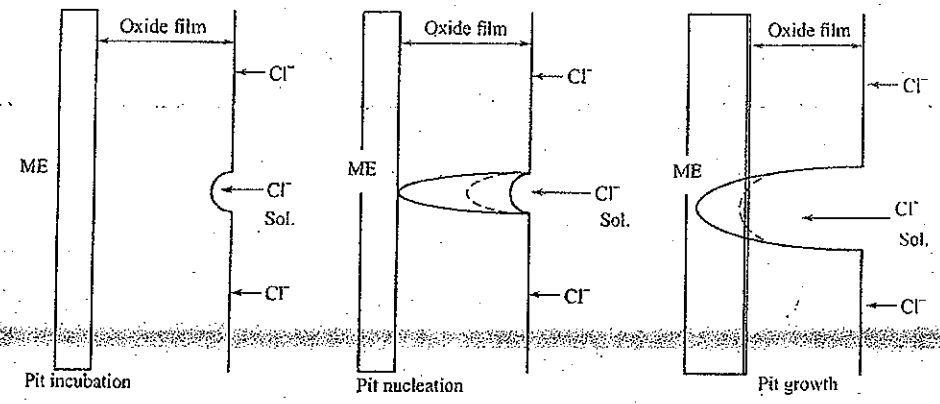


Fig 9. 9 Mechanism of chloride ions pitting corrosion of the passivation film

erentially adsorbed by the metal with and replace the oxygen from the metal surface; the passivation status of metal is determined by oxygen, the chloride ion will compete at the adsorption point with oxygen, even replace the passivation ions forming metal chloride, but the adsorption of chloride on the metal surface is not stable and a soluble substance is formed, this will cause the acceleration of corrosion. Both theories come to a common conclusion; halogen ions including the chloride ion significantly damage the passivation layer, with the formation of pitting corrosion.

Cleaning with chloride ion solutions with high concentration and tap-water containing chlorine may be the primary cause of stainless steel corrosion. Tap water is often containing residual chlorine used to inhibit growth of bacteria, and activated carbon or UV lamps are normally used to remove residual chlorine during generation of purified water; cleaning water must be chloride-free deionized water for a clean fluid process system, tap water with residual chlorine is not allowed to be used when cleaning the system, otherwise, very severe chloride ion corrosion will occur rapidly. Fig 9.10 shows the chloride ion corrosion of a system caused by cleaning with tap water.

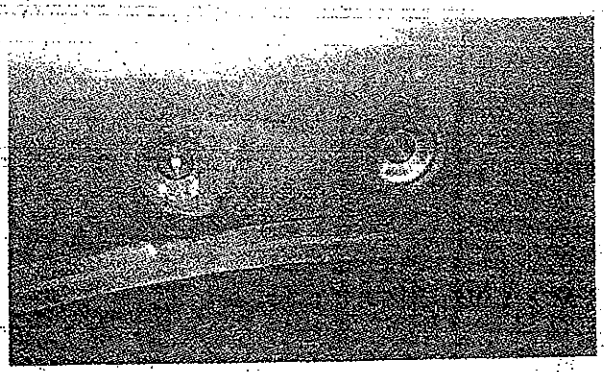


Fig 9.10 Rouging due to chloride ion corrosion (see the color pages behind)

i. Strong acid treatment. The mechanism of derusting is the chemical reaction of an acid solution with rouge. At present, strong acids, like nitric acid or hydrofluoric acid are used by many enterprises to periodically, deal with rouging but there are pros and cons for each method. Nitric acid, sulfuric acid and hydrofluoric acid are strong acids, corrosion be occur on the interior of the pipe if strong acids are periodically used for derusting clean fluid systems. Fig 9.11 shows the interior of a system after being treated with nitric acid by the author.

As can be seen from the above diagram, there is a lot of corrosion-pitting inside the system pipeline after treatment with a strong acid, the presence of corrosion-pitting can accelerate electrochemical reactions, and speed up the regeneration of rouge inside the system. Therefore, weak acid or moderate acids should be used for periodical cleaning and derusting of the interior of the system.

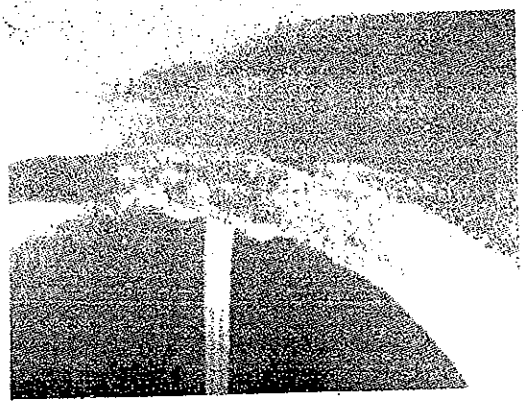


Fig 9.11 Internal surface after derusting with the nitric acid method (see the color pages behind)

9.4.2 Endogenous Rouge

Endogenous rouge is caused by the material of construction or operating parameters of the clean fluid process system itself. The primary generation cause of endogenous rouge is the damage of the chromium oxide-based passivation layer resulting in iron oxide generated by redox reaction on the interior iron-rich layer and exterior oxide layer. Common factors that accelerate formation of rouge in the pharmaceutical industry include operating parameters of the system (temperature, pressure, flow rate, etc.), long-term halt, stainless steel material, spraying deadleg, dry grinding of spray ball, frequent disinfection/sterilization, tank with high liquid level for a long time, etc.

a. Temperature. The influence of temperature on rouge formation speed is related to electrochemical corrosion, the occurring of electrochemical corrosion has two necessary preconditions: one is that the material should include substances with at least two different electrode potentials; another is that the material must be in electrolyte environment (Fig 9.12).

During the electrochemical corrosion process, the larger the difference in electrode potential, the faster the electrochemical corrosion speed. It is generally known that water is a very weak electrolyte, and the temperature has a great impact on the electrolysis of

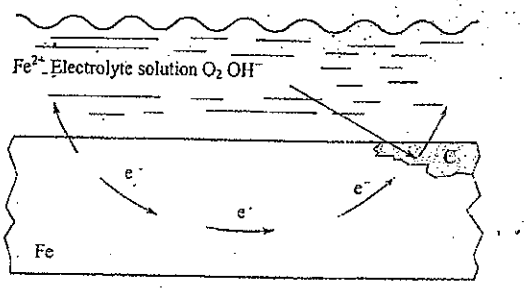


Fig 9.12 Schematic Diagram of Electrochemical Corrosion

water; the ionic product constant of water, $K_w = c_{H^+} \times c_{OH^-}$; when there is no external acid-base involved, and the temperature is constant, K_w has a fixed value. Ionization is an endothermic reaction (Q is the heat quantity), that is

$$H_2O + Q \rightleftharpoons c_{H^+} \times c_{OH^-}$$

As an endothermic reaction, the ionization of water will promote the forward reaction following the rise of temperature, that means K_w will be increased, for example, at 22 ℃, K_w of water is 1.0×10^{-11}; at 50 ℃, K_w of water is 5.6×10^{-11}; at 80 ℃, K_w of water is 34.0×10^{-11}; at 100 ℃, K_w of water is 74.0×10^{-11}.

The concentration of hydroxide ions at 80 ℃ is above five times that at 24 ℃; the concentration of hydroxide ions at 85 ℃ is more than six times that at 24 ℃, so the higher the temperature the stronger the electrolysis degree of water. The essence of rouge formation is electrochemical corrosion, hence, if the temperature is higher, the electrochemical corrosion is more severe and formation of rouge is faster. In actual manufacturing, water for injection system which is stored and circulated in high-temperature is always in a pasteurization status, so the formation of rouge is faster and stronger than when purified water is stored and circulated at room temperature, this further verifies the above viewpoint.

As stipulated in Article 99 of the *Chinese Good Manufacturing Practice* (*2010 Revision*), the generation, storage and distribution of purified water and water for injection should be able to prevent the growth of microorganisms. Purified water can be circulated, and water for injection can be circulated at a temperature of above 70 ℃. Considering the recommendation of the GMP on microorganisms inhibition of water for injection, it is recommended that the suitable temperature of storage, circulating and distribution of water for injection system is between 75-85 ℃; but, pharmaceutical enterprises should take into consideration the requirements of specific drugs and environments, water source, etc. of each region as well as the local conditions to verify whether the circulating temperature is appropriate, for example, some biological products enterprises can choose storage and circulating systems with low temperature, or high temperature storage and bypass the cooling circulating system, etc. usually, the temperature of high temperature storage, circulating systems for water for injection should be not too high on the premise that microorganisms can be controlled effectively, this is very critical to inhibit the rapid formation of rouge.

b. Pressure. This book mainly discusses the pressure in water distillers, pure steam generators or pure steam distribution systems, which causes the formation of rouge; the common characteristic of those three types of equipment/systems is that high pressure steam will be generated inside the equipment. The *Chinese GMP Inspection Guideline* (*2010 Revision*), *Technical Requirements on Pharmaceutical Water and Steam Systems* 3.2.3: high-pressure operation may cause steam friction at high vapor rates, which can cause intergranular corrosion of austenitic stainless steel on the interior of the cylinder and spiral-plate and chap, leakage of the evaporator will cause unacceptable pyrogens in the water for injection.

Theoretically, the oxidation rate of rolled steel (such as, 316 stainless steel) in steam is faster than in dry oxygen, its oxidation film is easily damaged. The reason why high-pressure steam has a significant influence on iron-base alloys, including stainless steel, corrosion, is that the protective oxidation film (known as passivation layer, its main ingredient is compact Cr_2O_3) is easily formed in dry oxygen, but is difficult to be formed in an oxygen environment with high steam concentration, or is most likely to have cracks after being formed. In addition, the protective passivation film formed on the surface of stainless steel in a dry environment is constituted of Cr_2O_3, α-Fe_2O_3 and $(Fe\ Cr)_2O_3$, the oxidation film will thicken and the layer gradually changes to Fe_2O_3/Fe_3O_4/iron-chromium oxides following the increase of steam concentration and pressure, and the oxidation rate will be increased following the increase of pressure, forming a black class Ⅲ rouge.

The damage of high-pressure steam to the passiva-

tion layer and the generation mechanism of iron oxide show that high-pressure steam can damage the original protective antioxidant film (passivation film) of stainless steel, and also catalyze and accelerate the generation of complex iron oxides which weakens the corrosion resistance of stainless steel. The above mentioned two mechanisms are widely accepted by the industry, but their root mechanism are not unified. However, an alternative viewpoint is that hydrogen in high-pressure steam (H_2O) will lose electrons at high temperature, protons with a diameter of 1.7×10^{-15} m penetrate the original compact oxidation film, thus resulting in the damage of the original stable protective film of Fe-Cr-O, making Fe and Cr positively charged and free Fe and Cr form single oxides, which have no protective effect of the surface of stainless steel.

c. Flow rate. Foreign research shows that the thickness of the passivation layer on the internal stainless steel surface will be reduced by about 0.9 μm [detected with auger electron spectroscopy (AES)] when exposed to a high temperature water flow with a rate of 10-40 m/s circulating for 1804 h in a stainless steel system. The above experiment shows that the rate water flow damages the passivation layer of stainless steel. The influence mechanism of the water flow to corrosion is complicated, on one hand is corrosion fatigue, on the other hand, the stronger lateral shear force can make the rouge particles which have been formed and adsorbed on the surface of stainless steel fall off, and enter the fluid system having an impact on water or product quality.

Corrosion fatigue means refers metal to components are in a corrosive environment and also endure the action of alternating loads at the same time. Compared with the conditions of alternating loads endured in inert environments, the combination of alternating loads and corrosive environment will significantly reduce the fatigue performance of components; this kind of fatigue damage is known as corrosion fatigue. Corrosion fatigue is mainly related to intergranular corrosion, and the corrosion mechanism of 316L austenitic stainless steel used in the pharmaceutical industry is mainly related to intergranular corrosion. Although the change of the flow rate will cause the reduction of corrosion fatigue and the damage of passivation layer, the flow rate of a clean fluid system is often low; hence its influence is relatively small.

The damage of a high flow rate to the pipeline can also be explained with the concept of cavitation (also called cavitation erosion), which means cavernous corrosion damage occurred on the metal surface in contact with fluid under the conditions of high speed flow and pressure changes of the fluid. Cavitation erosion generally occurs in high speed decompression areas, close to the blades of centrifugal pumps or the internal surface of spray balls, fluid will form a cavity, the cavity will be crushed in the high-pressure area then produce surge pressure which can damage the protective film on the metal surface accelerating the corrosion rate. A characteristic of cavitation is that many tiny pitting holes will be formed on the metal surface first, and then expand to larger cavities.

The mechanism of cavitation is that bubbles of gas or steam will be formed on the surface of a solid when the pressure of a liquid in contact with the surface of the solid is lower than its steam pressure, after that, the bubbles will be broken and will instantaneously produce a great impact force and high temperature when the bubble moves to a position where the liquid pressure is higher than the bubble pressure. If the surface of the solid bears this kind of impact force multiple times, fatigue shedding will occur, and small pits will appear on the surface, then develop into a spongy larger area and a pit will be formed on the surface by severe cavitation, its depth can be as large as 20 mm. Although cavitation is not caused only by the action of the high flow rate, the flow rate is an important factor for cavitation generation. Pitting corrosion caused by cavitation will present rouging under the action of electrochemical mechanisms. In pharmaceutical clean fluid process systems, the pump cavity and spray ball are the locations where rouging easily occurs and the degree is more severe.

In addition to cavitation, a high flow rate causes very strong turbulent flow of the fluid. The higher the flow rate, the larger the Reynolds number, and the larger the transverse shear force, and the rouge particles attached to the surface easily to move into the product. Reynolds number: $Re=1000\rho vd/\mu$, in which, Re is Reynolds number (non-dimensional); ρ is density of fluid, g/ml; v is flow rate of fluid, m/s; d is internal diameter of pipeline, m; μ is viscosity of fluid, Pa · s. In engineering, if $Re>4000$ turbulent flow occurs, $Re>10000$ complete turbulent flow regime.

From the point of view of microorganisms' inhibi-

tion, turbulent flow is helpful in increasing the transverse shear force and inhibiting the gathering and adhesion of microorganisms to the surface. It is mentioned in the *Chinese GMP Inspection Guidelines* (2010 *version*), *Pharmaceutical Water and Steam System* 3.4.7 *Technical requirements on Circulating Speed* that the common practice is to design the minimum returning flow rate of circulating loop as 3 ft/s (0.91 m/s) or higher, the Reynolds number in turbulent flow is more than 2100. However, a too high flow rate and too large Reynolds number will accelerate cavitation in addition to the safety risk in engineering operation; with a more turbulent flow, the degree of cavitation at the locations of pump cavity and spray ball will be more significant, therefore, enterprises should select appropriate flow rates which should not be too high as long as microorganisms can be inhibited.

d. Residual water stains. When the enterprise is not busy, purified water or water for injection systems may be halted for energy conservation. The system power is off during halting, the water inside system will be drained at the low point by gravity. The design, construction and validation of clean fluid systems are have an emphasis on the drainablity of the system; the system can be halted for treatment after the residual liquid "drained completely". However, even if the slope of the system meets the *ASME BPE Standard* completely, and each position of the clean fluid process system can be drained through a nearby low point, there is still a small amount of liquid retained inside the system, and the whole system cannot realize an absolute clean state.

Fig 9.13 clearly shows that there are water drops still retained inside the pump cavity after system halting for three years. At the same time, the corrosion degree of rouge at moist locations inside the pump cavity is higher than at dry positions; this is mainly because electrons easily migrate in a moist environment during the electrochemical corrosion process, and the dissolved oxygen content in the water film which is attached to the stainless steel surface is higher than in a continuously circulating water system.

For the planned halting for energy conservation, it is recommended that the enterprise takes the measures that mention in Section 10.5.3 (5) to avoid or reduce the formation and risks of rouge in the clean fluid process system.

The pure steam points of use that are rarely used



Fig 9.13 Residual liquid inside the pump cavity after halting (see the color pages behind)

also present rouge risk. The location points of use of pure steam in the *ASME BPE Standard* are described as follows: in pure steam systems, the high flow rate section can effectively be purged to avoid the continuous accumulation of iron oxide and other dirt on the pipe wall of this section and downstream migration of oxidation fragments, becoming a potential corrosion risk of the downstream pipeline.

It must be checked whether steam traps at points of use of pure steam can work normally; rouge risk will be higher if draining is not done on time. Because the steam trap is close to the points of use of pure steam, its quality problems will cause the draining of the points of use of the pipe to be slow and plenty of condensate water will be retained at this position. Although the oxidation layer in a pure steam system will be stable during the service life, it thickens gradually and the shedding of oxidation layer particles will be occur at sections with high flow rate, resulting in the occurrence of corrosion fatigue. The point of use of pure steam is at a high temperature and high pressure state when in use; and in a sub-high temperature state when not in use; this position bears large alternating loads of temperature and pressure. The pure steam system itself is a corrosive high temperature and high pressure environment; hence, the corrosion will be particularly severe at the points of use with larger alternating loads.

A thermal static force steam trap is the first choice for a pure steam distribution system. In order to guarantee the safety of the pure steam system, the steam trap is made of 316L stainless steel with a sanitary clamp connection. The thermal static force steam trap utilizes the deformation or expansion of a temperature-sensing element caused by the temperature differ-

ence between steam and condensate water to drive the valve core to open and close the valve. The thermal static force steam trap can utilize a part of the heat in condensate water, there is always condensate water with high temperature existing at the front of valve, there's no steam leakage and the energy-saving effect is significant.

In order to reduce the formation speed of rouge at points of use of pure steam, the recommended action is as follows. the operation should be: first the condensate water should be drained to reduce the corrosiveness of the environment; if the user point is rarely used, the standard operating procedure of pure steam distribution system should clearly specify that the condensate water at points of use should be drained periodically; routine maintenance and inspection procedures for pure steam distribution system should be established, to focus on the inspection on the draining capability of the thermal static steam trap.

e. Materials and polishing of pipelines. The *Chinese GMP Inspection Guideline* (2010 *Version*), section on water systems stipulates that the material widely used in storage tanks and pipes for water in the *Chinese Pharmacopoeia* (purified water, water for injection, sterile water for injection) is 300 series stainless steel (generally 316L); polyvinylidene fluoride (PVDF) with higher heat resistance is also used for pharmacopoeia water. The materials selected should be consistent (all are 316L or 304L, etc.) for the whole distribution, storage and treatment system if periodic passivation is required.

Obviously, the metal burrs on metal surface are smaller if the surface roughness of stainless steel is good, the formation of a passivation layer is adequate after passivation, and redox reactions for formation of rouge are difficult to occur; on the contrary, the metal burrs on metal surface are larger if the surface roughness of stainless steel is poor, the formation of passivation layer is inadequate after acid pickling and passivation, and redox reactions for the formation of rouge easily occur.

304L and 316L stainless steel have become the first choice of metal pipeline systems for their advantages: higher nickel-chromium content and ease of argon welding, a sulphur content of less than 0.04% is optimal for welding. Compared with the 304L stainless steel, the 316L stainless steel has less carbon and sulphur content, and is suitable for high welding quality; therefore it is widely applied in pharmaceutical water systems, formulation systems and CIP systems at home and abroad. The occurrence of endogenous rouge has a close association with the physicochemical properties of stainless steel; Table 9.3 lists several common constituents of stainless steel.

Table 9.3 Constituents of Stainless Steel/%

Type	C max	Mn max	P max	C max	Si max	Cr	Ni	Mo	other
304	0.08	2.0	0.045	0.03	1.0	18-20	8-12		—
304L	0.03	2.0	0.045	0.03	1.0	18-20	8-12		—
316	0.08	2.0	0.045	0.03	1.0	16-18	10-14	2-3	—
316L	0.03	2.0	0.045	0.03	1.0	16-18	10-14	2-3	—

Due to different process control, the corrosion resistance performance is different, even though the same 316L austenitic stainless steel base metal is used. Therefore, a supplier audit is required during the materials purchasing stage, to check whether its production qualification meets relevant requirements; and the materials of construction and roughness should be checked during the validation stage to verify whether the corresponding furnace number and serial number is correct.

f. Spray deadleg. The *Chinese GMP Inspection Guidelines* (2010 *Version*), section on pharmaceutical water and steam systems stipulates that a spray ball can be installed at the returning loop to wet the top of the storage tank. In thermal systems, the spray ball can be used to maintain a uniform temperature of the water, to avoid the occurrence of alternate wetting and drying of the surface which may corrode the stainless steel and cause growth of microorganisms. At present, the cleaning effect validation for spray ball has received much attention in pharmaceutical enterprises; a good spraying effect not only helps to inhibit the growth of microorganisms, but also avoids the corrosion of stainless steel.

The *ASME BPE* 2014 explicitly mentions that the retention area is one of factors which have an impact on the formation of rouge. If the oxidizing fluid flow rate is within a certain range can it can protect the passivation film, too fast a flow rate and too much pressure will cause pitting corrosion and other problems. The deadleg of the spray ball is in a retention area, the passivation film is easily damaged in the moist environment, and an oxygen enriched liquid film is present at this position; the damage of the passivation film and

oxidation of iron will be very fast in this environment; on the contrary, if the spraying effect of the spray ball is good, each position is in a flowing environment, and these risks can be reduced.

The spray ball will lose its spraying effect if the liquid level of the water tank is higher than the spray ball. Usually, a too high liquid level can be caused by inadequate setting of the liquid level automatic control parameter, a too high setting of high liquid level alarm, liquid meter malfunction or error, automatic control circuit or module malfunction.

Fig 9.14 clearly shows that severe black rust (Class Ⅲ rouge) occurred at the connecting rod of the spray ball; it is hard to be removed once it occurs. The cause of rouge formation is the same as for the spraying deadleg of the spray ball, which is that an oxygen rich liquid film is present at this position; the damage of the passivation film and oxidation of iron will be very fast in this environment. Therefore, it is recommended that the enterprise should periodically inspect the calibration status of the liquid meter; and control the high liquid level at 80%-90%; the manager should establish annual routine maintenance procedures, and professional personnel should re-check the whole system, including the automatic control system.

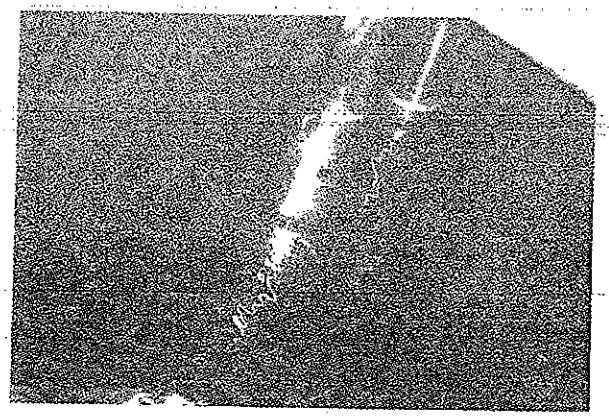


Fig 9.14 WFI tank with a too high liquid level (see the color pages behind)

g. The disinfection/sterilization cycle. Pharmaceutical enterprises should establish relative frequent disinfection/sterilization cycles during the PQ stage to ensure a sterile state, and this disinfection/sterilization cycle will be performed for many years once confirmed during the PQ stage. The variations of temperature and pressure of the environment in which the system is running will cause excessive alternating loads for the system, intensifying the corrosion fatigue of the passivation layer, thus resulting in deterioration of the physical strength and microscopic cohesiveness of the passivation layer, the passivation layer will be subject to damage from external mechanical and chemical action. It is recommended that the enterprise should strictly follow the principle of PQ, to establish an adequate disinfection and sterilization cycle of each pharmaceutical water system.

9.5 The Risk of Rouge

The International Society for Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers-Bio-processing Equipment (ASMPE), both internationally recognized professional associations in the pharmaceutical industry, place great emphasis on rouge in their published industrial guides (ISPE Baseline Guide and ASME BPE 2014).

The ISPE *Water and Steam (Second Edition)* has clearly stipulated that rouge is an anomaly that has been generally perceived in the industry as a nuisance or source of harm to stainless steel product contact surfaces, rather than a contaminant that may or may not adulterate the WFI, PW, pure steam, raw materials, or final products.

The *Drug GMP Guide—Facility and Equipment* is a detailed introduction to the *Chinese GMP (2010 Revision)*; a whole section is discussing rouging, and the term "rouge" appeared in the guide nineteen times. The rouging is described in the sections: "type of storage tanks", "case description of a water system", "selection of construction materials", "design considerations for microbial control", "continuous microbial control", "circulating temperature" and "rouge".

From a description in the *Drug GMP Guide—Facility and Equipment*, we can see the great attention given to rouge: "*There is a concern that after the formation of the rouge film, it will shed and be dispersed in the whole system. In fact, this is true and has been proved at points of use which have filters. The filter color is usually changed to auburn. Phosphoric acid, nitric acid, oxalic acid and ammonium citrate can be used for derouging, according to the severity of the problem. Oxalic acid is used for the worst rust cases, and passivation with nitric acid must be conducted after the rinsing of the oxalic acid.*"

Fortunately, rouging has gradually gotten the attention of pharmaceutical enterprises. For example,

when one Chinese biological products manufacturer was audited by the EU GMP, rust could be seen at the point of use of water for injection, so this enterprise failed the first audit; the second audit was passed successfully after the correction of the rouge problem and other quality defects. Another case is that one well known enterprise in Beijing was questioned twice whether cleaning and derouging of the system is conducted periodically during the audit of Chinese and EU GMP experts.

In the EU GMP, for example, the description of the system cleaning is as follows:

Eudralex The Rules Governing Medicinal Products in the European Union, Volume 4 *EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (Part I)*, *"Section 3.43 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken."*

Part Ⅱ - Basic Requirements for Active Substances used as Starting Materials

"Section 5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Section 5.2 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include: Assignment of responsibility for cleaning of equipment; Cleaning schedules, including, where appropriate, sanitizing schedules; A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment; When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning; Instructions for the removal or obliteration of previous batch identification; Instructions for the protection of clean equipment from contamination prior to use; Inspection of equipment for cleanliness immediately before use, if practical; and Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate."

The system lifecycle needs be used as a starting point to correctly understand rouge and its risks, and control it in the whole system; appropriate control measures on rouge should be taken during design, construction, validation, operation and maintenance stages. For example, a strict welding standard should be established during the construction stage of clean pipes to strictly control the welding quality; the rouging should be monitored periodically during the operation of the system, and maintenance plans for derouging of clean pipes should be established and executed strictly, etc.

It is crucial to conduct derouging effectively and reasonably; both indifference and taking too frequent derouging measures are not advisable, the pharmaceutical enterprises should seek a reasonable balance between control of rouge risk and maintenance costs according to their own situation. The hazard of rouge in pharmaceutical industry is divided into risks for quality, engineering, EHS and investment, this chapter will help related personnel in pharmaceutical enterprises make more scientific judgments on rouging in their enterprise.

9.5.1 Risk for Quality

Quality is related to satisfying or exceeding consumer demands, and driven by the consumer. For pharmaceutical products, this means providing products that are pure and in conformity with the efficacy on the product label. The public expects the efficacy of pharmaceutical products, without unknown adverse reactions or quality problems. Of course, for a pharmaceutical enterprise, there is a direct financial loss related to quality problems, also an indirect loss, the decline in the company's brand image, resulting in a decline in market credibility, thus the indirect loss is greater than direct loss to the pharmaceutical enterprise.

In the past, the FDA has always issued "tickets" pharmaceutical enterprises having quality problems, Form 483, this only pinpoints the quality problems, but it is unable to recognize the deep-seated roost, and this will mislead the manufacturers to believe that the objective is complying with relevant requirements of FDA but ignore that their responsibility is to manufacture products in conformity with efficacy and with reliable quality. Therefore, FDA is planning to "fundamentally change" their quality supervision practice, to better satisfy quality objectives and rise the "level of correct behavior". A good quality culture is an important part of correct behavior, the philosophy involved is not the traditional GMP conformance, but an upgrade on the GMP requirements. Thinking should

precede action; the manner in which the enterprise approaches the quality issues decides the quality of its management level.

The philosophy of problem management lies in "quality is equal to compliance", but the quality metrics philosophy of management thinks that "Quality is more than compliance". The update of the GMP is accompanied by renovations and upgrades of enterprises; the traditional philosophy is "quality is equal to compliance", which is equivalent to quality determined by "action limits". It comes with major risks, which means the quality may be lower than the compliance limit. At present, the implementation of the quality metrics rewarded by FDA can be described as "quality is more than compliance". It is the only way that the enterprise can handle quality "action limits" effectively, and ensure product quality.

The concept of "quality metrics" was first introduced by the FDA, with the purpose of making the quality system of pharmaceutical enterprise concrete and quantitative. The main contents include:

- Predict the shortage of drug products by collecting and analyzing the quality metric data submitted by enterprises.
- Formulate inspection plans based on risk.
- Provide significant production quality index support to procurement and reimbursement decisions of the buyer and payer of drug products.

Rouge has a major impact on visible foreign matters of injections. The *Chinese Pharmacopoeia (2010 Version)*, Appendix Ⅸ H *Visible Foreign Matter* states that visible foreign matter is the insoluble substance existing in injections, eye drops, which can be visually observed under specified conditions, with particle size or length usually larger than 50 μm. Injections and eye drops should be manufactured under conditions in compliance with *Good Manufacturing Practice* (GMP) requirements, and the products should be inspected with appropriated methods; unqualified products should be rejected prior to delivery. Visual checks under natural light (protected from direct sunlight) should be done before use, and the product should not be used if there are any visible foreign matters.

For large volume injections, the visible foreign matters may come from two sources, the manufacturing process and the production environment. The factors that introduce visible foreign matter in the manufacturing process mainly including visible foreign matters residue from packaging containers, inadequate growning procedures, visible foreign matter from raw materials, substances shedding from the stainless steel surface (such as rouge), improper cleaning of equipment surfaces in contact with the product, incompatibility between packaging materials and content, non-clean air mixed in the production process, etc.; for the production environment, the factors that introduce visible foreign matter include faulty design resulting in cross contamination of clean and non-clean ends, cross-contamination of products, non-conformity of air cleanliness, shedding may occur from materials of walls, etc.

The stainless fluid process system in pharmaceutical industry is mainly made of stainless or metal alloy, the quantity of free iron and colloidal particles of iron oxide will be relatively larger when rouging is very severe in the system; visible foreign mater may be present in injections if the aseptic terminal filter of the system cannot be used or the integrity of the terminal aseptic filter is compromised. During the quality control process, batches in which visible foreign matter is present in the product can be found and the product prevented from reaching the market. The whole batch of product which has quality problems should be disposed off; this will cause serious losses to the enterprise.

Some organic groups show strong affinity for iron ions, such as phosphoramidate salt, phosphonatemidate salt, phenols, EDTA (ethylenediaminetetraacetic acid), etc. For western medicine products with specified components, the risk of chelation is relatively controllable. But for TCM products with uncertain components, especially the TCM injections, some organic groups which have reactions with iron ions may be present, resulting in risk to product quality.

The above mentioned issues impact on product quality; moreover, rouge also is a risk to the quality of pharmaceutical water. In China, pharmaceutical waters included in the *Chinese Pharmacopoeia (2015 Version)* are purified water, water for injection and sterile water for injection; and rouging will have different effects to conductivity, non-volatile matters and microorganisms, etc. of pharmaceutical waters.

a. Conductivity. The main components of rouge are iron oxide and hydroxide; iron oxide will diffuse in liquid in the form of metal colloidal particles of 0.02-5 μm in size. Iron oxide can adsorb positive ions, so its surface will be positively charged. The conductivity of

water will be increased if there are more iron oxide colloidal particles in it. On the other side, rouging can cause the decline of surface finish, which will result in growth of microorganisms and some soluble salts will be generated during the metabolism of microorganisms which can also increase the conductivity.

b. Non-volatile matter. The liquid or solid substances which cannot be evaporated or sublimated to gas to be exhausted under special conditions. The provisions of the *Chinese Pharmacopoeia (2015 Version)* for non-volatile matter is: "*Take* 100 ml *water, and put in an evaporating dish with constant weight at* 105 ℃, *evaporate to dry on water bath, and dry to constant weight at* 105 ℃, *the residue should be not more than* 1 mg."

When non-volatile matter in water system is out of limit, the factors that need to be considered include: whether the generation system has functional problems; whether the test operator is qualified; whether the balance, water bath and constant temperature oven have been calibrated, and within the calibration due dates; whether the SOP (for example, whether the drying time is enough, whether the water in the water bath is not enough or not clean, whether there is bath water spilling inside the oven) are followed during execution; whether the quality of water and other quality indexes are acceptable; also the operating time of the water system and attachment conditions on pipeline: shed substances from the pipeline of the distribution system may cause the non-volatile matter to be out of limit. Rouge can be transferred to liquid in the form of colloidal particles with shed substances from the pipeline and indirectly impact the content of non-volatile matter in water.

c. Microorganisms. The generic term for invisible microscopic organisms, including prokaryotic bacteria, actinomycetes, mucoplasma, rickettsia, chlamydia, cyanobacteria (formerly called blue algae or blue-green algae), eukaryotic fungus (yeast and mould), protist and microscopic algae, and noncellular viruses, viroids and prions, etc. The *Chinese Pharmacopoeia* stipulates the microbial limit in purified water: total amount of aerobe is not more than 100 CFU/ml; in water for injection: total amount of aerobe is not more than 10 CFU/ml. Normally most of the microorganisms in pharmaceutical water systems are gram-negative bacteria and thermophilic bacteria, endotoxins are the metabolites released by them.

Microorganisms in pharmaceutical water systems are on the inner surface of systems in the form of biofilms; part of the microorganisms will be free in liquid water, and the out of limit of microorganisms level can be caused by many factors. For example, a potential contamination of the water generation system caused by external factors; contamination of raw water is the main external contamination source of water generation systems. The *US Pharmacopeia*, *European Pharmacopeia* and *Chinese Pharmacopeia* all specify that raw water of pharmaceutical water must meet specifications of potable water at least; otherwise, pre-purification measures must be taken. The presence of *Escherichia coli* is an obvious indication that the water is contaminated, therefore, the content of *Escherichia coli* in potable water is clearly defined internationally, and other contaminant microorganisms are referred to as "total bacterial count" and not additionally subdivided, but the main contamination microorganisms in a water generation system are gram-negative bacteria.

Other contamination sources exist in storage and distribution systems, microorganisms can form bacterial colonies on the surfaces of pipelines, valves and other areas then form biofilms and become persistent contaminant sources. The surface finish of a pharmaceutical water system is closely linked to the risk of microbial contamination. The formation of rouge will cause significant damage to the surface finish of stainless steel, and provide a hotbed for breeding of microorganisms, resulting in the forming of biofilms and microbial indexes or endotoxins being out of limits.

If the formation of rouge causes an un-even surface, the roughness may exceed the minimum size (50 μm) which is macroscopic. Fig 9.15 shows the metal surface with class Ⅱ rouge observed with an electron microscope, there are a lot of bumps and

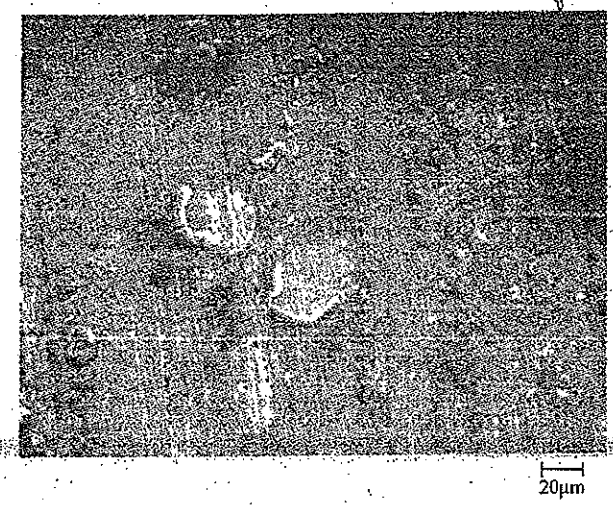


Fig 9.15 Metal surface conditions of class Ⅱ rouge

cleaning deadlegs at the microscopic level, which provide opportunities for attaching of microorganisms. The cleaning effect is difficult to be guaranteed in these conditions.

Rouge will damage the surface finish of stainless steel, and cause overall surface roughness, creating the risk that microorganisms may exist on the surface. The metabolism of microorganisms will generate complex metabolites; the increase of TOC may follow. Lots of dead microorganisms are produced after the sterilization of system, if this is not cleaned timely and completely, endotoxins will remain on the surface of stainless steel, resulting in endotoxins being out of limit of.

Rouge, as a risk source to product quality, must be managed with quality metrics. The quality risk of rouge is mainly reflected in that visible foreign matter exists in drug products, the number of insoluble particles is increasing, water quality (conductivity, nonvolatile matter, microorganisms, TOC and endotoxins) is affected, the cleaning of the product is affected, physicochemical reactions with products occur, etc.

d. Visible foreign matter. The *Chinese Pharmacopeia (2015 Version)* Appendix Ⅸ H *Visible Foreign Matter Test Method* states: "*visible foreign matters are insoluble substances which can be observed visually under specific conditions in injections, eye drops, with particle size or length usually larger than* 50 μm".

Visible foreign matter in injection can be divided into soluble and insoluble, soluble visible foreign matter is crystallized and separated from a supersaturated solution at a certain temperature. As stipulated in the *Chinese Pharmacopeia*, it can be dissolved at appropriate temperatures when using. For example, mannitol crystals separated in mannitol injections. Insoluble visible foreign matter includes chips of glass, fiber, rubber, terylene, insects, rouge particulates, etc. The visible foreign matter may carry microorganisms according to its different source and cause severe contamination to drug products. Microorganisms can produce pyrogens, which will make the patient experience cold, fever, sweating, collapse and other symptoms, that can even be life-threatening. Insoluble particles can block the microcirculation and capillaries, and make the granuloma form in the body, especially in the lungs.

There are two sources of visible foreign matter in injections; one is the manufacturing process, the second is the manufacturing environment. During manufacturing process, the main reasons for the presence of foreign matter are that the air purification of the plant is not conforming to requirements, particulates are out of limit, vial washing is not adequate; visible foreign matter is not removed from packaging containers; procedures are not followed by personnel when putting on work gowns, caps, gloves, masks; equipment is aging, filtration of raw materials is not conforming to requirements or damaged, resulting in filtration of drug products not acceptable; the material of pipeline easily sheds substances; clean doors and windows are not closed tightly during manufacturing, resulting in unpurified air of non-clean areas entering and contaminating the drug products and equipment, materials in contact with drug products, stoppers, terylene are handled improperly; plastic bottles (bags) are not produced in clean areas or the purification class is not conforming to requirements, resulting in particles and visible foreign matter entering bottles directly, caps used for plastic bottles are contaminated with visible foreign matter or particles attached; the materials of plastic bottles are incompatible with drug products, resulting in visible foreign matter and particles generated during sterilization or storage; there are no effective facilities in the plant to prevent the entering of visible foreign matter, insects and small animals, or no extermination equipment, etc. The inconformity of manufacturing environment is that visible foreign matter occurring in infusion solutions is due to an unreasonable layout of the facility and the particles and other substances shed from walls, also the sealing of pipelines interlinked with clean areas and exterior is not tight resulting in foreign matter entering clean areas through gas in pipelines, thus increasing the number of particles and visible foreign matter in the air and the opportunity to enter drug products. This shows that visible foreign matter and particles in injections come from diverse sources, and quality control during the manufacturing process and manufacturing environment monitoring must be strengthened.

The materials of above mentioned pipeline can shed rouge particles. Iron oxide does not always attach on the surface of stainless steel, but migrate in the fluid and fall off. For injections, the aseptic unit terminal is relatively safe, but the filter element still has risks of blockage or downstream contamination due to above mentioned causes.

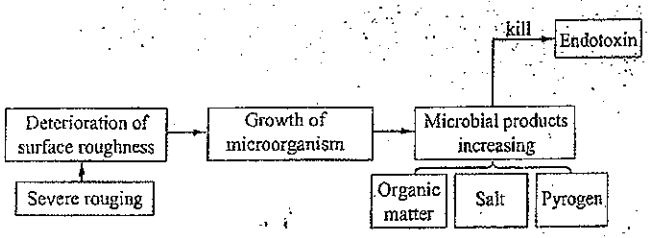


Fig 9.16 Rouge and TOC

e. Insoluble particles. The *Chinese Pharmacopeia (2015 Version)* Appendix Ⅸ C *Insoluble Particle Test Method* states that "*this method is to check the size and quantity of insoluble particles in intravenous injections (solution for injection, sterile power for injection, concentrate solution for injection) and sterile APIs for intravenous injections when the visible foreign matter is meeting the requirements*".

Test methods include the light blockage method and microscopy counting method. When the test results of the light blockage method fail to meet the requirement or this method is not suitable for test samples, microscopy counting methods should be used for testing, and the test results will be taken as judgment basis.

Water used for particle detection must be tested first, the criteria for light the blockage method are that the number of insoluble particles with size equal to and above 10 μm in 10 ml of water should be less than 10; number of insoluble particles with size equal to and above 25 μm in 10 ml should be less than 2. The criteria for microscopy counting method is that the number of insoluble particles with size equal to and above 10 μm in 50ml should be less than 5. Otherwise, it means the water (or other appropriate reagent) for the particle test, glassware or test environment are not suitable for this test, the test samples can be tested only after meeting these requirements.

Insoluble particles come from many sources which are similar to the sources of visible foreign matter. We should improve the cleanliness class of the manufacturing environment and at the same time strictly control the quality of raw materials and excipients, improve the cleaning of glass infusion bottles, correctly select and handle the butyl rubber; and deal with the substance shedding from the surface of stainless steel timely. If roughing particles with size less than 50 μm are formed and not visible to the human eye, they will increase the number of insoluble particles, even exceeding the limit. Insoluble particles can cause harm to patients, also cause pyrogen reactions, allergic reactions, damage of lung function, as well as embolism, phlebitis, partial granulomas and tissue necrosis. So pharmaceutical enterprises must strictly control the factors that may cause an increase in the number of insoluble particles.

f. TOC. The abbreviation for total organic carbon. The carbon in water can be organic carbon (OC) and inorganic carbon (IC), in which OC including HCO_3^-, CO_3^{2-}, CO_2, etc. is coming from dissolved carbon dioxide in air; sources of IC are diverse, such as decaying plants and animals, industrial emissions, pollution of agricultural chemicals, domestic use detergents and human and livestock excrements, etc. The TOC test in the pharmaceutical industry was developed in the nineties, Fig 9.16 explains the reason why rouging can increase the TOC level.

g. Endotoxin. It is one ingredient in the cell wall of gram negative bacteria, known as lipopolysaccharide. It is toxic to the host. Endotoxins are released only when bacteria die and are dissolved or the bacterial cell is mechanically damaged, its main toxic ingredient is the lipoid A. Endotoxins exist in the mukopeptides in the outermost layer of the cell wall and the cover of the cell wall.

Endotoxins are not proteins, so they are extremely heat-resistant. They will not be damaged even by heating at 100 ℃ for 1 hour; its biological activity can be stopped only when heating at 160 ℃ for 2-4 hours or boiling in strong alkali, strong acids or strong oxidants for 30 minutes. Endotoxins is different from exotoxins in that, the toxicity of endotoxins cannot be eliminated with dilute formaldehyde solutions (don't become toxoids); although a certain amount of specific immune product (antibody) may be produced when injecting the endotoxin in the body, the antibody's offset of the toxic effects of the endotoxin is weak.

The toxic effects of endotoxins from various bacteria are weak, and similar: fever, microcirculation disturbances, endotoxin shock, and disseminated in-

travascular coagulation, etc. Endotoxins are heat-resistant and stable with weak antigenicity.

For water systems, periodic disinfection or sterilization will be conducted by pharmaceutical enterprises; this will produce plenty of dead microorganisms, which can release endotoxins. The surface finish can be impacted by rouging resulting in the growth of microorganisms and finally causing the increase of endotoxins level.

h. Cleaning validation. Cleaning is the process of removing the visible and invisible impurities on a surface through physical processes or chemical action. The cleaning is one of the critical processes during manufacturing of drug products, any equipment or system should be cleaned in a timely manner after the process production. From the GMP point of the view, cleaning is an effective way to prevent contamination and cross-contamination; from the microbial contamination point of view, although cleaning is unable to replace disinfection or sterilization, good cleaning can effectively inhibit the growth of microorganisms, at the same time, the surface of clean equipment is easier to be sterilized than a dirty surface.

In the same conditions, the higher the inner finish of the equipment, the shorter the cleaning time required with better cleaning effect, and vice versa.

i. Physicochemical reactions. The process in which a product is damaged by rouge is a complexation of iron ion with a chemical group.

The amino acid, angelica polysaccharide, tea polysaccharide, carboxylic acids, arene, gallic acid, etc., which may have complex reaction with iron can all be used in pharmaceutical systems, if there is extensive rouge in the system, reactions may occur, with effects on production and quality of drug products. The risk is higher in the traditional Chinese medicine industry due to the unknown specific ingredients in Chinese herbal preparations; the higher viscosity of traditional Chinese medicine more easily causes rouge on surface of stainless steel in preparation systems, thereby there's a potential for reactions to occur.

In addition, iron or iron ions are also having an impact on the production of drug products in the biopharmaceutical industry. For example, the presence of iron ions will have an impact on the proliferation of SH-SY5Y cell and tau protein phosphorylation. The iron foreign substances is easily cause damage on the structure and function of the eye, and the decomposition of iron can produce late-onset chemistry and cause retinopathy in addition to mechanical injury and inflammation effect.

9.5.2 Engineering Risk

Engineering risk has been one of the hot topics in the current construction field; the risk degree is larger with the greater scale, more novel and complex technology of projects.

For injections manufacturing facilities, as the direct product of corrosion, rouge's direct hazard is often in engineering. Rouge normally exists in systems with high temperature, high pressure, and water for injection and pure steam systems are typical in pharmaceutical industrial. Risk of rouge on engineering can be analyzed for the filter, process equipment and surface finish, etc.

a. Risk for the filter. Filtration is an important operation guaranteeing the clarity, non-pyrogenicity and sterility of injections, and normally divided into rough filtration and fine filtration. When there is more precipitate in drug solutions (especially when activated carbon is used), rough filtration should be conducted first before fine filtration, to prevent the membrane of the fine filter from being blocked by precipitate. The filter materials used for rough filtration normally include filter paper, macrofiber, degreasing cotton, silk, lint, and nylon cloth, etc. Filter aids are porous and incompressible, which can prevent the precipitate from contacting and blocking the filter medium, the normally used filter aids are paper pulp, diatomite, talcum powder, and activated carbon, etc. Commonly used filters include triangle glass funnels, Buchner funnels, titanium stick filters, and plate-and-frame filter presses. Common fine filters include sintered glass funnels and microporous membrane filters, etc.

The plate-and-frame filter press is only used for rough filtration, and normally for the filtration of larger granules in viscous liquids, with the filter medium of made of filter paper and silk, etc. Sand filter-sticks are used for rough filtration in large scale production. For sintered glass filters including sintered glass funnels, sintered glass filter bulbs and sintered glass rods, the larger the number the smaller the pore diameter. Sintered glass filters have the advantages of strong chemical stability, no shedding, no absorption, and ease of cleaning and hot-pressurized sterilization, etc. but they are expensive and easily broken. For sin-

tered glass filters, the G3 type is used for normal pressure filtration; G4 for pressurization or vacuum filtration; G6 for aseptic filtration and can resist hot pressurized sterilization, it should be pump washed with water after use and soaked with cleaning agent. It is required by the *Chinese GMP (2010 Revision)* that the drug solution should be filled and sealed in a contained environment before and after fine filtration, therefore, open-type sintered glass funnels are used less frequently in the production of injections.

There are two types of titanium stick filters: titanium filter sticks and titanium filter discs; the filter element is manufactured with titanium powder using powder metallurgy technology. Titanium stick filters have good heat resistance, high strength, light weight, and less filtration resistance, with filtration pore size of above 1 μm normally, and are usually used for filtration of activated carbon during formulation of injections. Activated carbon has fine and black particles, improper handling can result in nonconformity of the clarity of the product; the circulation decarburization method is recommended when a titanium stick filter is used to remove activated carbon, this method can effectively ensure that a compact filtration bed of activated carbon is formed on the sintered titanium stick and no leakage of activated carbon occurs.

Stainless steel sintered mesh is a frequently used standard structure sintered mesh, it is a type of new filtration material stacked and vacuum sintered with five layers of stainless steel mesh in sequence. This material has characteristics of stable filtering precision, good strength and ease of reverse cleaning, etc. The stainless steel sintered mesh has very high mechanical strength and compression strength, good processing, welding and assembling performance, and it is easy to use 316L stainless steel is used; hence it has very good corrosion and heat resistance and can be used for filtration at temperatures between −200-480 ℃ and acidic or basic environments. The stainless steel sintered mesh has a great surface layer filtration structure with good backwash cleaning effect and long operating life, it can be used repeatedly. The filtration precision usually is 0.5-50 μm.

The microporous membrane filter is mainly used for fine filtration or aseptic filtration. The pore diameter is between 0.025-14 μm, so its characteristics are small and uniform pore diameter, strong interception capability, large filtration area, less filtration resistance and high filtration speed. Microporous membrane filters have no impact on the pH of drug solutions, less adsorption, do not cause cross-contamination, but they are easily blocked. The common microporous membranes including cellulose acetate fiber and nitrocellulose mixed lipid membranes, polytetrafluoroethylene membranes, nylon membranes, polyvinylidene fluoride membranes, and polyether sulfone membranes, etc.

Aseptic filtration is the process of separating all microorganisms except viruses from a liquid. The aseptic filter is a type of microporous membrane; it must retain all microorganisms in the drug liquid, but not impact the quality of the product. One widely adopted method is to dissolve the ingredients in a solvent (such as water for injection) and prepare a solution, then filter the solution through a 0.22 μm aseptic filter; this method can be applied to ingredients with good water solubility but poor stability. Another method is to turn the filtered liquid into a sterile powder by aseptic crystallization, precipitation (or freeze-drying), but the handling and operation of this method is more complicated, hence, contamination risk in production is higher.

Aseptic filtration is widely used for terminal sterilization products and non-terminal sterilization products, but the purpose of those two applications is different. For non-terminal sterilization products, aseptic filtration is the sterilization measure required by pharmacopeia, to ensure that there are no live microorganisms present in the drug liquid after filtration; hence, it is the finial protection step to guarantee the sterility and absence of particle contamination of the product. But for terminal sterilization products, the combination method of aseptic filtration and moist heat sterilization can be adopted; to effectively control the risk of microorganisms by conducting moist heat sterilization on the drug liquid after the aseptic filtration; filtration can also remove some foreign particles in the drug liquid.

An aseptic filter presents a very large risk when it is used as the terminal sterilization measure for non-terminal sterilization products. In production operation, a low risk measure is to manufacture one batch of product with one filter membrane, but considering the cost factor, the filter elements are normally used repeatedly in a pharmaceutical enterprise, and this practice is accepted and validated by filter suppliers. In actual operation, many pharmaceutical enterprises find that the aseptic grade filter element has insufficient

flow or is blocked before reaching the number of filtrations specified by the supplier, and a reddish coloration is found on the filter element after disassembly (Fig 9. 17).

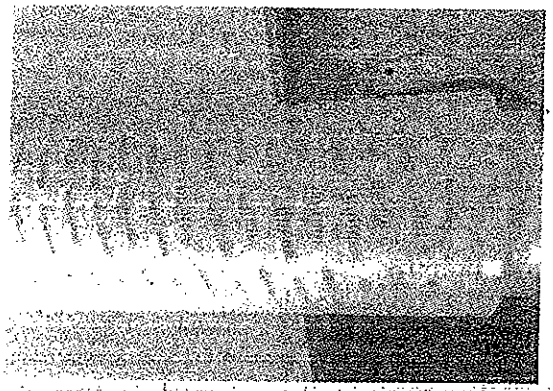


Fig 9. 17 Rouging on filter element
(see the color pages behind)

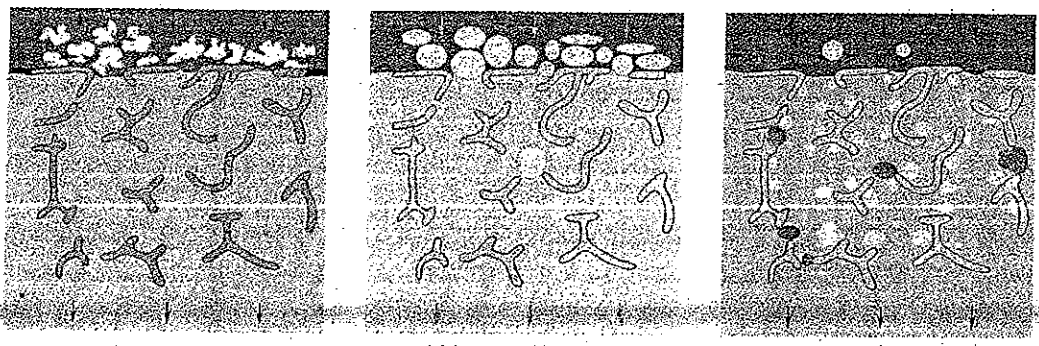
When the aseptic filter element shows color changing, off-line cleaning with water for injection is normally ineffective, the coloration of filter element after cleaning is still visible; if it is used continuously, the colored particles adsorbed in the filtration pores may reach the end of the filter following the product for filtration with the processing of filtration, then enter into the product resulting in the occurrence of visible foreign matter. In general, the main contaminant turning the filter element red is rouge particles.

The whole production process will be stopped when the aseptic filter element is blocked. Experience shows that particles existing in fluid may be one of the reasons for the aseptic filter element blockage, and those particles include non-deformable particles, such as resin particles, drug crystals, carbon granules, diatomites, rouge, etc.; and deformable particles, such as protein, fat, saccharides, and products, etc. The blocking is in the form of a filter cake, complete blocking, and gradual blocking. In general, non-deformable particles easily cause blocking in the form of filter cake; and deformable particles can cause complete blocking, with the premise of lack of pre-filtration or particles larger than the pore diameter; gradual blocking (Fig 9. 18) which develops during a continuous filtration process is the most common form in pharmaceutical enterprises.

An aseptic grade filter is also called a terminal filter, and materials in common use are PVDF, PES and nylon, etc., a few of the filters use PTFE. Those non-metal materials will have negative electric charges on the surface due to the flow friction of the liquid, for rouge particles, this causes very strong electrostatic adsorption no matter whether the filtration materials are polytetrafluoroethylene (PTFE), polypropylene (PP) or polyvinylidene fluoride (PVDF). Rouge particles with large size may be retained outside the membrane; small size rouge particles may enter into the interior of the filtration pore and be adsorbed. The number of adsorbed rouge particles will gradually increase and block the filter and interfere with the process of filtration.

The particles are likely to block the pore passage or surface of the filter element regardless if they are non-deformable or deformable particles, this is a normal phenomenon. The blockage of the filter will bring several risk factors on engineering and production:

- Reduction of filtration flow rate. It may be below the required flow rate, such as filling speed.
- Rise of the filtration pressure. It may exceed the differential pressure tolerated by the filtration system.
- Inadequate clarity Particles may pass through the filter and contaminate downstream.
- Increase of filtration cost. Blockages will cause the increase of duration, cost of product and filtration.
- Stoppage of the manufacturing process. A



(a) Filter cake (b) Completed blocking (c) Gradual blocking

Fig 9. 18 Blocking of the filter element

stoppage occurs or the filter needs to be replaced during manufacturing.

For a terminal aseptic filter, the safest process method is to replace the filter element along with the batch. Considering the operation cost, enterprises can also adopt validation methods to prove that the filter element can be used repeatedly under the prerequisites of assurance of retention rate and integrity. The occurrence degree of rouge and surface character of stainless steel will be changed gradually with the long-term operation of a stainless steel system, and the original validation basis is changed. Hence the enterprise needs to conduct periodic derouging and secondary passivation of the system, and prepare for the revalidation work for the aseptic filter.

b. Risk on process equipment. The process equipment is the core of the whole pharmaceutical manufacturing process; risk for the process equipment means risk for the production process, the process equipment at risk for rouging includes vial washing machines, water distillers, centrifugal pumps, formulation systems, etc.

• Vial washing machine. It is a core process equipment in the manufacturing of sterile products. For injections, a vial washing machine is necessary. Washing media of vial washing machines include purified water, water for injection, etc. If there is heavy rouging present in the distribution pipe systems of water for injection, the pressure of the feed water may be insufficient, which will make the start-up of the vial washing machine more difficult, and impact the normal operation of the whole production line resulting in unplanned halts of the enterprise.

When rouge particles are present in the pharmaceutical water systems, and purified water or water for injection are used by the vial washing machine to wash the vials, ampoules and glass bottles, a small number of rouge particles retained cannot be removed, quality problems due to inadequate clarity will occur at the light inspection post after the filling of the drug liquid. In order to avoid the impact of rouge and other particles on the clarity of the drug product, the water feeding end of vial washing machine often needs to be equipped with a group of terminal filters, its main purpose is not sterilization, but to retain the rouge and other particle contaminants.

• Water distiller. This is one of the core utilities in the manufacturing of sterile products, its main function is to remove the pyrogens in water. Regardless if it is a multi-effect water distiller or a thermocompression water distiller, the main work principle is heat exchange and distillation. As a raw water generation equipment for the whole clean fluid process system, the water distiller is upstream of the whole sterile process system, iron oxide particles will be rapidly diffused to the distribution systems downstream and the whole manufacturing process which may bring the risk of product rejection if rouging of the water distiller is severe (Fig 9.19). The influence of rouge on the water generation capability of a distiller is mainly reflected in the heat conduction efficiency and water quality.

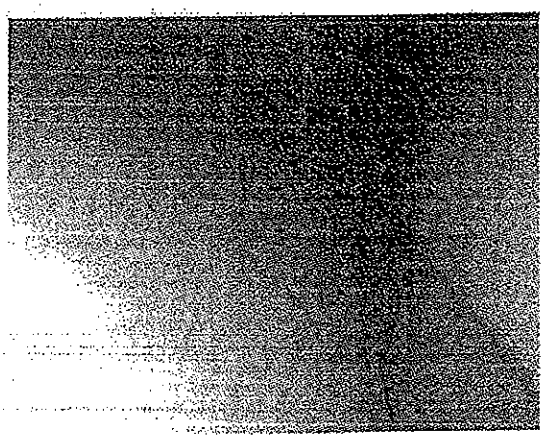


Fig 9.19 Rouging in the Interior of a water distiller
(see the color pages behind)

The heat conduction of iron oxide is mainly depending on photons (vibration of lattice), however, the heat conduction of metals is depending on electrons, therefore, the heat conduction coefficient of oxide is far smaller than that of a metal. If rouging is very heavy, rouge whose main component is iron oxide will be attached in large quantity, and greatly reduce the heat conduction coefficient, as well as the water production rate of the distiller resulting in increased energy consumption.

A distiller is the generation equipment for water for injection, if there is more rouge in the distiller, the rust layer attached on the surface of stainless steel will continually shed tiny rust particles resulting in the iron oxide particles that diffuse to the distribution system downstream, and then enter the terminal equipment of the formulation system, and are very likely to be diffused in the finial products.

• Water for injection distribution systems. In order to better inhibit the growth of microorganisms, the GMP recommends that the circulating temperature

of water for injection storage and distribution systems is above 70 ℃, but high temperatures can also rapidly induce the formation of rouge, its risk for engineering is the corrosion of the internal surface of the system, such as damage to surface finish, damage to pump cavity, impact on spray ball, etc.

Taking the circulating pump of water for injection as an example, there is a cavitation risk, even if the liquid level of the water for injection storage tank is higher and the selection of the pump is reasonable, but the rapid rotation of the impeller in the pump cavity will produce a cavitation effect, and result in strong physical shocks to the impeller and internal surface of the cavity, and the passivation layer will be destroyed. Hence, the pump cavity is a location where rouge is easily formed in water for injection systems. Therefore, class Ⅱ rouge (Fig 9.20) is very likely occur in the pump cavity after the system being in operation for two months when the sterilization cycle of the enterprise is frequent, or the circulating temperature is higher (above 85 ℃).

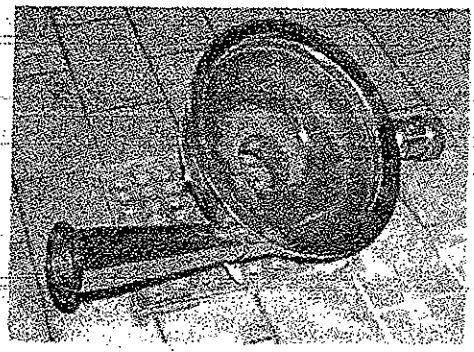


Fig 9.20 Rouging of the pump cavity
(see the color pages behind)

In the pharmaceutical manufacturing and biological technology fields, the cleaning of containers is a critical cleaning task in pharmaceutical formulation systems; spray devices are mainly used in on-line cleaning of container equipment, such as fermentation tanks, storage tanks and formulation tanks, etc. and its main functions are:

-Providing sufficient spraying pressure to realize the mechanical action of equipment cleaning.

-Ensuring sufficient contacting time of the cleaning agent and equipment surface, to realize the chemical action of equipment cleaning.

-Achieving the complete wetting of the internal surface of the tank, and ensuring the uniform temperature distribution inside the tank.

At present, cleaning in place technology of automatic cleaning pharmaceutical formulation tank has been widely recognized by modern pharmaceutical industry, and selection and installation of the spray devices to tanks is crucial to the cleaning validation of formulation tanks. The spray ball is the second highest risk area after the centrifugal pump due to the high speed impact of water for injection. The rouging of the sprayer for water for injection of one enterprise after running for twelve months is shown in Fig 9.21, the appearance is of primary stage of class Ⅱ rouge.

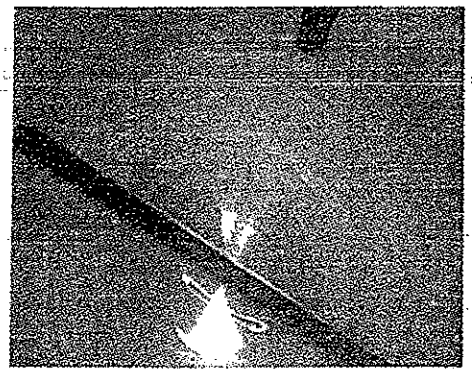


Fig 9.21 Rouging of the sprayer
(see the color pages behind)

In clean fluid systems of pharmaceutical enterprises, a deadleg is not allowed in the purified water system, water for injection system, CIP system, formulation system, etc. and valves which may produce dead water, like the ball valve, are not allowed to be used in the clean end. Therefore, the diaphragm valve without a deadleg is widely used. A diaphragm valve is a block valve with special shape, and was developed in the 1920 s. Its open-close piece is a diaphragm made of soft material, to separate the inner cavity of the valve body, inner cavity of the valve deck and drive part, the outstanding feature is the separation of the inner cavity of the bottom valve body and inner cavity of the top valve deck with a diaphragm, this can protect the valve rod, valve clack and other components on top of the diaphragm from the corrosion of medium; it eliminates the packing leak-proof structure, so the corrosion and leakage of the medium will not occur.

When fluid flows in a clean pipeline, friction will be produced at the surface layer of the diaphragm, this will produce static electricity with negative charge because polyvinylidene fluoride, polypropylene or polyether sulfone are all insulating substances. Metal oxide or hydroxide exists as colloidal particles in the fluid,

and this kind of colloidal particle is positively charged. When the colloidal particles of metal oxide or metal hydroxide flow through the diaphragm of the diaphragm valve, electrostatic adsorption will occur. Therefore, severe rouge particles accumulation will occur on the diaphragm after the system runs for a period of time (Fig 9.22), the accumulation is more significant on the internal surface of the stainless steel pipe.

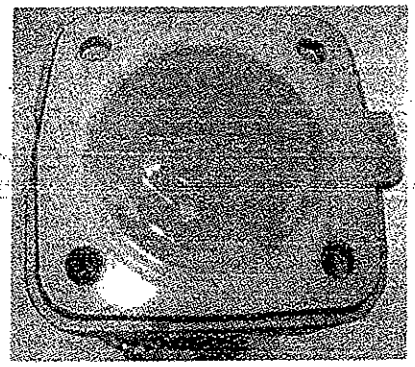


Fig 9.22 Rouging of the diaphragm
(see the color pages behind)

• The formulation system. Some pharmaceutical enterprises will observe yellow, red or black particles occurring regularly on the internal wall of the tank during manufacturing, this kind of particles can be removed by wiping, but will appear repeatedly. Possible reasons may be:

First, the tank it is not completely cleaned by the CIP, resulting in activated carbon particles or product particles retained on the wall of the tank. The occurrence of this condition may be due to the imperfect validation of the cleaning process, too low temperature of the reagent used for cleaning, components or cleaning duration, or improper surface finish of the tank, or non-polishing. The influence of surface finish on the cleaning effect has been mentioned above.

Second, if more rouge exists upstream of the water for injection systems, CIP system or pure steam pipes, it will result in black particles attached on the surface of the tank. The tank itself can produce rouge due to unavoidable corrosion, but it is impossible to form plenty of rouge in a few days. Substance with halogen ions may be added during the formulation process, such as sodium chloride. The halogen ions are the main reason of pitting corrosion of stainless steel surface, and the corrosion of stainless steel and rouging is more severe after a formulation process with halogen ions is operating for several years.

• Autoclave. Due to corrosion factors such as improper welding treatment, improper materials selection, strong acid treatment and rouge formation, etc., will lead to a poor surface finish of stainless steel; at the same time, the damage on the surface finish of stainless steel will also promote the formation of rouge, this is a vicious circle process in mutual promotion based on the principle of electrochemical corrosion and pitting corrosion. Many enterprises will notice that white sterile cloth will change to yellow or red after cleaning and sterilization. One possible reason is the rouging in the distribution pipes of pure steam for sterilization is very severe, and rouge will be dispensed on clean clothes with the high pressure steam and then attach on the cloth. Rouge is one type of visible particles, it may have an adverse impact on air cleanliness if attached on sterile clothes, and severe rouge may enter into products resulting in the occurrence of visible foreign matter.

c. Risk for the surface finish. Under the same conditions, the higher the finish of the equipment internal surface, the shorter the time required for cleaning of equipment with better cleaning effect. The cleaning effect will decrease once the surface finish is heavily damaged due to corrosion. When the minimum visible size of particle is 50 μm, rouge can destroy the surface finish of stainless steel resulting in uneven surface which can be visually observed. Fig 9.23 shows rouging on a pipe of the water for injection distribution systems after continuously running for 12 months. In addition to being difficult to be cleaned, microorganisms easily adhere to it and breed at the microscopic valley bottoms of the stainless steel surface on which the finish is damaged, thus leading to microorganisms being out of limit.

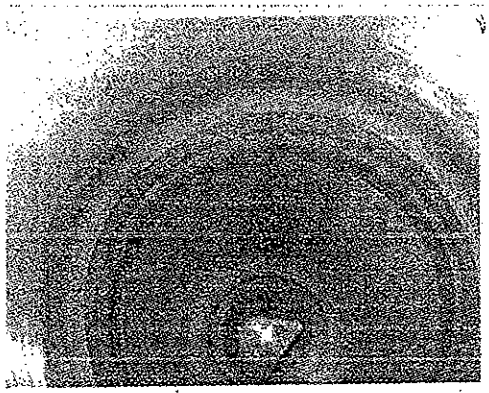


Fig 9.23 Rouging of a pipe (see the color pages behind)

9.5.3 Risk for EHS

EHS is the abbreviation of Environment, Health

and Safety. The EHS management system is based on two systems: the environment management system (EMS) and other occupational health and safety management system (OHSMS), it is an improved new type of management system.

Rouge is the corrosion products on the stainless steel, the corrosion of stainless steel will certainly cause potential safety hazard of equipment. If corresponding protective measures were not taken against corrosion in the pharmaceutical water systems, machine halts will occur due to corrosion damage of equipment, impacting the normal production of the enterprise and bringing relevant economic loss to the enterprise. At the same time, plenty of acid and alkali needs to be used to handle the rouge, the stainless steel of equipment will be thinned which will bring hazards to safety, environment, etc.

The pressure vessels used in clean fluid process systems are mostly made of stainless steel materials. The common pressure vessels in clean fluid process systems of the pharmaceutical industry include reactors, sterile crystallizing tanks, fermentation tanks, water for injection storage tanks, heat exchanger and process preparation tanks, etc. The GB 150.4—2011 *Pressure Vessels-fabrication, Inspection and Testing and Acceptance* stipulates that the pressure vessels should be inspected periodically by qualified personnel (radiographic inspection qualification, ultrasonic inspection qualification, etc.). The full inspection period for pressure vessels shall be shorter properly in following conditions: the corrosion is serious or the stress corrosion is occurred during application, the corrosion is deteriorated due to the changing of media, the liquefied petroleum gas is used as media and the stress corrosion is occurred. The full inspection shall take the macroscopic measuring, wall thickness check, surface damage check as the principal items. The thickness of pressure vessel shall be designed as the sum of the effective thickness, the thickness tolerance of corrosion allowance and stainless steel; the consideration of the corrosion allowance is to prevent the risk of rouge.

Corrosion (including pitting corrosion, stress corrosion, etc.) and surface defects are the main inspection items in the safety grade evaluation of pressure vessels, and the management and control on this type of surface defects is stricter than for other hidden defects. The irreparable damage caused by intergranular corrosion and stress corrosion, etc. are all 4 or 5 grade safety conditions. As one corrosion product, rouge has direct impact on the surface condition of pressure vessels, and more severe rouge may cause potential safety hazards, hence the maintenance of the pressure vessel is crucial, such as periodic derouging, corrosion prevention, and second passivation.

Strong acids and strong alkalis will be used in the derouging process. Strong acids include sulfuric acid, hydrochloric acid, nitric acid and other chemicals. Strong alkalis include sodium hydroxide, potassium hydroxide, potassium oxide, potassium carbonate, and other chemicals. It is easy to incur burns, poisoning accidents when coming in contact with these chemicals, and the accidents will cause more damage if emergency processing is not timely.

The traditional method used to remove rouge is using sodium hydroxide as a cleaning agent, to remove the organic matter and biological film on the surface of rouge, then use nitric acid or citric acid as cleaning and passivation agent to remove the rouge on the surface of stainless steel to re-form the passivation layer. Plenty of waste liquid will be produced after derouging, the waste acid and waste alkali are the two typical hazardous wastes listed in the hazardous waste list of China, so the EHS system of pharmaceutical enterprise needs to manage this as a whole; it is easily to cause environment pollution and impact on environment safety once the management is poor and disposal is improper.

Human life is of paramount importance, life and health are always the premise of social harmony and progress. In recent years, the Chinese government has been paying high attention to the quality and safety of drugs, and the National Ministry of Health, Food and Drug Administration and relevant functional administrations are constantly strengthening the efforts on quality and safety supervision of drugs, and had good results. As the common particle contamination risk in the pharmaceutical industry, rouge is an issue of concern for the pharmaceutical industry.

9.5.4 Risk for Investment

If severe rouge is present in the system, the surface of the stainless steel will be in a relatively poor state, larger surface drag needs to be overcame by the flowing fluid and the heat-exchange efficiency will be greatly reduced. Although the impact is not large in a short time, if the situation persists, the energy consumption and maintenance costs caused by rouging can-

not be ignored.

In order to control the microorganisms risk for water for injection systems, some domestic pharmaceutical enterprises will deliberately increase the circulating temperature of WFI, this will cause a major outbreak of rouge in a very short time. This risk can be reflected in many aspects, such as the quality testing of pharmaceutical water, clarity of products, difficult booting of the vial washing machine and blockage of filters, etc. which affect the normal operation of the whole production line and will bring a considerable loss to the pharmaceutical enterprise. The rapid forming of rouge greatly impact the service life of stainless steel systems, and cause hidden risks to personnel security and enterprise investment.

a. Risk for efficiency reduction. The formed rouge cannot be found immediately during manufacturing. The productive efficiency of the equipment will be obviously reduced when the rouge on some critical components progresses to class Ⅱ or Ⅲ from class Ⅰ due to long-term accumulation, and the energy consumption in production will be increased significantly in order to meet production requirements.

As can be seen in the characteristic curve of a pump (Fig 9.24), the efficiency of a pump often has the maximum point in the optimum production flow, and the efficiency of the pump will decrease very fast if it is running in non-optimum production conditions. If the user wants to achieve required production conditions, then additional energy consumption in production is often required, and not only is the effect uncertain, but the service life of pump is greatly impacted.

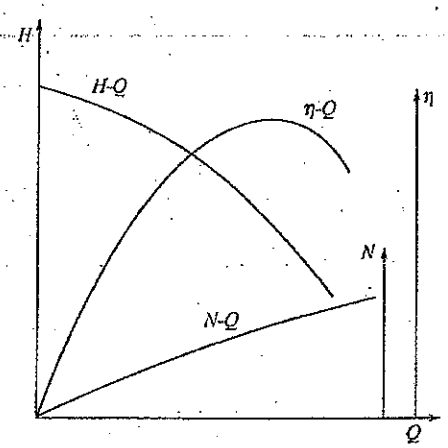


Fig 9.24 Characteristic curve of a pump

b. Equipment halt risk. The service life of equipment is often reduced by 20% or more due to the hazard of rouging. Rouge is formed most frequently in purified water systems, water for injection systems, pure steam systems, CIP systems, freeze-drying machines, tanks, autoclaves, etc. and the one-off investment in those systems or equipment is often very large. If the effective service life of equipment is reduced significantly due to the improper maintenance management to rouge, then the costs required to re-maintain or re-establish those systems are also considerable for the enterprise.

More losses are caused by the shut-down of the production line. The formation of rouge is the main direct product of the corrosion of stainless steel. Data from the nationwide corrosion conference shows that the economic loss caused by corrosion in China has exceeded 1,500 billion RMB in 2013. The environment pollution and casualties caused by corrosion are significant. The GDP of China in 2012 is close to 52,000 billion RMB; losses due to corrosion are between 1,560 billion and 2,600 billion RMB. Relevant experts think that the surface treatment industry of China can recover at least 30% of the corrosion losses annually, hence, rapid development of anti-corrosion technology, improvement of surface treatment processes have been urgent priorities in minimizing the losses due to corrosion and promote resource saving.

In recent years, the losses caused by corrosion in China are approximately 4% of the gross national product (GNP) each year; a rough calculation can be performed: the annual economic profit of one preparations plant is about 100 million RMB, the annual loss due to corrosion is about 100 million×4%=40 million RMB, and the corrosion in the plant mainly occurs in the pipe network of purified water, water for injection systems, pure steam systems, formulation systems, and pipe network of tap water. If the proportions of losses due to corrosion are 10% for the purified water systems, 30% for the water for injection systems, 30% for the formulation systems, 10% for the tap water systems, then the annual loss of the above systems is 400,000 RMB for the purified water system, 1.2 million RMB for the water for injection system, 1.2 million RMB for the formulation system and 400,000 RMB for the tap water system.

Chapter 10

Derouging Stainless Steel Systems

Rouge is a common engineering phenomenon of stainless steel materials used in pharmaceutical water systems. Rouge will occur in any of the pharmaceutical water systems made of stainless steel after the system has been running for a certain period of time, whether at an elevated temperature or at the ambient temperature. Fig 10.1 shows the simulated relationship diagram between the operation time of a WFI storage and distribution system running at 80 ℃ and the conditions of the stainless steel surfaces.

There are many factors that can cause the formation of rouge. Such factors as a high temperature or high pressure environment, a highly corrosive environment such as chlorides, non stainless steel parts, and improper surface fabrication (such as welding quality issues, material surface defects, improper washing or passivation, etc.) can all cause the formation of rouge. Rouge is a type of particle contamination. It can affect the clarity of the pharmaceutical water or drug product, increase the effective working load of a filter, affect the pressure endurance and corrosion resistance of a stainless steel system, or react physically or chemically with the final product.

Rouge can damage the surface finish of stainless steel parts and provide an environment that facilitates microbial growth. The development of stainless steel rouge is often accompanied by microbial contamination. A layer of sticky bio-film often exists on the surface of the rouge layer. The essence of Rouge Remediation technologies is the removal of microbes and particles on stainless steel surfaces by cleaning technologies. The removal of rouge can be mainly divided into three steps. The first step is base washing that is used to remove any bio-film or protein foreign matters. The second step is pickling that is used to remove the rouge by an oxidation reaction of the acid agents or mechanical measures. The third step is passivation that is used to reform a compact passivation protection layer. This chapter mainly introduces the cleaning technologies and the rouge removal technologies. For the passivation technologies, please refer to other chapters of this book.

10.1 Cleaning Technologies

Cleaning is the process of removing any visible or

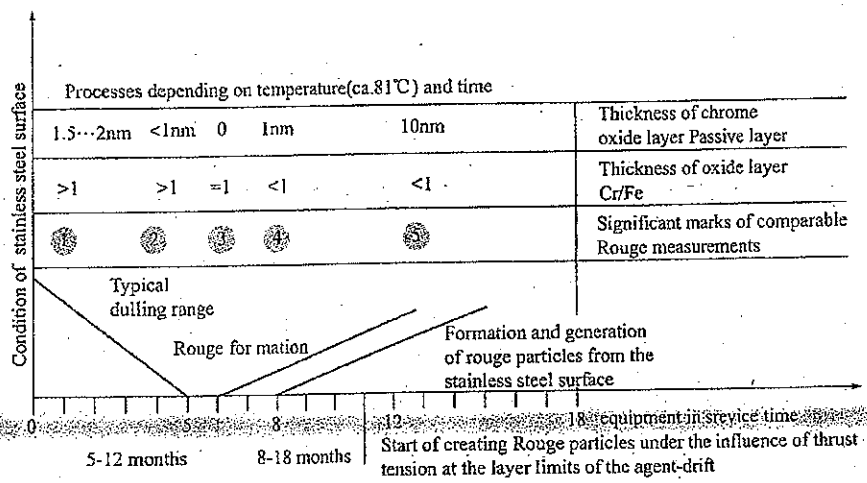


Fig 10.1 Rouge formation simulation analysis diagram

invisible foreign matters on the surface to be cleaned through physical or chemical actions. During the drug manufacturing process, cleaning is one of the critical process operations. Any equipment should be cleaned in time after production. From the GMP point of view, cleaning is an effective measure for the prevention of contamination and cross contamination. From the microbial contamination point of view, although cleaning cannot replace disinfection or sterilization, good cleaning can effectively inhibit microbial growth. And at the same time, it is easier to thoroughly sterilize a clean surface compared to a dirty surface. From the working environment point of view, clean equipment can make the users comfortable and proud. If an operator works in a clean and tidy environment, he or she can feel more comfortable and have better work efficiency. Therefore, performing effective cleaning before equipment sanitization or sterilization is very important for a modern pharmaceutical enterprise. As a type of particulate contaminant, rouge draws intensive attention from pharmaceutical enterprises and inspecting organizations.

The acceptance criteria for cleaning are about the degree of cleanness the surface to be cleaned needs to achieve. They can be mainly divided into the following categories:

- Physical cleaning, which is used to remove any visible contaminants from the surface to be cleaned.
- Chemical cleaning, which can not only remove any visible contaminants, but also any invisible sediment from the surface to be cleaned.
- Microbial cleaning, which can result in the killing of most of the bacteria or pathogenic bacteria attached to the surface to be cleaned.
- Sterile cleaning, which can result in the killing of all the microbes attached to the surface to be cleaned.

10.1.1 Regulatory Requirements for Cleaning

As a part of the quality management system, the Good Manufacturing Practices (GMP) are the basic requirements for drug manufacturing management and quality control to ensure the consistent production of drug products that are suitable for their intended use, conforming to the approved or specified registration requirements and quality specifications, while maximally reducing the risks of contamination, cross contamination, mix-up or error during the drug manufacturing process. It is crucial to use safe and reliable cleaning technologies to remove any residues in the pharmaceutical formulation systems. It is one of the most critical measures for the prevention of contamination and cross contamination during the drug manufacturing process. System impact assessment (SIA) indicates that the pharmaceutical formulation systems is the most critical process system of the drug manufacturing process. This system is in direct contact with the final product, is a direct impact system. Besides conforming to the relevant GEP regulations, the pharmaceutical formulation systems should also conform to the relevant validation principles.

A drug manufacturing process is mainly achieved through equipment. The equipment should be used and managed following the specified requirements in a standard way, which mainly include the cleaning, maintenance, servicing and use of the equipment. And all these activities should be documented and recorded. All the activities should be performed by qualified personnel that have been properly trained. The relevant records and equipment operation logs should be completed in a timely manner after each use. The equipment use or standby statuses should be identified at distinct places. These management measures are not only important measures for ensuring pharmaceutical manufacturing quality, but also critical elements for quality management and production management for drug manufacturing enterprises. If they are violated, it can not only result in the failure of the assurance of drug quality, causing disorders in the quality system and the production system, but also have adverse influences on the equipment safety, the environmental safety and even the personnel safety.

Please refer to the relevant articles of the *Good Manufacturing Practices* (2010 *Revision*) for the equipment cleaning requirements specified in the Chinese GMP, which are described in detail below.

Article 71 *The equipment design, selection, installation, modification and maintenance must conform to the intended use requirements. The risks in contamination, cross contamination, mixing or errors should be avoided as much as possible. It should be easy for operation, cleaning and maintenance, and necessary sanitization or sterilization.*

Article 72 *Operation procedures for equipment use, cleaning, maintenance and servicing shall be established and the relevant records shall be maintained.*

Article 76 *Appropriate washing and cleaning equip-*

ment shall be selected to prevent such equipment from becoming a source of contamination:

...

Article 84 The production equipment shall be cleaned following clear and detailed operation procedures. The production equipment cleaning operation procedures shall define the specific and complete cleaning methods, the cleaning equipment or tools, the name of the cleaning agent, its formulation method, the method for removing the identification of the previous batch, the method for protecting the cleaned equipment from being contaminated again before use, the maximum hold time of the cleaned equipment, and the method for checking the clean status of the equipment before use. The operators shall be able to clean various types of equipment with a reproducible and effective method. If it is required to disassemble a piece of equipment, the sequence and the method for disassembling the equipment shall also be specified. If it is required to sanitize or sterilize a piece of equipment, the specific sanitization or sterilization method and the name and the formulation method of the sanitizers shall also be specified. If necessary, the maximum hold time allowable for the equipment from production completion to cleaning shall also be specified.

Article 85 The cleaned production equipment shall be stored under clean and dry conditions.

...

Article 151 The cleaning method shall be validated to verify the cleaning effect and effectively prevent contamination and cross contamination. The cleaning validation shall comprehensively consider such factors as the use of the equipment, the cleaning agents and the sanitizers used, the sampling method and locations, and the corresponding sample recovery rate, the properties and the limits of the residues, and the sensitivity of the residue testing methods.

The equipment cleaning requirements specified in the *EU Good Manufacturing Practice Medicinal Products* (EU GMP) are as described below.

3.36 *Manufacturing equipment shall be designed so that it can be easily and thoroughly cleaned. It shall be cleaned according to detailed and written procedures and stored only in clean and dry conditions.*

3.37 *Washing and cleaning equipment shall be chosen and used in order not to be a source of contamination.*

3.43 *Distilled, deionized and, where appropriate, other water pipes shall be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.*

For the detailed equipment cleaning requirements, please see 211.67 of the current Good Manufacturing Practice of the US (FDA cGMP), as described below:

211.67 *Equipment Cleaning and Maintenance*

(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

Ever since the cleaning issue has been proposed in the various FDA documents (including the *Guide to Inspection of Chemical Drug Substance Manufacturers*, and the *Guide to Inspection of Biotechnological Product Manufacturers*), the validation of cleaning processes has provoked numerous discussions. The FDA documents clearly state that the cleaning processes need to be validated. The General Requirements section of the *FDA Guide to Inspections Validation of Cleaning Processes* specified that:

(1) FDA expects firms to have written procedures (SOP's) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenarios. Similarly, if firms have one process for removing water soluble residues and another process for non-water soluble residues, the written procedure shall address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may de-

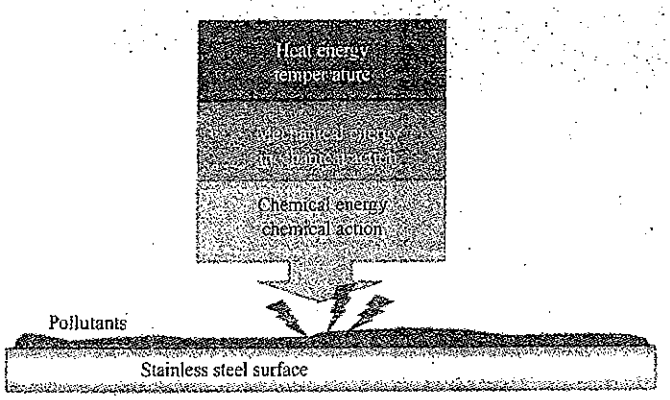


Fig 10.2 Principles of cleaning

cide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.

(2) FDA expects firms to have written general procedures on how cleaning processes will be validated.

(3) FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.

(4) FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which shall address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods.

(5) FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.

(6) FDA expects a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data shall support a conclusion that residues have been reduced to an "acceptable level."

10.1.2 Basic Principles of Cleaning

A cleaning system is composed of the cleaning media, the soils and the items to be cleaned. The cleaning media include water and the cleaning agents using water as the solvent, such as purified water, water for injection, base solutions and acid solutions. The soils are the foreign matters that are desired to be removed from the surface of the item to be cleaned, including organic substances, inorganic substances and microbes. The item to be cleaned is the cleaning subject, such as a formulation tank, a transfer pump and the pipes and valves. The basic principles of washing are to apply thermal energy, mechanical energy and chemical energy on the surface soil to be cleaned through such interactions as dissolution actions, heating actions, mechanical actions, surfactant actions and chemical actions, to effectively clean the item to be cleaned within a certain period of time (Fig 10.2).

Temperature, mechanical action, chemical action and time are the four basic elements of a cleaning process. They are called the TACT model in the field of cleaning technology (Fig 10.3). The temperature refers to the required temperature of the cleaning water and the washing solution. The mechanical action is mainly applied through the flow velocity, the flow volume and the pressure. The chemical action is related to the type and the concentration of the selected cleaning agent. The time is the sufficient contact and action time with the surface to be cleaned. In order to achieve the effective cleaning of the equipment, the four elements described above interact and supplement each other. When one of the elements is insufficient, the cleaning effect can be complemented by enhancing the other elements. The detailed theoretical formula is as described below:

$$C_R = T_i + A + C + T_c = 100\% \qquad (10.1)$$

in which, C_R is the cleaning criteria (acceptable

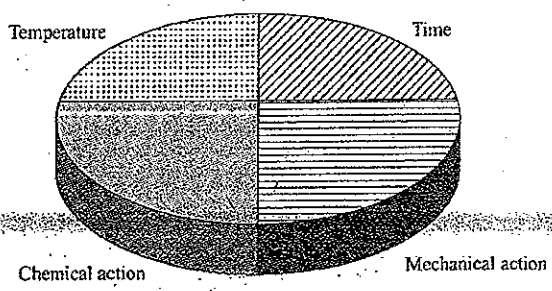


Fig 10.3 The TACT model

cleaning effects); T_i is the time (the sufficient contact and action time during the cleaning process); A is the mechanical action (the flow velocity, flow volume and pressure during the cleaning process); C is the chemical action (the type and the concentration of the cleaning agent); T_e is the temperature (the temperature of the cleaning water and the cleaning solution).

a. Temperature. The rise in the temperature can change the physical properties of the soils and the cleaning solution. Studies show that within a certain temperature range, the chemical reaction speed can be increased by 1.5 to 2 times for every temperature rise of 10 ℃, and the cleaning speed can also be improved correspondingly. Increasing the temperature can also increase the solubility of most of the residual drugs or particulate matters, and speed up the dissolution of such residues. At the same time, the dynamic viscosity of the washing solution will also be increased after it absorbs heat, which will also help to accelerate the washing speed. However, if the temperature is too high, it causes the denaturing of the proteins in the residues within the drug formulation systems, which can increase the binding force between the soils and the equipment and increase the washing difficulty. Fig 10.4 shows the relationship between the washing temperature and the washing time within a certain range. If the washing temperature is increased to an appropriate extent, it can help saving the washing time. However, when the temperature exceeds 85 ℃, there is basically no change in the washing time. Therefore, in order to improve the production efficiency, enterprises often shorten the washing time by heating the washing water or the washing solution. And the washing temperature is generally controlled to be from 60 to 80 ℃.

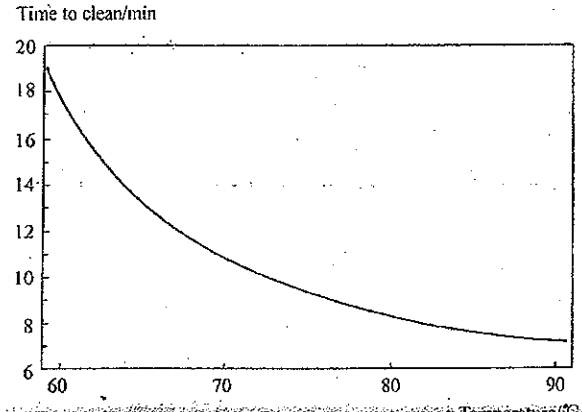


Fig 10.4 Effects of temperature on washing

Temperature is especially critical for ensuring the rouge remediation effects. Temperature requirements are involved in the recommendations on rouge remediation of any standards: Temperature can improve the solubility of the cleaning agents and the dust removal agents. And temperature can increase the scale of turbulence of the fluid. With the increase in the scale of turbulence, it will be easier for any matters attached to a surface to drop off into the fluid flow. The reaction involved in the rouge remediation process is $HM + Fe_xO_y \longrightarrow FeM + H_2O + Q$ (heat).

For this type of non-reversible reaction, the reaction speed can be increased by raising the temperature. According to van't Hoff equation, when the temperature is raised by 10 K (Kelvin), the reaction speed will be increased by 2 to 4 times approximately.

If a pharmaceutical enterprise plans to perform rouge remediation activities during an overhauling period, a set of rouge remediation equipment with necessary sensing devices and a heating function must be available if there is no plant steam.

b. Mechanical actions. Mechanical actions are essential to the cleaning process of a drug formulation system. They can remove the loose soils on the surface to be cleaned through flow velocity, flow volume and pressure. For fluid transfer pipeline components such as valves, pipes and bends, the turbulent flow action of the cleaning solution plays the most important role in removing the residues on the internal surface of the pipeline. For containers such as formulation tanks, the pressurized spraying action of the cleaning solution plays the most important role in removing the residues on the equipment internal surface.

During the early cleaning practices, the TAT model was used for the cleaning theory [Fig 10.5(a)] and the mechanical actions were not valued enough. In this model the influence of time is the highest, followed by the influences of the chemical action and the temperature. With the development of the modern industry, the TAT model can no longer satisfy the actual demands for industry development because of its long cleaning time and low cleaning efficiency. So mechanical actions were introduced into the cleaning theory and the TACT model [Fig 10.5(b)] was developed. In modern cleaning technologies, the effects of mechanical actions account for more than 50% of the effects of the entire cleaning process and the effects of the other three parameters are comparatively smaller in improving the work efficiency, protecting the environ-

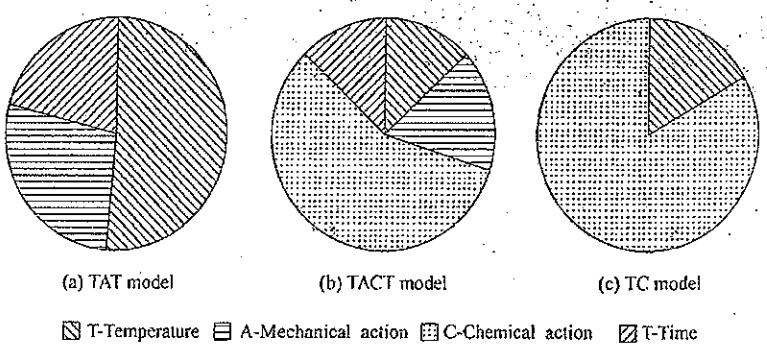


Fig 10.5 Classification of cleaning models

ment and saving cleaning time. For some difficult to clean situations, the TC model [Fig 10.5(c)] is more effective. In this model, the chemical action and the temperature are not included, and the effects of mechanical actions account for more than 80%. The other parameter is time.

The fluid flows within a pipeline can be divided into laminar flows, transitional flows and turbulent flows. For quantification, the Reynolds' test uses the Reynolds' number for the liquid flow status determination criteria. When $Re<2,000$, the fluid flow is a type of laminar flow, when $2,000\leqslant Re\leqslant 4,000$, the fluid flow is a type of transitional flow, when $Re>4,000$, the fluid flow is a type of turbulent flow, and when $Re>10,000$, the fluid flow is a complete turbulent flow. In the latter case, the friction coefficient of the pipeline is only related to the relative roughness and not to the Reynolds' number.

$$Re=\rho\times u\times d/\mu \qquad (10.2)$$

ρ is density in kg/m³; d is the internal diameter of the pipeline in m; u is the flow velocity in m/s; μ is the viscosity in N·s/m².

The fluid particles in a laminar flow move smoothly in a direction parallel to the pipe axis. The flow velocity of the fluid is the highest at the center of the pipe and the lowest near the internal wall of the pipe. The ratio of the average flow velocity of the fluid within the pipe over the maximum flow velocity is about 0.5. With the increase of the flow velocity, a wave like sway occurs gradually in the fluid flow. The frequency and the amplitude of the sway increase with the increase of the flow velocity. This type of flow is called a transitional flow. A turbulent flow is another type of fluid flow. When the flow velocity has been increased sufficiently, the streamline is no longer clearly distinguishable. There are many small vortexes in the flow field, and the laminar flow is disturbed with sliding and mixing of adjacent flow layers. At this time the flow is in irregular movement and there is a velocity component vertical to the pipe axis. The fundamental difference between a laminar flow and a turbulent flow is whether there is a radial pulsation. There is a radial pulsation in a turbulent flow and there is not a radial pulsation in a laminar flow (Fig 10.6). The ideal cleaning effect can be achieved only when the pipe is full of water and a turbulent flow is formed. Bubbles must be avoided during the cleaning process.

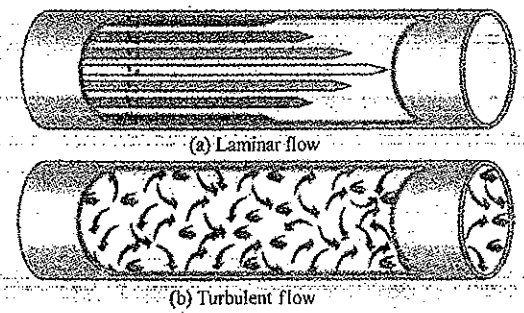


Fig 10.6 Classification of cleaning models

The Reynolds number is related to the flow velocity to some extent. The Reynolds number will be different for flows in pipes with different diameters when the flow velocity is the same. If the design flow is too low, a turbulent flow cannot be formed and the cleaning effect cannot be ensured. If the design flow rate is too high, the system pipeline will be vibrating when the system is running and there is a potential risk. Table 10.1 lists the relationship between the flow velocity and the pipe diameter when the Reynolds number is above 30,000 for ASME BPE pipes.

Concentric reducers and eccentric reducers are reducer pipe fittings that are often used in a pharmaceutical formulation system. The change in the pipe cross sectional area can affect the hydrodynamics of a fluid. With the same cleaning flow, the turbulent status required for cleaning can be reached with a flow velocity

Table 10.1 Relationship of pipe diameter, reynolds number and flow velocity

Tube nominal bore /inch	Hygienic tube ID /mm	Linear velocity (1.5m/s) /(L/min)	Reynolds no. >30,000	
			Linear velocity /(m/s)	Flowrate /(L/min)
½"	9.40	6	3.2	13
¾"	15.75	18	1.9	22
1"	22.10	35	1.4	31
1½"	34.80	86	0.9	49
2"	47.50	159	0.6	67
3"	72.90	376	0.4	103
4"	97.38	670	0.3	138

of 2 m/s in a DN 80 pipe. After a reducer to DN 65, the flow velocity is increased to 3 m/s, the Reynolds number is increased, the scale of turbulence is increased, and the cleaning efficacy is better. After a reducer to DN 100, the flow velocity is decreased to 1.2 m/s, the Reynolds number is decreased, the flow becomes a type of laminar flow, and the expected cleaning efficacy cannot be achieved.

Spraying devices are mainly used to realize the mechanical actions of a cleaning process. According to the different working pressures, spraying devices are categorized into two major types, washing balls and tank washing devices (Fig 10.7). Washing balls are spraying devices with a medium or low working pressure, including fixed washing balls, rotary washing balls and tangent water washing balls. Based on different washing angles, washing balls can be divided into many different types such as 90°, 180° upward, 180° downward, 270° upward, 360° and 360° high flow rate. Based on the installation mode, washing balls can be divided into welded, threaded, and plug-in washing balls. Tank washing devices are spraying devices with a medium or high working pressure, including medium driven tank washing devices and external motor driven tank washing devices.

On the other hand, for some stubborn rusts or when cleaning any equipment or locations with insufficient mechanical actions, it may be necessary to use such measures as manual wiping as supplementary measures. Manual wiping is a necessary supplementary cleaning measure to enhance the mechanical actions for the removal of rouge on a surface. If not down properly, the stainless steel surface can be scratched, causing the deterioration of the surface finish. So the rouge remediation contractor and the owner should coordinate with each other and try their best to allocate professional staff to perform the wiping activities to reduce the risk of scratching the surface to the minimum.

c. Chemical actions. The main principle of a chemical action is to change the solubility of the soil through the chemical reaction between the cleaning agent and the soil to turn the soil into a type of substance that is easily soluble in water. The chemical action is related to the selected cleaning agent and its concentration. An appropriate cleaning agent should have the following features.

-It should be able to make particles peel off from the surface of the item to be cleaned and be suspended or dissolved into the washing solution as smaller particles.

-It should be able to be dissolved into water rapidly.

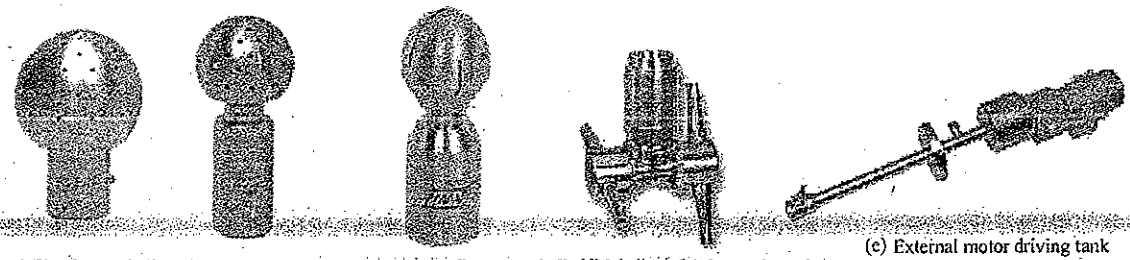
-It should have a surfactant activity and satisfactory permeability into the soil and decontamination capability.

-It should be possible to monitor and control the working concentration on line.

-It should have definite ingredients and should not cause any contamination or cross contamination.

-It should not have any adverse effects such as corrosive effects on any of the components of a pharmaceutical formulation system.

-It should easily go through waste water treatment and with little influences to the environment. It should



(a) Fixed spray ball (b) Rotary spray ball (c) Tangent flow spray ball (d) Medium driving tank washer (e) External motor driving tank washer

Fig 10.7 Categorization of spraying devices

be easy to store and have a low operation cost.

Chemical washing agents are mainly divided into three major categories, neutral washing agents, basic washing agents and acidic washing agents. Their major ingredients include water, acids, bases and surfactants. For example, the CIP 100 manufactured by STERIS (a US company) is a typical basic cleaning agent, and its CIP 200 is a typical acidic cleaning agent. The chemical actions include many forms, such as hydrolysis, permeation, emulsification, catalysis, saponification, chelation, oxidation, dispersion, suspension, collosol and complexation. Different chemical actions are required for different soils.

Generally speaking, a single cleaning agent can only achieve some certain cleaning functions. No single cleaning agent can meet all the cleaning requirements. An enterprise should rationally select the type of the chemical cleaning agent and its concentration considering the actual residues and soils. For example, the permeation and the emulsification actions of a surfactant, the dispersion action of a basic solution and the saponification action of a strong base can be selected for oily soils. The dissolution action of a basic solution or an acidic solution, the hydrolysis of an oxidant and the catalytic decomposition action of a protease can be selected for protein soils. The dissolution action of high temperature water can be selected for sugar and carbohydrate soils. The dissolution action of a basic or acidic solution and the decomposition action of an amylase can be selected for starch hydrocarbonate soils. The dissolution action of a basic or acidic solution and the chelation action of a chelating agent can be selected for mineral soils.

• Surfactants and dispersing agents. Surfactants have significant cleaning effects on the oily soils in a pharmaceutical formulation system. They are substances with fixed hydrophilic and oleophilic groups that can be arranged at a certain orientation on the surface of a solution and reduce the surface tension significantly. The molecular structure of a surfactant (Fig 10.8) is amphiphilic, with a hydrophilic group at one end and a hydrophobic group at the other end. The hydrophilic group is often a polar group, such as carboxylic, sulfonic, sulfuric, amino, amido or amine salt, hydroxy, amide groups and ether bonds. The hydrophobic group is often a non-polar hydrocarbon chain, such as a hydrocarbon chain with more than 8 carbon atoms. After a surfactant is dissolved into water, it can reduce the surface tension of the water and improve the solubility of organic compounds.

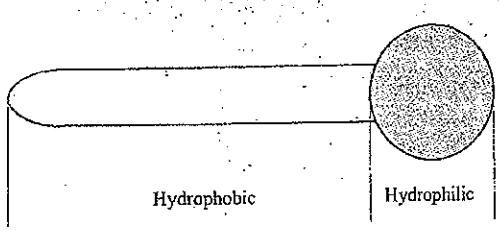


Fig 10.8 Surfactant structures

The working principle of a surfactant is that it uses the different affinities of the different parts of a molecule to the oil phase and the water phase, making both the phases viewing it as the constituent of the phase itself. The molecular arrangement of the surfactant is between the two phases, making both phases penetrate into the molecules, thus reducing its surface tension. Because both the oil phase and the water phase view it as a constituent of itself, there is no interface between the surfactant and the oil phase or the water phase. The interface between two phases is eliminated partially through the reduction of the surface tension and the surface free energy. For mechanical actions, a surfactant mainly provides such actions as permeation, emulsification and suspension (Fig 10.9). Based on the dissociation properties of the polar groups, surfactants can be divided into anion surfactants (such as stearic acids, sodium dodecylbenzene sulfonate, etc.), cation surfactants (such as quaternary ammonium salt, etc.), amphoteric surfactants (such as lecithin, amino acids, glycine betaine, etc.) and nonionic surfactants (such as fatty glyceride, fatty acid sorbitan, polysorbate, etc.).

As described before, the surface roughness is higher at an area of a clean pipeline that is covered by rouge, making it possible for the soil to be deposited at areas with a high surface roughness. If PW alone is used to rinse the pipeline, it may not come into contact with the soils concealed at the bottom of a crack because of the high surface tension. If a surfactant is used in such a case, it can be possible for PW to come into contact with the soil because of the reduced surface tension, thus increasing the cleaning and rouge remediation effects (Fig 10.10).

A dispersing agent is also a type of surfactant that is used for rouge remediation and re-passivation. A dispersing agent is a type of amphoteric agent that can be used to disperse the solid and liquid particles of

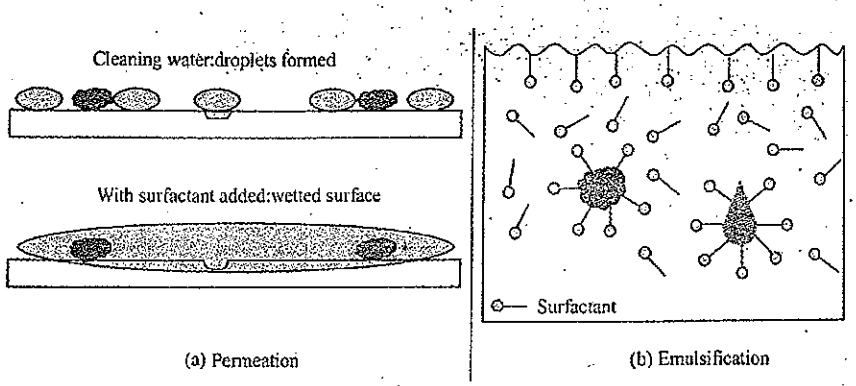


Fig 10.9 Mechanisms of action of surfactants

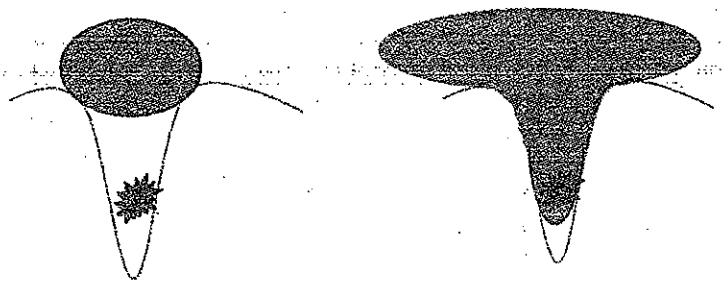


Fig 10.10 Cleaning effect comparison

inorganic and organic dyes that are difficult to be dissolved in liquids and prevent the sedimentation and the accumulation of the particles, to a stable suspension. Dispersing agents are generally divided into inorganic dispersing agents and organic dispersing agents. The commonly used inorganic dispersing agents include silicate dispersing agents (such as sodium silicates) and alkali metal phosphates (such as sodium tripolyphosphate, sodium hexametaphosphate and sodium pyrophosphate). Organic dispersing agents include triethylhexyl phosphonic acid, lauryl sodium sulfate, methyl anyl alcohol, cellulose derivatives, polyacrylamides, Gul gel, fatty acid polyethylene glycol ester, etc.

The mechanism of action of a dispersing agent is to disperse the various types of particles into a solvent, to make the various solid matters to be stably suspended in the solvent (or dispersing solution) through certain charge repulsion action or high molecular-steric effect. A dispersing agent must be dissolved in water when it is used. They will be selectively adsorbed onto the interface between a particle and water. The commonly used ones are the anionic agents. They are ionized into cations in water and have certain surfactant activities. So they will be adsorbed onto the surface of a powder. An electric double layer will be formed after the dispersing agent is adsorbed onto the surface of a particle. The anion is closely adsorbed onto the surface of a particle, and is called a surface ion. The ions with opposite charges in a type of medium are called counter-ions. They are adsorbed by the surface ions through static charges. Some of the counter-ions are closely bound with the particles and the surface ions. They are called bound counter-ions. They form a moving entity in the medium and have a negative charge. The other counter-ions surround the particles at the peripheral areas. They are called free counter-ions and form a dispersing layer. An electric double layer is formed between the surface ions and the counter-ions.

The electric double layer formed between the negative charge on the particles and the positive charge on the dispersion layer is called electrokinetic potential. The thermodynamic potential is the corresponding potential of the electric double layer formed between the anions and the cations. The dispersion action is achieved through the electrokinetic potential, not the thermodynamic potential. The charges of the electrokinetic potentials are unbalanced and with charge repulsions. The thermodynamic potentials have balanced charges. The polymer steric effect means that, for the formation of a stable dispersing system, in addition to the use of the electrostatic repulsion at the surfaces of the particles to prevent the adsorption and the aggrega-

Table 10.3 Comparison of performances of acidic cleaning agents

	Ingredients	Removal of minerals /scales	Emulsification	Permeation	Suspension	Water treatment agent	Foams	Non-corrosive to stainless steel	Non-corrosive to soft metals	Anti-interference	Passivation
In-organic minerals	Hydrochloric acid	A	C	B	C	C	D	D	C	D	DD
	Sulfuric acid	B	B	C	C	B	D	D	C	B	D
	Sulfonic acid	C	C	C	C	C	D	C	C	C	C
	Nitric acid	C	B	C	C	C	C	C	C	C	D
	Phosphoric acid	C	B	C	C	B	A	A	C	A	A
Organic acids	Citric acid	C	A	C	C	A	AA	A	C	A	A
	Acetic acid	C	A	C	C	A	AAA	A	C	A	A
	Gluconic acid	C	C	C	C	C	B	C	C	A	A
	Wetting agents	C	C	C	C	C	AA	C	C	A	A

A—Optimal; B—Satisfactory; C—With no efficacy; D—With negative efficacy.

extent corrosive to stainless steel. They should be neutralized and rinsed with clean water in time after use.

The essence of rouge remediation is the chemical reaction between the rust and an acidic agent. The rouge remediation agents traditionally used in the pharmaceutical industry include citric acid, nitric acid, sulfuric acid and hydrofluoric acid.

Citric acid is a medium strong acid. It is often used for the passivation after the welding activities for a stainless steel pipeline. Some of the pharmaceutical enterprises use citric acid as the cleaning agent for the periodic rouge remediation activities for their systems, although its rouge remediation effect is not satisfactory at a high temperature. Fig 10.13 shows the picture of a centrifuge pump chamber of a pharmaceutical enterprise after rouge remediation and passivation with citric acid. From the picture we can see that there is still a significant amount of class I rouge in the centrifuge pump chamber, which indicates that the rouge remediation effect is not satisfactory.

Nitric acid is a strong acid. It is highly instable, highly oxidative and highly corrosive. After rouge remediation with nitric acid, the internal wall of the stainless steel pipe is often left without metallic luster and is dark in color (Fig 9.11). If the concentration of the prepared nitric acid is not appropriate, the stainless steel surface may be corroded, causing the worsening of the rouge. And there are also rather high safety risks in manipulating nitric acid. Contacting nitric acid steam is also very dangerous. The nitric acid

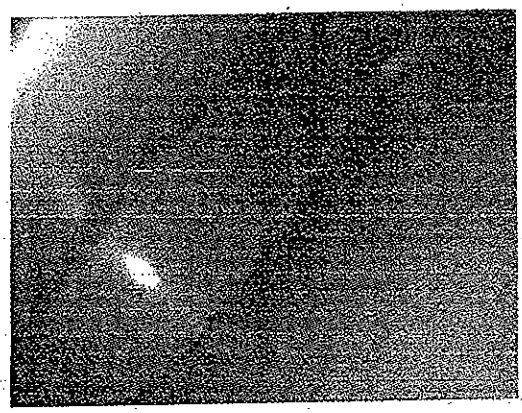


Fig 10.13 Rouge remediation and passivation effects of citric acid (see the color pages behind)

solution and the nitric acid steam are both highly irritating and corrosive to the skin and the mucosa. Nitrogen pentoxide can be released from the smog of concentrate nitric acid. A type of acid mist can be formed when it is in contact with water vapor and then it will be rapidly decomposed to release nitrogen dioxide. Nitric acid steam can be generated when concentrate nitric acid is heated. And it can also be decomposed to release nitrogen dioxide. After inhalation, acute nitrogen oxide poisoning can result. No significant injuries are observed for human beings when the concentration is lower than 12 ppm (30 mg/m^3). Pneumonia can be caused after inhalation. Acute poisoning can be caused after nitric acid mist is inhaled. After nitric acid is ingested, corrosive stomatitis and gastroenteritis can be caused, and shock or kidney failure can result.

The chemical mechanism of rouge remediation with sulfuric acid is the same as that with nitric acid. It is even more dangerous than nitric acid. This is because sulfuric acid is equally corrosive, and in addition, it is more oxidative. Dehydration is the process of removing the non-free water molecules, or removing the hydrogen and the oxygen within an organic substance by concentrate sulfuric acid in the composition ratio of water. The dehydration property is a property of concentrate sulfuric acid, not a property of dilute sulfuric acid. Concentrate sulfuric acid has a rather strong dehydration property. And during dehydration the hydrogen and oxygen are removed from the composition ratio of water. The dehydration process by concentrate sulfuric acid is a chemical change. During the reaction, concentrate sulfuric acid removes the hydrogen and oxygen of the substance that is dehydrated in the composition ratio of water, 2 : 1, or the non-free crystal water, such as copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$), of the substance that is dehydrated. The substances that can be dehydrated by concentrate sulfuric acid are generally organic substances that contain hydrogen and oxygen. Among them, such substances as the organic matters in sucrose, wooden chips, paper chips and cotton will become black charcoal after dehydration. This process is called carbonization. So if concentrate sulfuric acid is used for rouge remediation, complete safety measures must be taken. Once a drop is in contact with the human body, the consequences are unbearable because of the carbonization reaction.

Because the hydrogen atom and the fluorine atom have rather high binding capacity, the hydrofluoric acid cannot be completely ionized in water. So hydrofluoric acid with a low concentration is a weak acid. However, fluorine is the most active non-metal element and has a very strong oxidation activity, and the radius of the fluoride ion in the hydrofluoric acid is very small, even smaller than that of the oxygen ion, this gives it with a strong permeability, and even compact oxides cannot prevent its permeation. So the surface roughness can be very high if hydrofluoric acid is used to remove rouge. And it is not effective enough. If hydrofluoric acid alone is used to remove rusts for a clean pipeline without any subsequent passivation process, the surface of the pipeline can be severely corroded and the surface roughness will far exceed the industry specifications (Fig 10. 14).



Fig 10. 14 Rouge remediation with hydrofluoric acid (see the color pages behind)

The *ASME BPE* 2014 describes the rouge remediation for clean pipelines for pharmaceutical water systems in detail. It describes in detail the corresponding rouge remediation agents for different types of rouge inside the clean pipelines and the formulated high efficiency rouge remediation agents. Please see Table 10. 4 for the details.

The ASME BPE clearly recommends using phosphoric acid blends as the rouge remediation agent; they have significant rouge remediation effects on both class Ⅱ and class Ⅲ rouges. The acidic cleaning agent CIP 200 is a typical highly efficient rouge remediation agent using phosphoric acid as the major ingredient. Its ingredients include surfactant, dispersing agent, phosphoric acid and citric acid. The phosphoric acid mainly acts as the rouge remediation agent and citric acid mainly acts as the passivation agent. Fig 10. 15 shows a photo of a pipe surface after rouge remediation with CIP 200. From the photo we can see that the metal surface on the pipe internal wall is shining and bright and there are no etch pits. Etch pits are caused

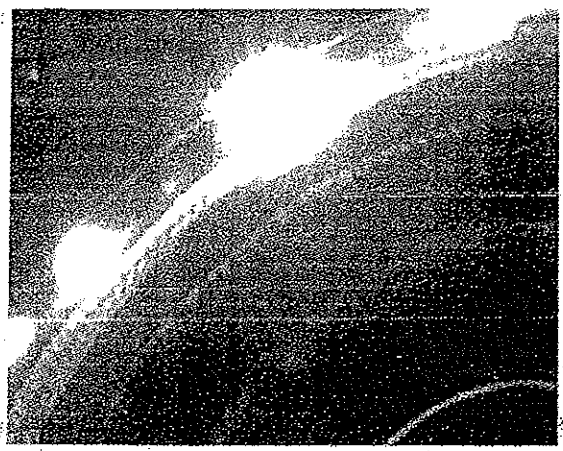


Fig 10. 15 Rouge remediation by CIP 200 (see the color pages behind)

Table 10.4 Introduction to ASME BEP rust removing agents

Class of rouge	Description	Comments	Chemistry	Reaction conditions
Class Ⅰ rouge	Phosphoric acid	Effective at removing iron oxides without etching the surface	5% to 25% phosphoric acid	2 to 24 hours at 40 to 80 ℃
	Citric acid with intensifiers	Effective at removing iron oxides without etching the surface	5% to 10% citric acid with additional organic acids	2 to 24 hours at 40 to 80 ℃
	Phosphoric acid blends	Can be used at a variety of temperatures and conditions	5% to 10% phosphoric acid plus either citric acid or nitric acid at various concentrations	2 to 12 hours at 40 to 80 ℃
	Sodium hydrosulfite	Effective at removing iron oxides without etching the surface but may generate sulfitefumes	5% to 10% sodium hydrosulfite	2 to 12 hours at 40 to 80 ℃
	Electrochemical cleaning	Useful in removing stubborn rouge without risk of etching the product contact surface	25% to 85% phosphoric acid	Limited to accessible parts of systems, primarily containers. Process times are approximately 1 min/ft²(10.76 min/m²)
Class Ⅱ rouge	Phosphoric acid	Effective at removing iron oxides without etching the surface	5% to 25% phosphoric acid	2 to 24 hours at 40 to 80 ℃
	Citric acid with organic acids	Effective at removing iron oxides without etching the surface	5% to 10% citric acid with additional organic acids	2 to 24 hours at 40 to 80 ℃
	Phosphoric acid blends	Can be used at a variety of temperatures and conditions	5% to 10% phosphoric acid plus either citric acid or nitric acid at various concentrations	2 to 24 hours at 40 to 80 ℃
	Oxalic acid	Effective at removing iron oxides. May etch electro-polished surfaces	2% to 10% oxalic acid	2 to 24 hours at 40 to 80 ℃
	Electrochemical cleaning	Useful in removing stubborn rouge without risk of etching the product contact surface	25% to 85% phosphoric acid	Limited to accessible parts of systems, primarily containers Process times are approximately 1 min/ft²(10.76 min/m²)
Class Ⅲ rouge	Phosphoric acid blends	Can be used at a variety of temperatures and conditions	5% to 10% phosphoric acid plus either citric acid or nitric acid at various concentrations	8 to 48 hours(or longer) at 60 to 80 ℃
	Oxalic acid	May etch electro-polished surfaces	10% to 20% oxalic acid	8 to 48 hours(or longer) at 60 to 80 ℃
	Citric acid with organic acids	May etch electro-polished surfaces	5% to 10% citric acid with additional organic acids and fluorides	8 to 48 hours(or longer) at 60 to 80 ℃
	Nitric acid + hydrofluoric acid	Will etch electro-polished surfaces	15% to 40% nitric acid with 1% to 5% HF	1 to 24 hours at no more than 40 ℃
	Electrochemical cleaning	Useful in removing stubborn rouge without risk of etching the product contact surface	25% to 85% phosphoric acid	Limited to accessible parts of systems, primarily containers. Process times are approximately 1 min/ft²(10.76 min/m²)

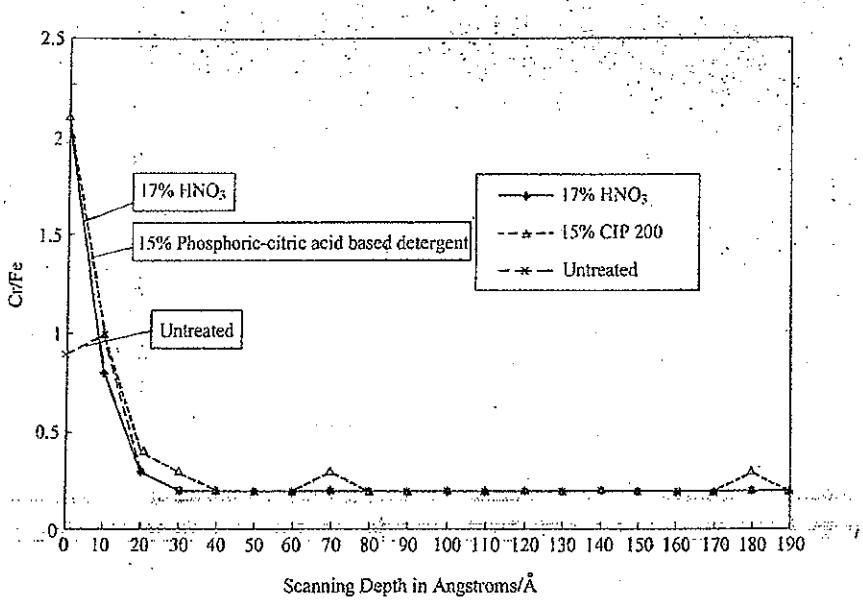


Fig 10.16 Comparison between the CIP 200 and Nitric Acid Passivation Effects

by rouge remediation with nitric acid or hydrofluoric acid.

CIP 200 is a highly efficient rouge remediation and passivation agent with both good rouge remediation and passivation efficacies. According to various study results, excellent passivation can be achieved together with rouge remediation. The effects of passivation for simultaneous rouge remediation and passivation are superior to the passivation alone effects by 17% nitric acid. As shown in Fig 10.16, the area marked with a dotted line is after the simultaneous rouge remediation and passivation by CIP 200. The ratio of chrome and iron in the passivation layer formed is higher than that in the passivation layer formed, as shown by the area with solid line, after passivation by 17% nitric acid. And discontinuous chromium rich layers can be formed deep in the stainless steel after treatment with CIP 200. The higher the ratio of chrome and iron and the deeper the passivation layer, the better the passivation effects will be. From this we can see that the rouge remediation and passivation effects of CIP 200 are outstanding.

• Neutral cleaning agents. Neutral cleaning agents are synthetic detergents that are neutral at their standard working concentrations. They are mainly the detergents with a pH of 6 to 8 at the standard working concentration at 25 ℃. The major ingredients of neutral cleaning agents are water, cleaning assisting agents and neutral surfactants. Neutral cleaning agents are odorless, with no gas volatilization, contamination free and safe to use. They are easily rinsed away without any residues. They are not corrosive to metal and stainless steel materials. They are safe to use for manual cleaning.

Each cleaning agent has its own optimal cleaning concentration. The cleaning effect will be reduced if the concentration is too high or too low. Increasing the concentration of the cleaning agent appropriately can promote the chemical reaction between the cleaning agent and the soil and thus improving the cleaning effect, shortening the cleaning time and supplementing the insufficient cleaning temperature. If the concentration of the cleaning agent is too high it can cause waste of resources and even cause some adverse effects (such as the etching of stainless steel). The development of modern industry comes with more and more rigorous requirements on energy saving, environmental protection and safety. All the waste water after cleaning must be effectively treated to be environmentally friendly before discharging. The measures that can be taken include reducing the acidity or alkalinity of the waste water by neutralization, choosing a type of cleaning agent with a low concentration of phosphorous as much as possible, and control the biological oxygen consumption and the chemical oxygen consumption of the waste water.

Rouge is a type of particulate contaminant that is closely attached to a stainless steel surface. A satisfactory cleaning effect cannot be achieved only by thermal energy or mechanical energy alone. Chemical actions play an important role in the rouge remediation process. Before rouge remediation, a basic solution should be

or undrainable spaces that may trap descaling agents, sludge, particles, or contaminated rinse water that might either result in eventual corrosion or adversely affect operation of the item after it is placed in service.

• Mechanical rouge remediation. Mechanical rouge remediation methods include abrasive blasting, power brushing, sanding, grinding, and chipping. Mechanical rouge remediation methods have the advantage that they do not produce such physical or chemical conditions as intergranular attack, pitting, hydrogen embrittlement, cracks, or smut deposits. For some materials, in particular the austenitic stainless steels when in the sensitized condition and the martensitic stainless steels when in the hardened condition, mechanical rouge remediation may be the only suitable method. Grinding is usually the most effective means of removing localized scale such as those resulted from welding. Disadvantages of mechanical rouge remediation are cost, as compared to chemical rouge remediation, and the fact that surface defects (for example, laps, pits and silvers) may be obscured, making them difficult to detect.

The surfaces must be cleaned before mechanical rouge remediation. Particular care must be taken to avoid damage by mechanical methods when descaling thin sections, polished surfaces, and close-tolerance parts. After mechanical rouge remediation, surfaces should be cleaned by scrubbing with hot water and fiber brushes, followed by rinsing with clean and hot water. Grinding wheels and sanding materials should not contain iron, iron oxide, zinc, or other undesirable materials that may cause contamination of the metal surface. Grinding wheels, sanding materials, and wire brushes previously used on other metals should not be used on stainless steel. The use of stainless steel shot or grit reduces the danger of rusting and iron contamination, but cannot completely eliminate the possibility of embedding residues of iron-oxide scale. If a totally iron and scale free surface is required, abrasive blasting may be followed by a brief acid dip.

In the ASTM A380, the specifications on rouge remediation are more from the point of view of new equipment, new systems and components. In reality, the old equipment, systems and whole sets of systems in the pharmaceutical industry are facing highest risks. The cleaning and rouge remediation guidance in the ASTM A380 for old equipment, systems and whole sets of systems can be summarized as below.

• Chemical rouge remediation and mechanical rouge remediation are the two most commonly used rouge remediation methods.

• Care should be taken for the selection of the rouge remediation agent for chemical rouge remediation to prevent over pickling. Mechanical rouge remediation should be done with discretion to prevent damages to any components.

• For a closed system, it is not practical to use the above described mechanical method for rouge remediation. However, the mechanical action is necessary. We generally need to ensure a complete turbulent flow and a sufficient pressure (sufficient enough to start the spraying balls).

• Cleaning is crucial in assuring the rouge remediation efficacy. This is because that in the pharmaceutical industry, a bio-film or product residues (often a type of organic film) will be attached to the stainless steel surfaces, if not thoroughly cleaned, the pickling rouge remediation agent cannot come into sufficient contact with the rouge affected surface, causing incomplete rouge remediation reactions and unsuccessful rouge remediation. Of course, this is only from the point of view of rouge remediation. From the points of view of microbes and cross contamination, these bio-films or organic films must also be sufficiently removed.

10.2.2 Approved Risk Assessment for rouge remediation

Rouge is a thin layer of membrane formed by iron oxides or hydroxides on a stainless steel surface. The rouge also has iron, chromium, nickel, etc.

For pharmaceutical enterprises, the frequency of rouge remediation and re-passivation is determined based on the rouge remediation intervals or visual inspection results on the system pipelines. At present, a scientific method for the accurate measurement of the rouge of a system is still not available. The rouge remediation and re-passivation cycle is often determined for a system based on the subjective experience of QA. So in the enterprise SOP the rouge remediation cycle will be defined as once a year, once half a year or every time the production is stopped based on the reasonable risk level assessed by QA. This is only an arbitrary definition in the SOP and it is not considered whether such a rouge remediation plan is appropriate or not.

The modern pharmaceutical water systems are

fully automated computerized systems. A large amount of on-line testing instruments have been used to replace the traditional lab tests. These on-line testing instruments and the automation system can provide the users with real time data and the system operation parameters can be controlled based on these data to ensure the normal operation of the system. A set of scientific rouge forming speed measurement methods can provide precise and accurate guidance on rouge remediation and passivation activities and accurately interpret the entire rouge formation process.

During recent years, people started caring more and more about the rouge remediation and re-passivation activities for stainless steel pipelines. rouge remediation and passivation are different stainless steel surface treatment processes. And they have many similarities. Generally, highly corrosive chemical agents are used to remove the rouge on a metal surface. Re-passivation of the metal surface can only be performed after the rouge has been completely removed. Passivation can be viewed as a type of special cleaning process that is used to remove any rusts, free iron ions and other surface contaminants and form a chromium rich protection layer. At the same time, passivation can also greatly reduce the generation of free iron ions on a stainless steel surface, and effectively inhibit the generation of iron oxides (rouge). Phosphoric acid, citric acid, nitric acid and other acidic agents are often used as passivation agents. And sodium hydroxide and ammonium hydroxide are often used to neutralize the acidic waste solution after rouge remediation and passivation. The neutralized waste solution is drained through the sewage system. In some cases, the waste solution also needs to be treated by a waste treatment system at the site. After rouge remediation and passivation, it is necessary to thoroughly rinse the system. The water system can only be put back into use after all the contaminants generated or introduced during the rouge remediation and passivation process have been completely removed. Otherwise, unpredictable and serious consequences can result, because any residual chemical left by the rouge remediation and passivation process will significantly change the process performance of the system. Generally speaking, a typical rouge remediation and re-passivation process will cause the system to be stopped for 2 to 7 consecutive days. This mainly depends on the number of the circulation loops and the volume of the entire system.

The formation of rouge in pharmaceutical water systems (including WFI storage and distribution systems, PW storage and distribution systems, pure steam distribution systems and other clean fluid systems) is a natural phenomenon affected and interfered with by external factors. Generally speaking, the severity of rouge mainly depends on the following factors.

- The stainless steel material quality and grade selected for the pipelines of the clean fluid process system.
- The fabrication processes for the clean fluid process system, such as welding, surface finishing and passivation.
- The operation environment of the clean fluid process system, such as the water quality and purity, the chemical process associated with the system, the operation temperature, pressure and flow velocity, the mechanical stress undertaken by the system, and the oxygen content of the environment it is exposed to.
- The maintenance of the clean fluid process system.

The generation of the rouge pitting products can severely deteriorate the quality of the stainless steel pipe and significantly increase the risks of quality events. So it is especially necessary to assess the potential risks on the production process and the long term running of the system caused by the existence of rouge in the associate pharmaceutical water systems. The various types of factors that can cause the formation of rouge in pharmaceutical water systems can be divided into the following three categories.

- The first type of variables has low influences on the formation of rouge. This type of factors provides the theoretical references for the influences of the variables listed in Table 10.5 and Table 10.6 on the formation of rouge.
- The second type of variables has higher influences on the formation of rouge. This variable is supported by certain amounts of experimental data. They should be considered during the design of the clean pipeline construction process.
- The third type of variables has significant influences on the formation of rouge. This variable is supported by rather complete and mature experience data from this industry. They must be considered for the clean pipeline construction process.

Table 10.5 Risk assessment during the construction phase

Influence factors	Comments
Category 3(high influence)	
Material selection	Whether the selected material(such as 316L stainless steel)is reasonable depends on the corrosion resistance of the selected material in its use environment. For example, low carbon steel has better corrosion resistance that that of high carbon steel. The selection of a proper material can inhibit the premature or the accelerated corrosion process. Improving the content of nickel can effectively improve the corrosion resistance of stainless steel
Mechanical polishing	Residual particles generated during the polishing process can be left in the grains created on the metal surface by cold processing technologies. The nonhomogeneity in the surface polishing can cause the increase in the area of the surface, which can make the material more vulnerable to corrosion
Electric polishing	Electric polishing can reduce the area of the material that is directly exposed to an oxidative fluid or chloride, and reduce the chances of micro pitting caused by the various types of mechanisms(such as corrosion by chlorides, and corrosion by heat stress). The number of surface suction points can also be reduced with the improvement of the surface finish
Passivation	Passivation can effectively inhibit the development of corrosion on a stainless steel surface. The efficacy of the passivation method, including the passivation depth and the optimized distribution of the surface metal elements(such as the ratio of chrome and iron) will decide the resistance to corrosion and the corrosion speed after the passivation process
Constituents of metal elements	The metals mainly include molybdenum, chromium, nickel, etc. The performances of the metal microstructure can affect the sedimentation of the grain boundary impurities. The migration of these impurities can accelerate the invasion of a corrosion source from the surface inward. The sulphur content of different welded joints can be different because of the variations in the weld pool, causing failure in through welding. Such points are very likely to become the initial points of corrosion
Welding processes, parameters and inflation methods	Improper welding methods can cause the loss of chromium at the heat affected zones thus reducing the corrosion resistance ability of the metal. The noncontinuity during welding can provide chances for molten droplets to carry some impurities. Cracks in defective welding seams can cause notches around the active corrosion source on the passivation film. Proper inflation methods can effectively prevent welding contaminations caused by tempering color oxidation films and the accompanying damages in the corrosion resistance. Passivation cannot reverse any adverse consequences caused by improper inflation
Product types and processing methods	The forming process can significantly influence the final content of ferrite(for example, the ferrite content in forged pieces is far lower than that of casted pieces). The gaps of the forging lines on the surface of a forged piece will increase the risk of the metal to form microdots and then pitting corrosion. Reducing the difference in the sulphur content can improve the success rate of high quality welding
Category 2(high influence)	
Installation environment	Possible corrosions that can be caused by carbon steel corrosion, scratches, exposure to a chemical environment, and the retention of condensate or liquid in the pipeline should be removed before passivation. If the possible corrosions that can be caused by the installation environment are overlooked, the final passivation effects can be affected
System renovation and expansion	In a system that is newly put into operation, the oxide formation speed will be different from that of an existing system. And at the early stage class Ⅰ rouge can be formed. Because of the existence of an oxidation film, an old system has more chemical stability and only a small amount of ferric oxide or chromium oxide will be generated. Class Ⅰ rouge can be generated and distributed throughout the entire system for a new system. So the causes of the corrosion are very difficult to identify

Table 10.6 Risk assessment during operation phase

Influence factors	Comments
Category 3(High influence)	
Corrosive process fluids	A corrosion cell, such as a chlorine corrosion cell, usually forms at a gap in the passivation film and can gradually accelerate the corrosion mechanism. Its effects on such a system as a high-salt buffer tank are extremely high
High cutting/high flow velocity environment(pump impellers, spraying balls and tees)	The corrosive factors can consume or erode the passivation film and expose the particles of the base metal in the running system. Severe cases include the pitting corrosion formed at the end of a pump impeller, or the pitting corrosion formed on a pipe wall under the effect of a flowing fluid. In a pure steam system, the high flow velocity part can effectively blow and wash the pipe wall to avoid the continuous accumulation of such contaminants as ferric oxide on that part of the pipe wall and carry the ferric oxide chips to the downstream area, which brings potential risks of pitting at the downstream area
Operating temperature and temperature gradient	The operating temperature and the temperature gradient of a system can affect the type(classes Ⅰ, Ⅱ or Ⅲ rouges)of the final ferric oxide formed, its difficulty of removal, its sticking performance, and the stability or the mobility of the oxides. The rouge remediation and passivation effect is largely dependent on the operating temperature of the system. For example, in a pure steam system where black ferric oxide (class Ⅲ rouge) has been formed, rouge remediation should be performed before passivation. A number of spectral analysis methods can be used to identify these impurities
Gas phase components(including dissolved gases)	For a WFI system and a pure steam system, within the defined conductivity and TOC ranges and with the protection of a passivation film, the dissolved gases only have limited influences on the formation of rouge. The impurities can migrate together with the dissolved gases during the distillation and vaporization processes
Process parameters, process media and frequency of use	The type of the oxides, the corrosion risks, the rouge remediation methods and the rouge formation time canbe significantly influenced by the operation parameters(temperature, process, etc.). SIP, the flow velocity, the temperature and the sealing performance can influence the class and the position of the rouge deposition A rational design can help reduce the adverse influences described above. A bad sealing performance often puts the system under the stress of a pressure gradient, thus introducing the corrosion products into the system through the condensate. The long term running and the agitation in a high-salt buffer tank can accelerate the corrosion process. The risk of corrosion and the difficulty in the subsequent rouge remediation and passivation can be increased by improperly designed CIP and SIP
Selection of system CIP and cleaning methods	The exposure of the system to the CIP circulation and any chemical cleaning agents can greatly influence the risk of rouge. The risk of the formation or the accumulation of rouge can be reduced at CIP exposed parts of the system. Whether there are any acid or hot acid in the CIP system formulation is an important factor for the formation of rouge. The pickling process and the temperature of the CIP process are very important. For example, the use of phosphoric acid at a constant concentration(2% to 20%)in the cleaning circulation can maintain and recover the passivation film
Redox potential	The disinfection of PW or WFI by ozone can effectively inhibit the development of corrosion
Category 2(high influence)	
System maintenance	Such system components as worn steam regulating valve bodies, misaligned gaskets, damaged valve membranes and pump impellers, and corroded heat exchanger pipes are all considered as breeding grounds for class Ⅰ rouge

cont

Influence factors	Comments
Category 2(high influence)	
Stagnant areas	A flowing oxidative fluid can protect the passivation film. (Studies have shown that the nitrogen blanket of a WFI storage tank has a negative action on the passivation film. This is because the existence of nitrogen inhibits the oxygen content in the fluid) Liquid condensate that is not immediately removed from a steam conduit or that collects from improper valve sequencing can concentrate and transport surface oxidation products or steam contained solubles. These substances can accumulate at a branch terminus such as a spray ball, dip tube, etc. These deposits are usually lightly held forms of ferric oxide. Although they can be easily removed, they can be difficult to remove in large pipelines and fail to meet the criteria of "visually clean"
Pressure gradient	This is only for pure steam systems. The pressure changes in the distribution system will affect the amount of steam condensate as well the steam quality. If different system sections are exposed to different pressure ranges, the condensate cannot be effectively removed from the horizontal sections and will be re-vaporized at higher pressures, which will lower the steam quality and transport any impurities in the steam condensate to the steam
System service life	It depends on how the system has been maintained in regard to frequency of passivation or rouge remediation, CIP treatment and formation of a stable passivation film. Studies show that, compared with old systems, new systems can generate disproportionate amounts of class Ⅰ rouge formations. In pure steam systems, although the formations of oxide layers become stable with age, they can also be prone to particle sloughing in high velocity sections while becoming thicker and thicker. System time in use can have both beneficial and negative effects on rouge formation and regular system monitoring is important in identification of incipient corrosion

There are many high risk factors that can cause the formation or the rapid spreading of rouge during the running process of a pharmaceutical water system. For example, a corrosive process fluid of a formulation system, especially when there is chlorine in the fluid, can easily pit the surface of the stainless steel pipeline of the system and accelerate the development of rouge. More common rouge formation risks lie in the setting of the operation parameters of the process fluid system, such as the flow rate, the operating temperature, the operating pressure and other routine operation parameters. Some scientific research organizations found that, when the flow velocity of a fluid is too high, the corrosive factors (including the high purity water) it contains will corrode and damage the passivation film on the stainless steel surface. This phenomenon is especially prominent within the chamber of a centrifuge pump and on the surface of the impellers of a process system of circulated fluids. The system operating temperature will directly decide the type of the rouge product. The class Ⅱ rouge in a WFI system and the class Ⅲ rouge in a pure steam system are characterized by the differences in their development process because of the different temperature of their respective oxidation environment. The instable gradient distribution of the system pressure can cause residual condensate in a pure steam system, which facilitates the formation of rouge and provides a breeding ground for microbes within the system. In addition, the system cleaning in place (CIP) and sterilization in place (SIP) processes, the system maintenance cycles and the specific maintenance activities, the rouge remediation and passivation treatment frequency and the rouge remediation and passivation process parameters can all accelerate the formation and the development of rouge during system running process.

10.2.3 Identification of Rouge Classes

Rouges in pharmaceutical water systems can be tested in the process fluid or the stainless steel surface in contact with the materials. The method of process fluid analysis can be used for the identification of the constituents of rouge in a process system to be tested. This type of method can be used to indicate the quality of the current process media and the rouge detection results. Many specific analytical methods for the dynamic

Table 10.7 Process Fluid Analyses for the Identification of Mobile Constituents of Rouge

Test methods	Test description	Test criteria	
		Advantages	Disadvantages
Ultra trace inorganic analysis(ICP/MS)	Concentrations of trace metals in such process solutions as PW and pure steam are directly analyzed by inductively coupled plasma mass spectrometry (ICP/MS)	Noninvasive sample acquisition. Highly quantitative information. Provides strong ability to trend data	Baseline must be determined for each system analyzed.
Laser particulate analysis (via light)	A liquid sample is subjected to a laser light, which scatters upon contact with particles. The scattered light is collected, processed, and displayed as a specific count for each size range analyzed.	Noninvasive sample acquisition. Highly quantitative information. Provides strong ability to trend data	Baseline must be determined for each system analyzed
Electron microscope scanning(SEM/EDX)	Fluids are filtered via vacuum filtration, and particles are collected on a fine pore filter medium. The particles are then analyzed by scanning electron microscopy for size, composition, and topographical features	Provides highly detailed physical observation and elemental composition data	Limited to organic particulate identification only
Fourier transform infrared spectroscopy (FT-IR)	Organic analysis of liquid samples or extracts from wipe samples. Used to identify possible organic films or deposits	Potentially noninvasive sample acquisition. Allows for organic identification of elastomers or alternate organic contaminants	Organic contaminants must be profiled in a specific target compound library

monitoring of the fluid are listed in Table 10.7 and their respective advantages and disadvantages are also summarized.

Different from fluid analyses, surface analyses can provide the features of the surface micro-structures and the detailed constituents of the surface passivation film/oxidation film, based on which the quality of the fluid can be assessed and the potential threats from current rouge to the water quality can be predicted. Many surface analytical technologies for rouge study are listed in Table 10.8 and their respective advantages and disadvantages are also summarized.

10.2.4 Rouge Remediation Process Specifications

The rouge remediation process should be designed to remove ferric oxide and other surface rouges to reduce the damage to the surface finish by rouge. Rouge is generally formed on the surface (of a pipeline) and is originated from the migration and the sedimentation of corrosion or impurity particles onto the surface. Typically rouges are divided into class Ⅰ, Ⅱ and Ⅲ rouges. This section mainly describes the rouge remediation methods and the process parameters for the three classes of rouges.

a. Class Ⅰ rouge remediation. Class Ⅰ rouges are weakly attached to the surface and relatively easily removed and dissolved. This rouge is generally hematite (Fe_2O_3), or red ferric iron oxide with low levels of other oxides or carbon content. Phosphoric acid is effective in removing light accumulations of rouges and can be blended with other acids (citric, nitric, formic, or other organic acids) and compounds (such as surfactants) to promote its derouging effectiveness. Citric acid-based chemical agents mixed with additional organic acids are also highly effective at Rouge Remediation. Sodium hydrosulfite (such as sodium dithionite) is also fast and effective at the removal of class Ⅰ rouge.

The temperature and the duration of the rouge remediation process by the above described chemical agents are dependent on the severity of rouge, the system material and the rouge remediation agent concentration. The concentration of each agent is based upon the test results and the protocol criteria.

Table 10.8 Surface micro-structure analyses for the identification of mobile constituents of rouge

Test methods	Test description	Test criteria	
		Advantages	Disadvantages
Microscopic and human visual analysis	Micro-analysis of stainless steel surfaces are performed via polarized light microscopy(PLM), scanning electron micros copy (SEM), or alternative microscopy instrumentation	Good test for morphology determination. Can be coupled with energy dispersive X-ray (spectroscopy) (EDX) analysis for elemental composition information	Cannot be performed on line. Requires the periodic removal of the parts to be tested from the system and sampled for testing. The sample piece cannot be recovered
Scanning auger micronalysis or auger electron spectroscopy	Can be used for surface metal elemental composition analysis. Provides for detailed qualitative elemental composition data on both the stainless steel surface and the sub-surface	Highly accurate elemental composition data can be obtained and accurate thickness and the elemental composition of the stainless steel passivation film/oxidation film can be obtained	Destructive test. Requires the periodic removal of the parts to be tested from the system and sampled for testing. The sample piece cannot be recovered
Small spot electron spectroscopy for chemical analysis and X-ray photoelectron spectroscopy (ESCA/XPS)	The sample is subjected to a beam of X-rays of a high energy. Electrons are emitted from the surface and measured to provide elemental analysis of the surface layer	Highly accurate elemental composition data can be obtained and accurate thickness and the elemental composition of the stainless steel passivation film/oxidation film can be obtained. Provides complete and detailed elemental data analysis for the surface of the test piece and accurately present the micro-structure of the ferric oxide(rouge)	Destructive test. Requires the periodic removal of the parts to be tested from the system and sampled for testing. The sample piece cannot be recovered
Reflection grade ellipsometry	Spectral analysis is performed utilizing the diffractive properties to assess surface conditions	Nondestructive analysis The diffractive characteristics of specific elements are used to provide quantitative analysis of element to be tested based on the diffractive spectra	The component to be tested need to be removed from the system. On line monitoring is not possible and the requirements on the environment are very high
Electrochemical impedance spectrometry	The analysis of the external corrosion current on the stainless steel surface is used to analyze the corrosion properties of the test piece based on the surface corrosion limit analysis.	On line monitoring for real time observation of the corrosion trend	With high requirements on the field environment

Electrochemical cleaning can be used for Rouge Remediation when the product contact surface is considered as an anode. It uses phosphoric acid as the rouge remediation agent and a direct current is applied. As a cathode is moved over the product contact surface to be cleaned, rouge is readily removed. This method is applicable to the removal class Ⅰ, Ⅱ and Ⅲ rouges, but is limited to accessible parts of a system and is primarily performed on the product contact surfaces in pipelines.

b. Class Ⅱ rouge remediation. Class Ⅱ rouge remediation methods are similar to those for the remediation of class Ⅰ rouge with the addition of oxalic acid, which improves the effectiveness in removal of class Ⅱ rouge. This type of rouge consists mostly of hematite (Fe_2O_3) or ferric iron oxide with some amount of chromium and nickel oxides as well as small carbon content. All of the above agents remove the rouge without damaging the surface finish with the exception of oxalic acid. Oxalic acid can etch the surface under certain use conditions at certain concentration. Class Ⅱ rouges are more difficult to remove than class Ⅰ, and usually require longer cleaning time, even higher cleaning temperatures and increased concentrations.

c. Class Ⅲ rouge remediation. Class Ⅲ rouge is much more difficult to remove compared to class Ⅰ and class Ⅱ rouge, both due to its different chemical composition and structure. Ferric oxides deposit at

high temperatures and magnetite iron oxide is formed with some substitution of chromium, nickel, or silica in the compound structure. Significant amounts of carbon are generally present in these deposits due to the reduction of organics present in the process fluid, which can produce a black film that may form during derouging. The chemical agents used to remove this class of rouge are very aggressive and will affect the surface finish to some degree. Phosphoric acid-based derouging agents are generally only effective on very light accumulation of this class of rouge. The strong organic acid blends with formic and oxalic acid are significantly effective on some of these high temperature class Ⅲ rouges, and being less aggressive, produce much less potential for etching of the surface finish.

The citric and nitric blends with hydrofluoric acid or ammonium bifluoride can rapidly remove these class Ⅲ rouges, but will definitely etch the surface wherever the base metal is subjected to the derouging fluid. The amount of etching or the increase in the surface finish roughness is dependent on the process conditions, the chemical concentration, and the variability of the rouge thickness and the level of initial surface finish roughness. The condition of use for this type of derouging processes is highly variable both in temperature and time settings required to effectively remove the rouge and leave the surface prepared for subsequent cleaning and passivation. Agents with low chemical corrosiveness (such as CIP 200) require higher temperatures and longer time for derouging (Fig 10.17). The highly corrosive chemicals as nitric acid-based fluoride solutions are often used at ambient temperature to 40 ℃, while the citric acid-based fluoride solutions are used at higher temperatures and shorter contact times.

The times and temperatures given above are in direct relation to the percent by weight of the base reactant (s). A change in a formulation will often change the series of corresponding parameters. The fluid cleaning mode (circulation or soaking), the overall sealing performance, the surface cleaning after derouging and the correct decontamination measures are all critical factors for the rouge remediation process. The waste fluids generated by these processes can be classified as hazardous due to their chemical constituents or heavy metals content.

Effectively removing rouge from product contact surfaces can reduce the potential for oxide particulates from being carried over into the process fluids. Derouging processes are required prior to proper cleaning and passivation of the stainless steel surface for restoration of the passive layer after corrosion. Analytical testing of utility fluids can be useful in identifying the level of particulate generation and levels of metal oxides contained in these fluids as corrosion degrades the surface.

10.2.5 Rouge Remediation Inspection Procedures

a. Rouge inspection procedures for water storage units. When performing a rouge inspection for a water storage unit, the inspector should confirm the inspection time with the customer in advance. The customer should ensure that the storage tank has been emptied, the storage tank temperature has been reduced sufficiently and it has been strictly verified that there is no pressure held in the storage tank. After the inspectors arrive at the site, the inspection can be started after verifying that the inspection conditions have been met for the WFI storage unit following the sequence from the tank body, the distribution pipeline and the return line, and then the storage tank water outlet pipeline. When inspecting the tank body, it is recommended to inspect the storage tank for traces of rouge from the top

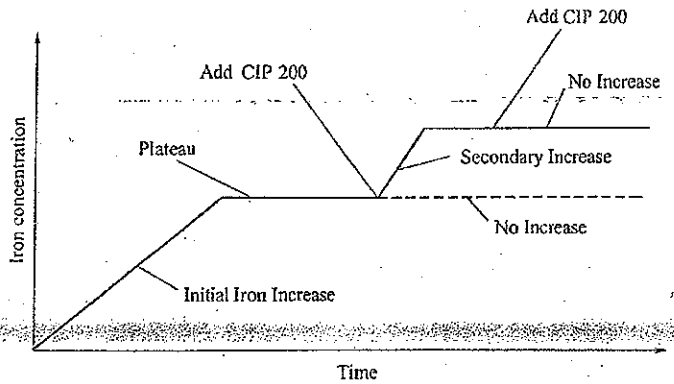


Fig 10.17 Routine rouge remediation processes

to the bottom.

• Manhole Inspection.

When inspecting a manhole cover, it is generally required to climb to the top of the tank. It is specified in the national standard *Classification of Works at Heights* (GB/T 3608—2008) that any activities at a place with a height of fall of no less than 2 m from the base level with a possibility of fall are "works at heights". According to this specification, when performing any activities within a building, it should be deemed as works at height when the activities are done on a shelf of no less than 2m. In such as case, the inspector should wear a safety belt when climbing the ladder and a stable structure on the tank body should be used as the fixation point for the safety belt, and there should be at least one dedicated operator ensuring the fixation of the ladder until the inspector has safely returned to the ground. When the inspector has reached the working height for opening and closing the manhole cover, he or she should first verify the external surface temperature of the tank body and the manhole cover, and any inspection operations should be started only after it has been ensured that the tank body temperature is within the range that can allow the operator to access it at a short distance. When the manhole cover is opened at the working height, the manhole cover should be fixed at a place that can facilitate the observation and ensure that there will be no such safety events as the automatic recovering of the manhole cover. Then the internal situations of the tank can be inspected. It can be felt and seen whether the temperature within the tank is suitable for the inspection and whether there is any residual liquid in the tank. After verifying that the inspection conditions are met, the inspection of the manhole cover can be started. The internal wall of the manhole cover can be inspected visually. The items to be inspected include any rouge etching on the internal surface of the manhole cover, any rouge etching on the internal wall of the manhole cylinder, and the intactness and the status of the manhole gasket. The spraying coverage of the top of the tank by the spray ball can be deduced by observing the range of rouge on the internal surface of the manhole cover. Based on experience, the area of the internal surface of the manhole that can be covered by spraying is prone to the deposition of rouge, and the shinny and clean part of the manhole cover may not have been covered by the spraying. When performing such an inspection, a white towel can be used to wipe any rouge deposited on the manhole cover and the manhole cylinder for a simple rouge class identification. If after wiping the surface is shiny and clean, the rouge on the internal surface of the manhole cover is class Ⅰ or Ⅱ. Satisfactory rouge remediation effects can be achieved through the normal chemical methods. If the rouge on the internal surface of the manhole cover is dark red or dark brown in color, with reticular distribution of different depth and cannot be wiped away, the rouge can be severe class Ⅱ rouge, and special chemical agents are required to remove it and mechanical and chemical cleaning need to be performed if necessary. If the rouge on the manhole cover is very severe, it can often indicate that there is more severe rouge within the tank. During the inspection, image data of such important inspection areas as the internal wall of the manhole cover should be obtained for comparison after rouge remediation. After completing rouge remediation and passivation, the selected reference areas can be compared to assess the derouging efficacy. Generally speaking, satisfactory rouge remediation results can be obtained if the spray ball spraying effect can be used during the manhole cover cleaning process. For some manhole covers with severe rouge etching, manual wiping can be used after rouge remediation. Care should be taken that sanitary white towels are soaked in the designated rouge remediation agent before wiping. The wiping force should not be too strong. The wiping should be performed gently along the same direction. After the rouge remediation of the manhole cover is completed, the internal surface will recover the stainless steel luster. No visually observable residual rouge on the surface can be used as the visual inspection criteria for the rouge remediation efficacy test.

• Tank body inspection. The inspection of the rouge on the tank body is mainly used to inspect the corrosion on the internal wall of the tank body. Because the volume of a storage tank is usually rather large, a WFI storage tank is usually not equipped with a sight glass, and such optical devices as an endoscope cannot work normally within a storage tank, the inspection of the internal wall of a storage tank is usually performed visually. When inspecting the internal wall of a storage tank, it must be verified first whether the temperature inside the tank is suitable for the inspection. If the temperature is too high, the inspection must be performed after the storage tank has been cooled down.

During the inspection, the inspector needs to observe all the internal surface of the storage tank through the manhole. Because there can be a large amount of steam vapor inside the storage tank, the visibility is low and a strong flash light should be used. When the visibility inside the tank is acceptable for the inspection, the tank wall and the tank bottom can be inspected together from the top to the bottom. As described above, the tank level is usually maintained at 30% to 80% of the tank volume when the WFI system is running, so any rouge is not distributed evenly on the tank internal wall. Generally speaking, the corrosion is more severe at the upper part of the tank wall than at the lower part of the tank wall, which is because the lower part of the tank is soaked in water for a long period of time, the water dissolved oxygen level is far lower than the oxygen level in the air at the upper part. Although there is water, which is essential for corrosion, the corrosion speed at the lower part is far lower than that at the upper part of the tank where there is higher oxygen level and the surface is wet. In addition, for a large storage tank, the spray ball covered area is mainly at the upper part of the tank. Depending on the spray ball selected, the spraying coverage may not reach the theoretical design value, and some part of the internal tank wall may be wet but not sprayed, which can result in the uneven distribution of corrosion. When inspecting rouge on the internal tank wall, it can usually be seen that there are unevenly distributed rouge areas in belts at the upper part of the tank and the color is brown or red. The corrosion is more evenly distributed at the lower part, with red rouge distributed on the entire surface. For some small formulation tanks, the corrosion of the tank wall can be severe, the color of the rouge can be brown or blue as influenced by the process flow constituents and the temperature, and the rouge is often distributed in belts. The rouge at the bottom of the tank mainly results from the alternation of a full tank and an emptied tank and the migration of the free iron ions in the fluid within the tank. When inspecting the rouge within a tank, the image data of parts with rouge etching should be saved for typical and representative parts. And a comparison should be made after completing rouge remediation for these representative parts. The tank cleaning and rouge remediation effects usually depend on the spraying effect of the spraying balls. When cleaning the tank body, a spray ball is usually installed at the reserved port at the top of the tank. If there is a reserved port at the manhole cover, it is preferred to install it on the manhole cover to obtain better spraying effects. The criteria for the rouge remediation effect inspection for the internal wall of a tank include the surface roughness of the tank internal wall, with no visible rouge adherence, with no visible rouge within the reserved port on the top of the tank, and a conductivity difference of no more than 0.2 μS/cm between the water drained from the tank and the water used to rinse the tank. If any residual rouge is observed on the tank internal wall that cannot be cleaned away after completing rouge remediation, relevant measures, such as the manual wiping of the tank internal wall, should be taken based on the situations at the site.

• Inspection of the return loop and the spray balls. After completing the rouge inspection of the manhole and the tank body, the manhole should be closed in time to prevent the tank from being contaminated. After closing the manhole, disassemble the connection between the return loop and the tank body to separate the return loop and the tank, and fix them respectively. Carefully take out the spray balls and the connecting rod, and place them on a piece of clean white towel. When inspecting the rouge in the return loop, an electronic endoscope is required. The electronic endoscope should be water proof in design. It is recommended to verify that any residual water inside the loop has been emptied before inserting the probe into the loop because the endoscope is used very frequently and the loop is rather complicated. After inserting the probe into the loop, the first welding seam can be seen on the screen after about 5 cm. This is the welding seam between the clamp connector and the pipe and it can be used as the reference welding seam. Position the probe toward the welding seam and start recording. Before rouge remediation, rouge can often be seen through the endoscope on the internal wall of the pipe. Taking a WFI system as an example, the circulation temperature is usually about 80 ℃ or above, and rouge can generally be seen in the system after about 5 months. The parts of the pipeline where rouge can first occur are the welding seams, the heat affected areas and the pipe butting welding seams. So when inspecting the pipeline for rouge, a welding seam should be used as the reference point to obtain a satisfactory rouge remediation effect comparison before and after cleaning. When inspecting a welding seam, the probe of the en-

doscope should be slowly rotated by 360° at a constant speed to observe the color and the amount of rouge attached to the welding seam and it should also be inspected to see whether there are any traces of rouge at the heat affected areas around the welding seam. At this time, the focus of the camera can be adjusted to amplify the image appropriately to assist the determination of the rouge class and distribution, so that the inspector can have a more accurate assessment of the corrosion within the pipe. This can help the technicians to work out a more effective rouge remediation plan, select the optimal rouge remediation agent and ensure the cleaning effect. The recording time during an endoscopic rouge inspection can be determined based on the conditions of the rouge in the inspected system. Generally the recording time should be about one minute, the probe movement speed should be no more than 5 mm/s, and the video recorded should be stable. There should be stops at typical rouge distributed areas and the screen should be frozen for such areas. And the video should be attached to the rouge inspection report.

After completing the inspection of the return loop, take the separated spray balls and inspect them. The rouge inspection for a spray ball includes the inspection of the external surface and the inspection of the internal surface. The external inspection is mainly performed through visual inspection with the help of white gloves. The external wall of the spray ball, the spray ball nozzle, the rod connection and the external surface of the connecting rod are visually inspected for rouge. The rouge high risk areas on the external surface of a spray ball device include the external surface of the balls, the spraying nozzle and the external surface of the connecting rod. The spray ball external surface and the spraying nozzle are prone to local stress corrosions because they are under the stress of the starting pressure and the high water temperature. And the connecting rod, especially the part used to fix the spray ball is difficult to be covered by the spraying. The connecting rod cannot be sprayed continuously, thus is very vulnerable to oxidation corrosion under the wet environment in the tank. The rouge distribution on a spray ball is rather complicated. Red, reddish brown and blue rouge can often be seen on the body of a spray ball. The rouge on the connecting rod is mainly reddish brown in color. Some of the rouge attached on the surface of a spray ball can be wiped away, which is class Ⅱ rouge. Satisfactory rouge remediation effects can be obtained using the routine chemical methods. The inspection of the internal surface of a spray ball can be performed through a light aided visual inspection or with an endoscope. Severe rouge within a spray ball can be observed through a visual inspection with the aid of an external light source. However, it is difficult to identify the class of the rouge. Using an endoscope video inspection can provide a clearer and better understanding of the corrosion within a spray ball. When performing the inspection with an endoscope, the video should be taken mainly for the welding seams on the connecting rod, the fixation pin of the spray ball and the internal surface of the spray ball. Generally there can be a large amount of rouge accumulated within a spray ball, which is generally class Ⅱ rouge. Because of the high starting pressure and the high speed flushing status, the internal surface of the spray ball can be continuously under high speed flushing at the time of cleaning, so the rouge remediation effect is generally very good.

After completing the rouge remediation, the external surface of the spray ball is inspected for the rouge remediation effects. After the rouge remediation and cleaning of the external surface of a spray ball, the external surface of the ball should be shiny and clean, there should be no rouge around the spraying holes and their sides, and the metal luster should be restored at the connecting rod and the socket of the spray ball fixation pin. If rouge remediation is failed or partially failed at any of the above parts, appropriate manual swabbing methods can be considered for rouge remediation. Soft and clean white towels or other optional materials can be used for the swabbing to avoid causing any secondary damages to the spray ball surface. No hard wire cloths should be used and no such highly corrosive acids as hydrofluoric acid should be used. The acceptance criteria for the rouge remediation inspection for the internal parts of a spray ball are that the welded pats inside the connecting rod and the internal wall of the connecting rod should be clean and without any rouge, the gaps between the spray ball fixation pin and the socket, and the internal surface of the spray ball should be with satisfactory metal luster. When verifying the rouge remediation efficacy, the video taken at the reference parts before rouge remediation should be used as the reference to allow a visual comparison after rouge remediation. This can provide documentation supports to the rouge remediation and

cleaning validation activities.

• Inspection of tank outlet. Because of the design requirements, the height of the tank outlet from the floor is rather small and the space for inspecting the outlet pipeline is limited, which brings significant difficulties for the inspecting engineers. And the butt joint of the pipelines at this area is under certain stress; after completing the inspection, it is difficult to reassemble them. So, professional help is required when inspecting the pipelines around the outlet. When performing the inspection before rouge remediation, it should be verified first whether the tank has been emptied, and whether there is no water in the outlet pipelines. The inspection can be started only after the verification. An endoscope is required for the rouge inspection at the pipelines at the tank bottom outlet. The diameter of the pipeline at the tank bottom outlet depends on the diameter of the water inlet of the circulation pump. In principle, the diameter of the outlet pipeline should not be less than that of the pump. A pharmaceutical facility often has high demand for WFI. So according to the design requirements, the diameter of a tank outlet pipeline is generally above DN40. Because this part of the pipeline has only limited laying space, and the pipeline diameter is rather high, care should be taken to any adverse effects of the residual stress, as well as the good storage of the pipeline. During inspection, principles similar with those described previously will be followed. Such areas vulnerable to rouge development as the welding seams and the heat affected zones inside the pipelines should be prioritized during the inspection. And attention should be paid because this length of pipe is connected to the tank at one end and the circulation pump at the other end; the movement of the fluid within it is rather complicated when the system is running. Considering the combination of the vacuum sucking effect from the pump and the depositing effect at the tank outlet from the large amount of water accumulated in the tank, the internal wall of the pipe, especially the internal wall at the bend, is under stress for long periods of time, and the fluid temperature is very high, so the corrosion here is often complicated and severe. When inspecting this area, video evidences should be kept for the welding seams, the heat affected areas, the internal wall at the lower side of the bend and any possible reducers, which can be used as the reference for rouge remediation efficacy comparison after the rouge remediation is completed. In addition, there is often a manual valve or a pneumatic diaphragm valve at the tank bottom outlet. If possible, the diaphragm valve should be disassembled to observe the condition of the diaphragm. And the relevant video evidences before and after rouge remediation should be kept. Attention should be paid that, after completing the inspection of the pipe at the tank bottom outlet before and after rouge remediation, two operators are required to work together to reassemble the pipe installation. Any stress resulted from the butt join of the pipe should be avoided.

b. Rouge inspection procedures for water distribution units. The pharmaceutical water distribution system is the core unit of the entire storage and distribution system. The major function of the distribution system is to transfer the pharmaceutical water conforming to the pharmacopoeia requirements to the process points of use, and ensure that the pressure, flow rate and temperature can meet the production or cleaning requirements. The major components of a distribution system include transfer circulation pumps with variable frequency controls, heat exchangers and their heating or cooling regulation devices, sampling valves, diaphragm valves, 316L stainless steel pipes and fittings, temperature sensors, pressure sensors, conductivity sensors and transmitters, TOC sensors, and their supporting integrated control system (including the control cabinets, the I/O modules, the touch panels and the paper recorders, etc.) The 316L austenitic stainless steel pipelines form the point of use circulation loop are the backbone of the water distribution system. The point of use circulation loop starts from the distribution unit in the water generation room, goes through all the process points of use and returns to the distribution unit in the water generation room. Its major function is to provide pharmaceutical water conforming to the pharmacopoeia requirements to each of the points of use through the stainless steel pipelines. The major components of the point of use distribution loop include sampling valves, diaphragm valves, pipes and fittings, supports and accessories, insulation, etc. For a WFI system, there are also temperature reduction modules for cold points of use. It should be noted that sampling is a critical measure for the PQ and the quality control for a pharmaceutical water system. The FDA requires that the sample size should not be less than 100ml for WFI. It is preferred to be from 100 to 300ml. In order to ensure the sam-

pling safety and prevent any artificial cross contamination, the ISPE recommends the use of dedicated sanitary sampling valves to take line samples for PW and WFI. Sampling valves are mainly installed at the outlet of the water generation system, the main supply of the distribution system, the main return of the distribution system, and the points of use at hard connections that cannot be disassembled at any time.

The pipes and fittings of the point of use distribution unit mainly include pipes, bends, tees, U tubes, reducers, clamps and gaskets. Generally speaking, the total pipeline length of a typical distribution system is recommended to be no more than 400 meters to control the quality of the system and facilitate the management. The rouge detection for a distribution system should concentrate on the points of use. The points of use of the pharmaceutical water systems are mainly divided into open points of use and hard connection points of use. For example, the PW point of use in a janitor's room is an open point of use. The valve at this point of use can also be used for sampling. The water supplementation valve of a formulation room is a hard connection point of use. An independent sampling valve must be installed at this point of use to facilitate the sampling operations. Before sampling, the sampling valve must be flushed. The hard connection points of use can be further divided into the direct butt joint type and the indirect butt joint type. The distance from the valve to the process equipment is very short for a direct butt joint type point of use. There is a longer pipe from the valve to the process equipment for an indirect butt joint type point of use. In order to avoid any microbial contamination, the distribution loop should be blown or sterilized by clean compressed air or pure steam.

At present the rouge inspection for a water distribution system is mainly done by visual inspection. Because the distribution system is mainly composed of pipelines, an endoscope is often used to assist the visual inspection. The parts to be inspected for a water distribution system generally include the rouge within the pump chambers and at the points of use of the water systems.

• Inspection of rouge within pump chambers. Sanitary 316L stainless steel centrifuge pumps are usually used as the source of the driving force for pharmaceutical water systems. When a centrifuge pump is working, the impellers will be rotating at a high speed driven by the motor, forcing the liquid between the impellers to rotate with them. And under the centrifugal force, the liquid will move from the center of the impellers outward. The liquid will obtain energy during the movement through the impellers and leaves the outer edge of the impellers to enter into the spiral pump shell at a high speed. Within the pump chamber, the speed will be reduced because of the gradual widening of the flow channel, during which process some of the kinetic energy is turned into static energy, which results in a higher pressure, and the fluid flows out to the pipeline along the tangential direction. While the liquid flows towards the outer edge from the center of the impellers, a vacuum is formed at the center of the impellers. One end of the sucking pipe of the pump is connected to the center of the impellers, and the other end is dipped into the liquid to be transferred. Under the differential pressure between the liquid surface (usually the atmospheric pressure) and the pressure within the pump (negative), the liquid enters the pump through the sucking pipe. As long as the impellers do not stop, the pump will continue sucking and expelling liquid. During this process, the stainless steel impellers and the internal chamber wall of the centrifuge pump are under high stress from the liquid in the vacuum or negative pressure environment, the passivation film of the surface will be under adverse effects from the circulated load. In addition, if the installation height of a centrifuge pump of a WFI system is not appropriate, the pressure at the pump inlet can be too low. When the pressure at the pump inlet is lower than the corresponding saturated vapor pressure of the liquid to be transferred at that temperature, the liquid will be vaporized. The generated bubbles will be condensed rapidly because of the rapid increase in the pressure when they move with the liquid from the inlet to the peripheral areas; i. e. a reverse phase change. The bubbles disappear instantly. This makes the surrounding liquid to move towards the center of the bubble at a very high speed, creating impacts with a very high frequency and a very high instant pressure. This can cause fatigue and corrosion of the surface of the internal chamber wall and the impellers of the centrifuge pump. This is known as cavitation. Generally speaking, when the pump is running, if the absolute pressure of the liquid to be sucked is lowered below the vaporizing pressure of that type of liquid under the corresponding temperature because of any reason at the local areas with the over flow of liquid (usually somewhere a little behind

the inlet of the impellers), the liquid starts vaporizing at that place. And a large amount of vapor can be generated to form bubbles. When the liquid carrying a large amount of bubbles moves through the impellers to the high pressure areas, the high pressure liquid around the bubbles make them shrink rapidly and collapse. When the bubbles collapse, the liquid particles fill the cavity at a very high speed. A very strong water hammer is generated instantly and it strikes the metal surface a very high frequency. The strike can be several hundred to several thousands of the atmospheric pressure and the striking frequency can be tens of thousands of times per second. The wall can be broken down in severe cases. When cavitation occurs, some noises can be generated in the centrifuge pump, making the pump vibrate and causing the deterioration of the pump performance and leakage at the mechanical seal. At the same time, with the generation of steam the apparent density of the liquid decreases, and the actual flow rate of the liquid, the pressure at the outlet and the efficiency all drop. The liquid cannot be transferred at all in severe cases. For the stainless steel parts in the chamber of a centrifuge pump, intercrystalline corrosion of the microstructure on the surface of the stainless steel parts can result under the impact wave transferred to the impellers and the pump shell during cavitation and chemical corrosion of the stainless steel surface cause by the small amount of oxygen dissolved in the liquid. After a certain period of time, a large amount of rouge and crevices and even sponge like shedding flakes, can result on the surface.

Before inspecting a pump chamber, it should be verified that any residual water in the pump chamber has been emptied through the pump bottom discharge valve and the circulation pump has been switched off to ensure that the pump will not be accidentally switched on during the inspection. When performing the inspection, disassemble the pump bottom discharge valve first (usually this discharge valve is connected through a DN15 clamp). The disassembled valve parts should be handled with care. Place the 6 mm probe of an endoscope into the pump chamber. Carefully rotate the probe cable to thoroughly inspect the internal chamber wall and the impellers. As described above, rouge can often develop on the surface of the pump chamber wall and the impellers because of such factors as cavitation. And these parts have rather outstanding structural features and it is easy to identify the reference parts, such as the impeller surface and the impeller swivel. So inspecting the internal pump chamber and obtaining the video records can provide visual references for the comparison before and after rouge remediation and the evaluation of the rouge remediation effects. It should be noted that the structure within a pump chamber is very complicated and the space is limited. When using an endoscope for the inspection it is strictly forbidden to rotate the probe cable too hard to prevent the cables from being wound around such parts as the impellers. When the inspector can clearly feel the resistance to the movement of the probe within the pump chamber, he or she should stop the inspection immediately, shut down the endoscope, and take the cables out of the chamber slowly. When withdrawing the cables, he or she can try to slowly rotate the cables in the other direction, which can facilitate the smooth withdrawal of the cables out of the pump chamber.

• Inspection of rouge at points of use. The points of use of WFI or pure steam distribution systems are most frequently inspected for rouge. This is because the pipes and fittings at the points of use of the distribution loop are easier to be disassembled and re-assembled, and the end of a point of use is usually a direct tube or a U tube, which is usually without any complicated structures inside the pipe. So they are easy to inspect, through both simple visual inspection and endoscope. In addition, the cleanness of the point of use can directly affect the quality of the final product because it is often directly connected to a piece of pharmaceutical equipment and even in direct contact with the material (such as the point of use for pure steam sterilization). Therefore, it is very important to perform periodic rouge inspection and evaluate the rouge remediation efficacy after rouge remediation and passivation for the points of use of a distribution loop. The points of use of a WFI system are generally in the form of a U tube, the points of use are usually controlled through a clamp connected manual diaphragm valve, and the connection between the pipe above the point of use diaphragm valve and the U tube of the distribution loop is designed to be conforming to the $<3D$ design concept. When performing rouge inspection for the internal side of a point of use, the diaphragm valve should be disassembled. If the point of use is connected with a piece of equipment, this section of the pipe should be kept in a safe place. And it should be inspected for rouge after completing the inspection of the point of use

distribution loop. For a point of use distribution loop with a large diameter, an external light source can be used to help the simple visual inspection of the port of the point of use. For deeper parts of the distribution loop and point of use pipes with smaller diameters, an endoscope can be used to help the rouge inspection. During the inspection, the inspectors should insert the endoscope probe from the port of the point of use, rotate the probe cables slowly and raise it at a constant speed. It is recommended that the inspection depth should be until the first bend of the distribution loop penetrating into the technical layer. When inspecting the rouge on the internal wall of the distribution loop, places with good reference values should be selected. They can include the welding seam between a U tube and the distribution pipeline, the welding seams at both ends of the bend where the distribution loop penetrates into the technical layer, and the welding seam connecting the point of use pipe to the U tube. The video records for these parts before and after rouge remediation should be saved to be used as the references for the rouge remediation efficacy assessment. It should be noted that when performing the rouge inspection for the distribution loop, it is not recommended to allow the endoscope probe cable to go through two or more bends, to prevent the over stress of the cable because of the forced bending. After completing the rouge inspection for the point of use distribution loop, the pipes connecting to the equipment should be inspected. These pipes are usually short and are monitored off line. Both endoscopic inspections and direct visual inspections can obtain satisfactory results. After completing the inspections, the pipes should be reconnected in time. And care should be taken to avoid any stress in the pipeline during the installation process.

The points of use of a pure steam system are different from those of a WFI system. These points of use are usually directly connected to the equipment and clamp connected sanitary manual ball valves are most common for the switches at these points of use. When performing the rouge inspection for a pure steam point of use, the clamp connected manual ball valve at the steam trap pipe of the point of use can be disassembled. The pipes below this valve are steam trap pipes, and they are out of the scope of rouge remediation and passivation. So the inspection will be performed from this area upwards to obtain thorough information on the conditions of the internal parts of the pipe. Before performing the rouge inspection on the point of use distribution loop pipelines of a pure steam system, it must be verified that the pure steam system has been stopped. At the same time, it should be verified that the pipelines of the pure steam system have been cooled down to a suitable temperature for the inspection to avoid burning any person. During the inspection, the steam trap at the point of use should be disassembled and carefully stored. Insert the endoscope probe cables from the port of the point of use, rotate the probe cables slowly and raise it at a constant speed. It is recommended that the inspection depth should be until the first bend of the distribution loop penetrating into the technical layer. Compared with a WFI system, a pure steam distribution loop that has been running for over half a year has more severe rouge inside it. And most of the rouge is class Ⅲ rouge that is difficult to remove by the routine chemical agents. So when performing the rouge inspection on the internal side of a pure stream distribution loop, such typical places that are vulnerable to rouge as the welding seams, the heat affected areas and the clamp connections should be inspected for rouge identification, and a comparison will be make for these inspected areas after rouge remediation to evaluate the rouge remediation efficacy.

10. 2. 6 Rouge Remediation Efficacy Inspection

a. Visual inspection. Visual inspection is one of the important measures for industrial non-destructive inspections. It is a type of method that uses only human eyes or with the help of some optical instruments to observe or measure the surface of an industrial product. The typical way is to restrict the limit of detection to the range of the electromagnetic spectrum of visible light. Visual inspections can be divided into direct visual inspections and indirect visual inspections. Direct visual inspections mean the inspections using the human eyes only or an amplifier with an amplification of less than 6 times. Indirect visual inspections are inspections using various types of optical instruments or equipment, such as reflectors, telescopes, industrial endoscopes, light-guide fibers or other suitable instruments, for areas where direct inspection is not possible.

The visual inspection technologies and the establishment of the relevant standards have been thoroughly studied overseas and these technologies have been widely used. Especially in such highly developed countries as

the US and the European countries, the studies and the establishment of the visual inspection standards have been highly developed. There are specific descriptions on visual inspection in such standards as the International Standardization Organization (ISO) standards, the ASME standard of the US, the BSEN standards of the UK and the standards of the European Standards Institute. And different standardization systems have been established. In 2007 the General Administration of Quality Supervision of the People's Republic of China issued the GB/T 20967—2007 *General Rules on Non-destructive Visual Inspections*. This standard specifies the general rules for direct visual inspections and indirect visual inspections when using visual inspection for the determination of whether a product can meet the requirements (for such items as the surface conditions, the alignment of matching surfaces and the shapes of a workpi-ece).

The visual inspection of the rouge remediation effect includes two parts, the inspection of the pipe wall cleanness and the visual inspection of the rouge remediation effect. The pipe wall cleanness inspection is mainly used to assess the efficacy of the de-greasing and cleaning procedures before rouge remediation (pickling) to verify whether the cleanness of the internal wall of the pipe to be treated can meet the relevant specifications. According to the ASTM specifications, after the de-greasing and the cleaning of a clean pipe, there should be no residual greases, dusts, abrasive grain or other chips inside the pipe. The purpose of a visual inspection for rogue remediation efficacy is to verify the removal of rouge from the internal wall of a pipe or a pipe fitting through visual inspections. According to the ASME BPE in the US, the class Ⅰ and class Ⅱ rouge in a clean pipeline can often be removed, while the class Ⅲ rouge that is usually found in pure steam systems is difficult to be removed by the usual chemical cleaning methods. Therefore, the visual inspections on the rouge remediation efficacy for different clean process pipelines should be different based on the different classes of rouge within the pipeline.

Visual inspections should be performed under a certain illumination, including environmental illumination and supplementary illumination. It is recommended in the ASTM specifications that the illumination for visual inspection should be at least 100 footcandle (1076 lx) and it is recommended to be at least 250 footcandle (2690 lx) for the optimal inspection of a surface. If the clean pipeline is installed in a clean room with white light illumination, the pipes and fittings that can be disassembled or opened, such as valves, clamp connected Tees, temperature probes and storage tank manhole covers, can be inspected under the room illumination. The pipeline internal walls generally cannot be inspected under the room illumination because the pipe diameters are rather small (the nominal diameter is usually no more than 150 mm). In such a case, an external light source (such as a torch) is required to facilitate the inspection of the internal parts of the pipeline that cannot be accessed or difficult to observe. Care should be taken to avoid the bright dazzling at the surface to be inspected when placing such supporting light sources.

The visual inspection of the pipe wall cleanness is mainly used to check whether there are any visible particulate contaminants and whether there are any hydrophobic surface contaminants on the internal wall of the pipe to be inspected. When inspecting whether there are any residual particulate contaminants on the pipe internal wall after de-greasing and cleaning, such physical inspection methods as white gloves (or filter paper, clean white cloth, etc.) can be used to verify the results. When this inspection method is used, the inspection can be performed both when the surface is still wet and when it has been dried after the pipe and fittings have been washed. The internal wall of the pipe or fitting to be inspected is swabbed with a certain force with white gloves, filter paper or clean cloth to identify whether there are any color residues or stains on the swabbing surface. If there is any of the materials describe above on the swabbing surface, it indicates that the cleaning efficacy is not acceptable. If no significant visible stains are identified on the swabbing surface, the visual inspection is passed. It needs to be pointed out that, if the visual inspection method cannot be used to verify the cleaning efficacy after completing the de-greasing and cleaning of the pipes and fittings, a water break test should be performed to see whether there are any colorless and transparent hydrophobic residual contaminants on the pipe wall. If the water is continuous without break, it means that there are no hydrophobic surface contaminants.

Because the visual inspection methods is convenient, rapid, effective and with a low cost and a certain level of validation credibility, visual inspections are generally used as the major method for the verification

of the pipe surface cleanness after the pipes and fittings to be passivated are de-greased and washed before rouge remediation and passivation. The de-greasing and cleaning before rouge remediation and passivation can effectively remove any organic soils or bio-films attached on the pipes and fittings. During the cleaning process, the turbulence generated by the cleaning solution provides the mechanical scouring force to remove the soils and particles, making the rouge directly exposed on the stainless steel pipe wall, which is very significant for the smooth and successful rouge remediation and passivation process.

The visual inspection on the rouge remediation efficacy can also be aided with white gloves. If any residual rouge is observed on the pipe wall, it indicates that the pickling and passivation effect is not satisfactory. If the swabbing material can remove the residual rouge, the subsequent treatment decisions for the pipes and fittings to be treated should be made based on the color and the properties of the rouge and the amount that can be swabbed away. If through the visual inspection it is found that there is any residual rouge on the pipe wall, and the rouge cannot be removed by the swabbing material, it can be suspected that it is the class Ⅲ rouge that is difficult to remove by the routine chemical methods. The specifications in such regulations as the ASME BPE and ASTM regulation requirements explain the tolerance and the acceptance criteria for the clean pipeline on class Ⅲ rouge. Generally the acceptable rouge remediation criteria are: the pipe wall surface should be homogeneous silver in color, bright, clean, without any significant corrosion marks, without any significant oxidation tint at the welding seams or heat affected areas, without any welding oxidation slag that can be shed at the welding seams and the surrounding areas, and without any spots that are inhomogeneous in color on the pipe wall.

b. Industrial endoscope inspection. The industrial endoscope inspection is a type of non-destructive visual inspection. The most obvious difference between the industrial endoscope inspection and other non-destructive inspections is that it can directly reveal the conditions on the internal surface of the item to be inspected without the need of data comparison or the judgment of whether there is a defect based on the skills and the experience of an inspector. And along with the inspection, an industrial endoscope can provide the video or photo records of the entire dynamic inspection process, perform the quantitative analysis on the identified defects, and measure such data as the length and the area of the defects.

Currently, industrial endoscope inspections have been widely used in various industries. They are involved in such area as mechanical, chemical, pharmaceutical, automobile, aviation, railway engineering vehicle and transportation vehicle development and manufacturing, and maintenance, and even in such engineering and construction processes as the construction of bridges and tunnels. And they can also be used for maintenance and repair activities.

Based on the material, endoscopes can be divided into hard pipe endoscopes and soft pipe endoscopes, or hard endoscopes and soft endoscopes. A hard endoscope is composed of three major parts, the image transmission device, the illumination device and the air vent. The image transmission device is composed of the object lens, the relay system and the ocular lens. The illumination device uses a type of cold light source and light-guide fibers are used. The air vent is used to transfer air, water and as biopsy forceps. The endoscopes that use fibre-optic bundles to transmit images and light or use CCD to transmit images are soft endoscopes. Because of their excellent flexibility and convenient operation performances, soft endoscopes can be handily used to access areas that hard endoscopes cannot. With a bending device at the head, it can also eliminate any blind areas.

Based on the imaging form, industrial endoscopes can be divided into optical endoscopes, optical fiber endoscopes and electronic endoscopes (Fig 10.18). Optical endoscopes transmit the images of the internal parts of the item to be inspected through light transmission to the eyes of the inspector without any distortions. The most outstanding features of this type of endoscopes are that the images have a high fidelity and sharpness. The imaging form of optical fiber endoscopes is similar to those of optical endoscopes. The characteristic of optical fiber endoscopes is that they have rather thin light guiding soft tubes that can access narrow spaces. The fiber bundle used to transmit images is the core part of an optical fiber endoscope. The fiber bundle is composed of tens of thousands of very thin glass fibers. According to the complete light reflection principle, there must be a layer of membrane with a low refractive index outside all the glass fibers to ensure that all the light transmitted by all the internal fibers can be completed reflected. The light transmitted by a single fiber

can only generate a light spot. If we want to obtain an image, a large amount of fibers must be integrated into a bundle. If we want to obtain the same image at the other end of the bundle, each of the fibers must be at the same position at the two ends. This type of bundle is called an image guide bundle. If any of the image guide bundle fibers is broken, there will be a black spot on the image. The positions of a light guide bundle at the two ends do not need to be the same. If many of the light guide bundles are broken, the luminance will be significantly decreased. The working principle of an electronic endoscope is that the image obtained from the object lens is transmitted to the CCD and the CCD turns the light image into electronic signals, then the data are transmitted to the video endoscope control group, and the control group exports the image to a monitor or computer. The CCD solid-state image device is called a CCD image sensor, which is the core component of an electronic endoscope. Its structure is composed of many photosensitive diodes arranged on a silicon base. They are used to replace the image guide bundles in transmitting the image signals. And the signals are converted to video signals at the image processing center. Although the structure of an electronic endoscope is basically the same as a fiber endoscope, and can be simply considered as using the CCD to replace the image guide bundles, an electronic endoscope has many functions that are beyond the capability of an optic fiber endoscope.

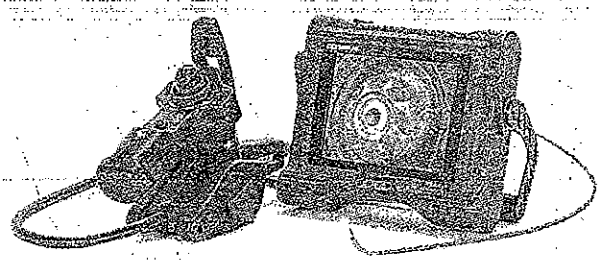


Fig 10.18 Electronic video endoscope

The selection of the type of the device to be used depends on the specific conditions of the item to be inspected. Endoscopes with straight rods are convenient to use, durable and with good imaging effects. This type of endoscopes can be used for products with a detection range of less than 500 mm. They are mainly applicable to straight holes. Electronic endoscopes have powerful functions and are highly flexible, reliable and with a wide range of application. Their advantages are especially obvious for products with a complicated internal structure, or when quantitative tests or comparative analysis are required. However, the dimensions of the CCD chip on the probe cannot be made smaller because of the restrictions in the manufacturing technology, so it is difficult to make the probe diameter less than 4 mm. By contrast, the probe of an optic endoscope can be made very thin. So this type of endoscope is mainly used for the detection of areas with a diameter of less than 4 mm and difficult to access by other endoscopes. However, optic fiber endoscopes can be easily damaged, their service life is short and the image sharpness is not satisfactory enough. The imaging effect and the bending property are far inferior to the video endoscopes. So, electronic video endoscopes are preferred as the major inspection devices for equipment with a small diameter, a long pipe or a complicated internal structure. Table 10.9 list the comparison of the three common types of industrial endoscopes.

The pharmaceutical equipment and pipelines have very strict regulatory requirements on the cleanness, the welding seams and the surface roughness and surface finish of the internal wall surfaces. The internal structure of pharmaceutical equipment is very complicated, and the internal walls of the pipes cannot be inspected through the routine visual inspections, which increase the difficulty in the quality control of the pharmaceutical equipment and clean pipelines of the pharmaceutical industry. Industrial endoscopes can satisfactorily solve the above problems. Some of the leading pharmaceutical clean equipment and pipeline installation contractors in China have realized the importance of industrial endoscopes for the control of engineering quality. They started one after another to invest in purchasing advanced electronic video endoscopes to assist the quality control staff in more accurately and effectively control the quality.

Industrial endoscopes also play a very important role in such areas as the cleaning, rouge remediation and passivation of clean pipelines. This is because due to its excellent image transmission capability an endoscope can provide a panoramic view in the narrow and dark pipelines. The rouge conditions on the internal surface of a pipeline can be directly and accurately presented to the inspectors and the customers through the imaging unit of an endoscope. With the accurate presentation of the conditions on the internal wall of a pipeline to the technicians, it can help them work out the most suitable rouge remediation plan for that pipeline based on the information transferred by the endoscope to achieve the optimal rouge remediation and passivation efficacy.

Table 10.9 Comparison of operation performances of three types of industrial endoscopes

	Optical Direct rod endoscopes	Optical fiber endoscopes	Electronic video endoscopes
Structural features	Simple	Simple	Complicated
Functions	Less	Less	More
Curvature	Not bendable	Bendable	Bendable
Imaging effects	Good	With honeycomb effect restricted by the number of optic fibers	Good
Imaging principle	Optical imaging	Optical imaging	CCD digital imaging
Image signals	Optical signals	Optical signals	Electronic signals
Image transmission media	Glass lens	Flexible light guide fibers	Wires
Robustness	Good	Poor	Acceptable
Lens replacement	Cannot be replaced	Can be replaced	Interchangeable among multiple lenses
Visual angle	Generally from 0° to 90°	0°	0° to 90°
Minimum probe diameter	≤1mm	≤1mm	≥4mm
Probe length	Generally short, less than 500 mm. Some can have multiple rods connected together, with a length that can reach 10 m	Rather long, generally from 1 to 2 m	Very long, can be 20 m
Probe durability	Acceptable	Poor	Very good
Measurement functions	Not possible	Not possible	The measurement probe can be used to measure the length and the depth
Image storage and processing	Imaging acquisition system added later	Imaging acquisition system can be added later	Image storage and processing can be done directly
Product price	Low	High	Very high

When inspecting rouge in a pharmaceutical clean equipment pipeline, the characteristics of the internal structure of the item to be inspected, the specific inspection areas, and their locations should be understood first. The relevant instruments should be prepared according to the corresponding procedures, and it should be verified that the power supply and the grounding are reliable and the instruments are at a safe and stable place. Then appropriate probes, lenses and channels for entering the equipment or pipeline to be inspected should be selected. Before the inspection, any obstacles and objects that may damage the probe should be clearly understood. It should be noted that, when inspecting such difficult to inspect equipment pipelines as the distillation columns of a water still, the heat exchanger of a WFI/PW system, and the small diameter pipes of a pure steam system, the risk of the probe of the endoscope being jammed by some unknown structures in the equipment pipeline to be inspected, making it impossible to be withdrawn should be assessed. When inspecting in these structures it should be ensured that the probe can successfully reach the designated place. If the probe encounters any resistance during the insertion process, the insertion should be stopped immediately and the probe should be withdrawn. The probe should be withdrawn slowly. It should be pulled gently when it is jammed to avoid damaging the inspected item and the endoscope probe. In addition, for those items whose internal structures cannot be known or are very complicated, care should be taken to allow the lens to be positioned directly towards the area to be inspected as much as possible. Generally speaking, the movement speed of the endoscope probe within a smooth pipeline should be no more than 50 mm/s, and no more than 10 mm/s in a pipeline with the above structures. It should be ensured that the image is stable and easy to observe. When scanning a large area, the linear scanning method should be used and the scanning

width should be no more than 20 mm each time and the observation range of the probe should not be exceeded.

For the cleaning, rouge remediation and passivation of a pharmaceutical clean pipeline, the system (equipment) to be cleaned should be assessed for the class and the severity of the rouge through certain measures before and after the cleaning, so that the customer can understand the degree of corrosion of the system pipeline and have a direct comparison of the cleanness within the pipeline before and after the rouge remediation and passivation.

In a pharmaceutical enterprise, such equipment and pipelines as the WFI systems, the pure steam systems and the heat exchangers are areas severely afflicted by rouge. The rouge in the WFI pipelines is mainly class Ⅱ rouge, and the mixture of class Ⅱ rouge and class Ⅲ rouge is often observed in the pure steam systems and the heat exchangers. Before cleaning and rouge remediation, an endoscope should be used to inspect the rouge in the pipelines of the WFI system, including such components as the storage tank of the WFI system, the chamber of the circulation pump of the system, the outlet of the circulation pump, and the external surfaces and the internal chambers of the (cold) points of use and the spray balls. All these components are high risk areas for rouge of the WFI system. The volume of a WFI storage tank is often rather large. When the WFI system is running, the level in the storage tank is usually maintained at 30% to 80%. When the level exceeds 80%, the automation system will send an order to the water still to stop generating water. So a considerable part of the space in the storage tank is connected to the atmosphere through the vent filter, which provides an environment with sufficient oxygen for possible redox reactions within the tank. And the wetting of the tank internal wall by the spray ball of the storage tank can directly provide an environment with sufficient water for the redox reaction. The temperature of the water in the WFI storage tank is generally rather high. So, comparatively speaking, the passivation membrane of the storage tank internal wall has more chances of being corroded under the oxidation environment than that in the pipeline. The rouge on the tank wall resulted from the oxidation corrosion is often not even due to uneven coverage of the spray ball; which is difficult to be determined because of changes in pressure.

Because most of the PW or WFI distribution pipelines are located within the technical layer, and the pipelines of the distribution loop are usually welded together by pipes of 6 meters long, the length of the probe of an industrial endoscope cannot be used to inspect the entire distribution loop. So the inspection of the WFI points of use can help the cleaning personnel and the customer to get an overall idea about the internal conditions of the entire distribution loop. And endoscope can be used to inspect the pipe internal wall, the welding seams, the clamp connection joints, and the pressure or temperature sensors that can be referenced or compared for the points of use at WFI U tubes. As described in the previous chapter, the welding seams and the clamp connection joints are all typical high risk areas for rouge. The comparison of the images of these parts before and after rouge remediation and passivation can directly present the cleaning and rouge remediation effects of the system.

The *ASME BPE* (2014) specifies the recommended treatment time for rouge remediation based on different agents. The rouges are different in different enterprises. If the rouge problem is minor, the treatment time can be shorter. The pipeline can be corroded if the time is too long, thus reducing the service life and increase the potential risks. If the rouge problem is major, the rouge remediation difficulty will be increased and the treatment time is usually longer. So during the rouge remediation process, using data to verify the rouge remediation end point is a reasonable method to determine the reaction time. At present, one of the more accurate validation methods used in this industry is the on line iron ions test. In this method the iron ions produced in the reaction between acids and oxides reacts with a type of color developing agent through complexation, and the iron ions concentration can be quantitatively determined according to the Lambert-

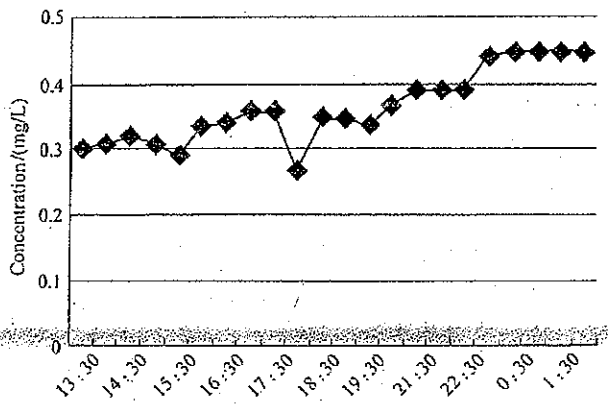


Fig 10.19 Iron ion concentration trend example

Beer's law. With the development of the reaction, the amount of ferric oxides reduces gradually, the amount of soluble ferric salts or iron ions increase gradually, until the concentration becomes constant, which is the accurate rouge remediation end point (Fig 10. 19).

10. 3 Rouge Remediation Quality Control

A project is a series of independent, complex and interlinked activities, which have a clear target or purpose, and needs to be completed within the specified time, budget, and resource limits and according to specified regulations. Generally speaking, the project parameters include the product scope, quality, cost, items to be tested and resources. The execution of a rouge remediation project, is the process during which a thorough, specific and clear plan is made for the target requirements, the scope of activities, the methods, and the procedures, and this plan is executed with the expectation to achieve the planned purpose. Establishing a thorough rouge remediation protocol is the prerequisite for the successful implementation of the project. The implementation protocol of a rouge remediation project is a critical control measure for the rouge remediation quality. A systematic and specific protocol describing the target effects of the project, the procedures during the early, middle and late phases of the project and the various parameters will be used to guide the smooth and successful completion of the rouge remediation project.

10. 3. 1 Rouge Remediation and Re-passivation Project

A rouge remediation and re-passivation project for a pharmaceutical water system is a relatively simple project with a short life cycle and a small scale. However, because the production systems of a pharmaceutical enterprise will be stopped when a rouge remediation and re-passivation project is executed, and a pharmaceutical enterprise has strict requirements on the time limits of the idling period, and the subjects of a rouge remediation and re-passivation project are the cleaning pipelines and equipment of a pharmaceutical water system, which has very strict and precise control procedures for each section of the treatment process and acceptance testing process, the complexity of a rouge remediation and re-passivation project is obvious. So a strict and thorough project execution protocol is the prerequisite for the success of a rouge remediation and re-passivation project. The project execution project has a specific protocol based on the specific project characteristics. It is unique and special. However, a project execution protocol is also universal in some senses. Generally speaking, a project execution protocol includes the plan for the organization structure (the structure, the responsibilities and the inter-relationship of each of the functional departments), the plan for the personnel (project responsible person, the department responsible persons, and the principal responsible persons), the technical plan (the schedule, the plan for the critical technologies, and the plan of the critical execution steps), the safety plan (the overall safety requirements, the construction risk factor analysis, the safety measures, the safety plan for the major construction steps; etc.), the plan for the material supply [the material supply procedures, the reception and inspection procedures, the provisional (emergent) material procurement procedures, etc.]. An implementation protocol for a rouge remediation and re-passivation project is also prepared and executed based on the design principles of common project implementation protocols described above.

The organization of a rouge remediation and re-passivation project mainly includes a project responsible person (project manager), a project technical team, a project safety and quality control team, and a construction team. The project responsible person should be responsible for the normal operation of the entire project life cycle, the project plan, the progress, the development of the implementation protocol, and the coordination of the internal and external affairs during the middle and the late phases of the project. The project technical responsible team leader should be responsible for the preparation of the technical protocol and the schedule of the project and provide technical support during the project execution process. The project safety and quality responsible team leader should be responsible for the construction safety training and supervision, and the inspection and control of the project execution quality. The construction responsible team leader should be responsible for the specific execution activities of the various phases of a rouge remediation and re-passivation project, and reasonably allocate resources and construction workers based on the schedule requirements. Because a rouge remediation and re-passivation project is small in scale, it may not

be feasible to construct a project team office and warehouse at the site. So the construction team leader should also be responsible for the machines and equipment (mainly cleaning equipment) and the materials (mainly the chemical agents for cleaning, rouge remediation and passivation) required for the execution of the project. Generally speaking, the management of the cleaning equipment and chemical agents for rouge remediation mainly involves the safety aspect. So the project safety team leader often is also responsible for the management of the equipment and the materials, and a dedicated construction person is designated to be responsible for the specific management activities.

There are just a few types of activities. They are mainly the cleaning, rouge remediation and passivation of the clean stainless steel pipes and equipment. So the technical protocol of a rouge remediation and re-passivation project should mainly include the cleaning technology plan, the rouge remediation technology plan and the passivation technology plan for the system to be treated. The project safety team leader should establish the relevant safe construction plans based on the specific processes and the selected agents specified in the technical plans for each of the treatment steps of the project. At the same time, a detailed material supply plan should be established after discussing with the procurement department of the company based on the predicted required amount and the inventory of the selected chemical agents, as well as such detailed information as the properties, the prices and the storage conditions.

10.3.2 Design of the Technical Plan

A reasonable schedule and appropriate human resources, the supervision and the guidance strictly following a safety and quality management system, the satisfactory operations of the required equipment, the timely supply of materials are required for the successful completion and acceptance of a project. A rational and feasible technical protocol is the most important factor to ensure the successful completion of a project.

The early phase design of the technical implementation plan of a rouge remediation and re-passivation project for the clean pipelines and equipment of a pharmaceutical water system should be made considering the endoscopic rouge inspection report for the process system to be treated and the site investigations on the system. Generally, the following information needs to be referenced for the early phase design of the technical implementation plan of a rouge remediation and re-passivation project.

a. The type of rouge in the system to be treated. The type of rouge in the system can directly decide the agent to be selected for rouge remediation and passivation. If the rouge in the system is class Ⅰ rouge that can migrate, it can indicate that the system has not been put into use for a long period of time or the system operation environment does not have significant corrosive effects on stainless steel, so rouge remediation agents that are weakly acidic (such as citric acid) should be used. The rouge remediation is comparatively easy, and the requirements on the rouge remediation process parameters (such as the temperature, the agent concentration and the flow rate) are relatively lower. The remediation of class Ⅱ rouge is more difficult and the corresponding passivation procedures are more complicated. Rouge remediation agents and passivation agents with higher acidity (such as nitric acid, phosphoric acid and oxalic acid; oxalic acid is rather corrosive to stainless steel surfaces) should be selected. Because of the increase in the acidity, more effective protective measures (such as the addition of corrosion inhibitors) should be taken during the cleaning process for the stainless steel surfaces, and the requirements on the parameters of the rouge remediation and passivation process are also higher. For class Ⅲ rouge, the highly acidic hydrofluoric acid needs to be used for the rouge remediation, and after rouge remediation nitric acid or other passivation agents with equivalent effects must be used to passivate the system for a sufficiently long period of time. Class Ⅲ rouge is very difficult to remove, and after rouge remediation the surface roughness of the internal wall of the stainless steel pipeline will be adversely affected to different extents depending on the concentration of the hydrofluoric acid used and the cleaning process parameters.

b. The accumulation of rouge on the internal surface of a stainless steel pipe. When performing rouge inspection on the internal surface of a system pipeline through an endoscope, any rouge attached on the internal surface of the stainless steel pipeline can be observed directly. When there is only a small amount of rouge attached, the stainless steel surface will be slightly red or orange-yellow in color as observed in the endoscope video. The metal luster can still be seen. When the rouge is rather serious, the entire internal

surface of the pipeline can be covered by rouge as observed in the video and the metal luster almost cannot be seen. When the attached rouge has significantly affected the surface roughness of the stainless steel surface, biofilms, heaved rouge particles and even bubbles can be seen on the stainless steel surface. All these signs show that the surface roughness of the stainless steel surface has become far higher than the regulatory requirement. The different amount of rouge accumulated on the surface can affect the selection of the rouge remediation and passivation agent, and the agent concentration, the circulation speed and the temperature also need to be adjusted as appropriate.

c. System operations (including the system operation parameters and the sanitization method). The operations of the system directly determine the speed of rouge development and the severity of the rouge. For example, rouge can be observed earlier on the internal pipeline surface of a WFI system that is running at a higher temperature (generally above 85 ℃) than that of a PW system that is running at a lower temperature (generally below 40 ℃). The rouge observed in a WFI system is class Ⅱ rouge in most of the cases and class Ⅱ rouge can only be observed in a PW system that runs at a higher temperature and for a long period of time. A pure steam system generally runs at a temperature of more than 100 ℃, and condensate can often be formed on the internal surface of the pipeline. A high temperature environment with water and dissolved oxygen are the prerequisites for the formation of class Ⅲ rouge, which is very difficult to remove. In addition, the different sanitization or sterilization methods used for the system can also cause differences in the type of rouge and the degree of corrosion in the system. Pasteurization is a type of high temperature sanitization. During the sanitization or sterilization process, it is very easy for rouge to develop in the high temperature environment with water on the pipeline surface. Ozone sterilization is selected for the storage units of some systems. And with the long time attachment of a water film on the internal tank surface and the insufficient coverage of the spray balls, the rouge on the internal tank surface can be more severe than that on the internal pipeline surface.

d. System type. Different types of rouges can be identified in different types of systems because of the differences in the operation parameters, the operation modes, the functions, the system volume and the operation duration. So the selection of the rouge remediation and passivation methods can be diverse. Both a WFI storage and distribution system and a PW storage and distribution system are closed circulated systems with their own storage units and circulation units. When cleaning this type of circulated systems, it is acceptable not to use any external driving systems for the flowing cleaning of the system. So the overall technical scheme can be relatively simpler. The efforts only need to be concentrated on the identification of the rouge class and the selection of a highly effective rouge remediation agent. A WFI system is usually equipped with a heat exchanger, so it is not necessary to consider how the process temperature can be maintained sufficiently high for the cleaning and rouge remediation process for a WFI system. While a pure steam system is a non-circulated unidirectional distribution system. When performing the rouge remediation and re-passivation of such a system, it can be much more complicated than the case for a PW or WFI system. The cleaning method, i. e. circulated or soaking, should be selected based on the rouge class and severity within the system. If it needs to be circulated, a large amount of external pipes are required to be connected to the system to allow the circulation. And a rational and feasible external driving system is used to meet the technical requirements for the circulation of part or all of the system and ensure the rouge remediation and re-passivation effects. Additionally, the special valve arrangement of a CIP system and the complex process flows and system components of various types of formulation systems can all make the specific designs of the rouge remediation and re-passivation scheme very complicated and diversified.

10.3.3 Execution Prerequisites

The development of the technical protocol for the rouge remediation and re-passivation of the clean pipelines of a pharmaceutical water system provides the clear and specific technical guidance for a successful rouge remediation and re-passivation project. And the smooth and successful execution of a rouge remediation and re-passivation project depends, besides a rational and feasible protocol, on whether the necessary site conditions for the commencement of the rouge remediation and re-passivation activities are available. Generally speaking, the prerequisites for the execution of a rouge remediation and re-passivation project include the

system conditions and the site conditions. The system conditions can be viewed as the software and the hardware of the rouge remediation and re-passivation service provider. It should be verified whether the system conditions can meet the expected requirements from the customer on the rouge remediation and re-passivation effects. Specifically speaking, the software requirements include the professional degree of the service provider team in the rouge remediation and re-passivation business, their experience in executing rouge remediation and re-passivation projects, the professional quality and familiarity of their members with this type of projects, and whether the process quality control documentation system provided by the supplier can meet the regulatory and user requirements. The hardware conditions mainly mean the functions, the efficiency and the various technical parameters of the rouge remediation and re-passivation equipment. They should be verified to see whether they can meet the rouge remediation and re-passivation requirements, whether the technical pipes and fittings of the supplier can ensure that the cleaning, rouge remediation and re-passivation of the system to be treated can be carried out following the design concepts specified in the technical execution protocol, whether the rouge inspection equipment provided by the supplier can help the company and the supplier to get a direct understanding of the rouge and select an effective rouge remediation method based on the information obtained, and whether the various monitoring equipment and instruments and the relevant protocols used for the rouge remediation and re-passivation process can meet the process quality control criteria. A rich reservation of the software capacity and the hardware equipment of a company are important factors that can represent the emphasis of the company on the rouges of a pharmaceutical process system and their remediation. It shows that the company takes the domestic and international standards and regulations as the criteria it must follow and is doing all its best to promote the advancement of the industry.

Generally speaking, the major procedures for the execution of a rouge remediation and re-passivation project include the site verification of the overall conditions of the system pipeline to be treated, the isolation and the connection of external pipelines of the system to be treated, air tightness test of the system to be treated, water tightness test of the system to be treated, pre-cleaning treatment of the system to be treated, de-greasing cleaning of the system to be treated, rouge remediation of the system to be treated, passivation of the system to be treated, rinsing of the system to be treated, acceptance testing of the rouge remediation and passivation effects, recovery of the system after treatment The above procedures are the generally recommended procedures for the cleaning, rouge remediation and re-passivation activities for the clean pipelines and the equipment of a pharmaceutical water system. The above procedures can be changed or combined for a specific rouge remediation project based on the contract requirements, the technical process, the reagent efficacy and the site conditions. Among these procedures, the isolation and the connection of the system to be treated, the static water pressure test, the cleaning procedures, the rouge remediation and passivation procedures and the rinsing procedures are necessary procedures, i. e. the major procedures. The introduction of other procedures can facilitate the final rouge remediation and re-passivation efficacy for the internal stainless steel surfaces, i. e., they are the supporting procedures.

a. Isolation and connection of external pipelines. The first step of a rouge remediation and re-passivation project is to isolate the system to be treated from the original system or the systems connected to it. After the technical engineers of the project have investigated the overall conditions of the system pipelines at the site, the cleaning and rouge remediation scope should be identified according to the contract to confirm the areas to be cleaned. If the system to be treated for rouge remediation and re-passivation is a part of an integrate process, the system to be treated should be isolated by disassembling it at the connections (such as clamp or flange connections) or by closing the connections at the relevant connecting points (such as closing the relevant valves). If the system to be treated is an integrate process system, it should be isolated by disassembling or closing any connecting points to any other systems. It should be noted that, when isolating the system, all the precision on line monitoring and measurement instruments and other components that are not corrosion resistant, such as conductivity probes, TOC sensors, UV lamps and storage tank vent filters, should be removed from the system.

After it has been verified that the system isolation activities have been completed, the isolated system can be temporarily connected according to the cleaning

mode (circulated or soaking) specified in the technical protocol to allow the expected operation mode for cleaning, rouge remediation and re-passivation. Additional pipes and fittings and other components are required for the temporary connection of the isolated system. The stainless steel parts of these additional components should be made of 304 stainless steel and above and the non-metal parts should be made of materials conforming to ASME BPE and ASTM requirements.

b. Air tightness and water tightness test. After the system to be treated has been isolated and connected as specified in the technical execution protocol, theoretically the connected system should be closed and contained in order to allow the cleaning, rouge remediation and passivation activities. In order to verify the sealing performances of the system to be treated, usually a water tightness test will be performed. This is the so called "leak test". For the leak test, the pressure of static water on the internal wall of the pipeline is used to test the water tightness of the water distribution loop to check whether there are any leakages or small holes. Before the water tightness test of the system to be treated is performed, the system should be verified again to see whether there is any obvious leaking point. The pressure gauges to be used for the pressurization test should be calibrated and within their respective due dates. And the precision should be no less than grade 1.5. The range of the pressure gauges should be no less than the maximum operation pressure of the system. The procedures for a water tightness test are generally as described below. Fill the isolated system with water, and continue filling water into the filled system pipeline to increase the pressure, and maintain the pressure for a certain period of time after the pressure has reached that specified in the protocol. If there is a significant dropping of the pressure indicated by the pressure gauge within the specified time limit during the pressure maintenance period, it indicates that the system is with significant leaking points. If the pressure indicated by the pressure gauge does not change significantly within the specified time limit, it indicates that the system to be treated is closed and the cleaning cycle can be started.

If the conditions allow, an air tightness test should be performed for the isolated system before the water tightness test. For the air tightness test, the pressure of air introduced to the system on the internal wall of the pipeline is used to test the air tightness of the water distribution loop to check whether there are any leakages or small holes. The advantage in performing an air tightness test first for the system to be treated is that if any obvious leaking points are identified during the test, the pressure within the pipeline can be released through exhaust. The pressure release through the exhaust valve is faster and more convenient than that in a water pressure test and the re-pressurization time is significantly shorter than that required for re-pressurization with water. It is generally more difficult to maintain the pressure for the air tightness test than for the water tightness test under the same pressure. If the more convenient and faster air tightness test has been passed, the subsequent water tightness test can be completed smoothly. However, it should be noted that there is a safety concern about the air tightness test, especially that personnel injuries may result when releasing the system pressure. So the pressure release valve should be opened slowly for releasing the pressure. It is strictly forbidden to rapidly open a closed valve.

c. Alkaline washing procedures. The cleaning procedures can be started after the sealing performances of the system to be treated have been verified. The cleaning of stainless steel pipelines usually include degreasing and normal cleaning. Alkaline solutions, emulsion, solvents or cleaning agents, or their combinations are mainly used to soak, scrub or rinse the pipeline or equipment surfaces. Alkaline solutions are usually used as the cleaning agents for the degreasing of the clean stainless steel pipelines of the pharmaceutical industry. The saponification and emulsification effects of hot alkaline solutions are used for greases. The saponification is used to remove the greases that can be saponified and emulsification with surfactants is used to remove the greases that cannot be saponified. The commonly used basic cleaning agents include sodium hydroxide solutions, potassium hydroxide solutions, and some formulated cleaning agents prepared with basic solutions, surfactants and EDTA in certain proportions. In order to ensure the cleaning effects, heating is usually required for basic cleaning procedures to facilitate the removal of grease soils by the basic solutions. The time and the basic solution concentration for basic washing are generally determined based on the degree of corrosion of the system to be treated. According to the recommendations from the ASME BPE, the concentration of the basic solution, taking sodium

hydroxide solution as an example, should not exceed 2% (mass-fraction). The washing time should be no more than 1 hour when the washing is performed with circulation at an elevated temperature.

After the basic washing is completed, all the basic solution must be removed from the system. It must be neutralized to a pH value of 6.5 to 7.5 before discharging. Unless it is clearly specified in the material safety data sheet of the reagent selected that neutralization is not necessary, the basic solution must be neutralized before discharge. During the neutralization process, attention should be paid to the temperature of the basic solution. It is not recommended to perform the neutralization when the temperature is too high. Only after the temperature of the basic solution has been reduced to the appropriate range for neutralization (it is recommended to be below 50 ℃), can the neutralization be performed with a type of acidic neutralizer (such as dilute nitric acid and citric acid) that is widely used and with relatively smaller risks.

After completing the basic solution neutralization and discharging activities, the system pipeline should be rinsed in a timely manner to remove any residual basic solution on the pipe walls. Deionized water of better should be used as the rinse water. There are many methods for verifying that a pipeline is rinsed clean without any residual basic solutions. The combination of the water break test and the visual inspection is usually used for the inspection of the cleaning effect of the pipeline. It is worth mentioning that, before performing the basic washing of the system, the pre-rinsing of the pipeline can rinse away any possible soils loosely attached on the pipe wall. And the pre-rinsing cycle can be considered as a "practical drill" for the major cleaning, rouge remediation and passivation cycle. It can verify the reasonability of the system re-connection in the technical execution protocol before chemical cleaning to help the project execution operators make timely adjustments to the protocol.

d. Rouge remediation procedures. The rouge remediation procedures are the core procedures for the rouge remediation and re-passivation project for the clean pipeline of a pharmaceutical water system. The rouge remediation effects can directly affect the evaluation of the rouge remediation and re-passivation effects by the customer. Rouge remediation is the removal of heavy, tightly adherent oxide films resulting from hot-forming, heat treatment, welding and other high temperature operations. The chemical reagents usually used for the rouge remediation for the pipelines and the equipment of pharmaceutical water systems include phosphorous acid, nitric acid, nitric acid/hydrofluoric acid water solutions, such organic acids as citric acid and oxalic acid, and various formulated reagents. The concentration of the various reagents and the process operation temperature need to be determined considering the type and the severity of the rouges in the system. The specific information has been introduced in the early parts of this book and will not be repeated here. As recommended in the relevant sections of the ASTM regulations, rouge remediation can be accomplished by ①wetting the surfaces by swabbing or spraying; or ②partially filling the item with the pickling solution and rotating or rocking to slosh the solution so that all surfaces receive the required chemical treatment (the commonly used methods include circulated cleaning). The surface should be kept in contact with the agitated solution for the design duration or until inspection shows that complete rouge remediation has been accomplished. Without agitation (such as soaking), additional exposure time to the pickling solution may be required. If rocking or rotation is difficult to achieve, the pickling solution may be circulated through the item or system until inspection shows that the rouge remediation has been accomplished.

After completing rouge remediation, the acidic rouge remediation waste solution should be neutralized before discharge. Any acidic rouge remediation reagents must be neutralized before discharge until the pH of the waste solution is between 6.5 and 7.5. When neutralizing the acidic waste solution, industry level sodium hydroxide can be used as the neutralizer. After adding water to dissolve the sodium hydroxide, mix the obtained solution with the acidic waste solution slowly and evenly. It is strictly forbidden to directly pour the sodium hydroxide solution into the acidic waste solution at a relatively higher temperature. After neutralizing the waste solution, the neutralized solution should be discharged at the specified location according to the site rules and the local regulations.

e. Passivation procedures. The re-passivation of the stainless steel pipelines of the system to be treated is the final target for a rouge remediation and re-passivation project. It is an important aspect of the project quality. The ASTM A380—06 specifies that passivation is the process of the natural formation of a layer of in-

active chemical surface on a stainless steel surface exposed to the air or an oxygen containing environment. The industry once believed that oxidation is an essential step for the formation of a passivation film. However, it is now generally considered in the industry that the passivation film can be formed naturally in an oxygen containing environment once thorough cleaning and rouge remediation have been achieved on a stainless steel surface. The passivation process described in this book is a process of chemical treatment of stainless steel with such mild oxidization agents as nitric acid or citric acid solutions to promote the natural formation of a protective passivation film. Going through all the cleaning and the rouge remediation steps is essential for the passivation in a rouge remediation and re-passivation project; the natural passivation cycle is rather long.

Although the acidic rouge remediation reagents and the passivation reagents used in the rouge remediation process and the passivation process for a stainless steel surface are similar, the actions of the same acidic reagent in the rouge remediation process are different from those in the passivation process. During the rouge remediation process, the action of the acidic reagent is to react with the metal elements in the rouge (mainly the various types of iron oxides and chromium nickel compounds) attached on the stainless steel surface to remove the metal elements in various free states from the pipeline. In the passivation process the strong oxidative acidic reagent is used to contact the stainless steel surface to induce the oxidization reaction and then form the inactive chemical protective layer that is rich in chromium oxides. The commonly used passivation reagents include inorganic acids (such as concentrate nitric acid), organic acids (such as citric acid), chelating agents and some special formulated reagents (such as the mixtures of phosphorous acid, citric acid and surfactants). When some special formulated reagents and their dedicated processes are used, rouge remediation and passivation can be achieved in one step.

10.4 Rouge Remediation Case Study

Based on the years of rouge remediation experience of the author, the uses of a basic cleaning reagent, CIP 100, and an acidic cleaning reagent, CIP 200, for the water generation, storage and distribution systems of pharmaceutical water systems and pure steam distribution loops are summarized below.

10.4.1 Water Generation Systems

Compared with the rouge remediation and passivation of a storage and distribution loop or a single distribution system, the rouge remediation and passivation of such large pieces of equipment as multi-effect stills or pure steam generators are more difficult. For a multi-effect still, the heat energy of plant steam is used to evaporate the supply water (usually PW) multiple times to generate WFI conforming to the quality requirements from a pharmaceutical enterprise. During this process, the entire system is at a high temperature environment. In addition, the internal structures of the distillation columns are very complicated. The clean fluid exists in both gas and liquid phases within the column. Under such a highly corrosive environment, it is very easy for class Ⅱ and class Ⅲ rouges to develop on the stainless steel surfaces within the distillation columns.

The multi-effect still is the starting point of a WFI system. And WFI systems are vital for a pharmaceutical enterprise. So if there is a very severe rouge problem at the beginning of the WFI system, it will be very difficult to avoid the risk of rouge corrosion in the WFI system and the subsequent Traditional Chinese Medicine production processes. So the periodic rouge remediation and passivation of the multi-effect still should be considered as an important task in the maintenance plan by the engineering and technology innovation departments of a pharmaceutical enterprise.

Because the process design and the internal structures are very complicated, it is recommended that the relevant maintenance activities should be performed by professional rouge remediation and passivation service execution teams for the multi-effect still. Before starting the cleaning, rouge remediation and passivation activities, relevant small or non-corrosion resistant components should be disassembled. And they should be marked correspondingly and carefully stored to prevent any small parts from being lost. Then the pipelines of the multi-effect still should be temporarily disassembled and re-connected with modifications to meet the requirements for the execution of the rouge remediation and re-passivation protocol for the multi-effect still. When carrying out the rouge remediation and passivation activities for a multi-effect still, generally the cleaning can be performed in the order of the various effects of distillation columns, the pipelines and other components. Because the internal structures of a multi-effect

still are very complicated, it is recommended to use special formulated rouge remediation and passivation reagents that are easy to rinse. If a basic cleaning reagent, such as sodium hydroxide, and acidic rouge remediation and passivation reagents, such as nitric acid and citric acid, are used, the cleaning waste solution can be very difficult to be completely rinsed out of the equipment, resulting in adverse effects on the rouge remediation and passivation process.

A pure steam generator has similar working principles to those of a single effect distillation column of a multi-effect still. The cleaning process of a multi-effect still can be used for the cleaning, and the pure steam generator can be considered as the shell and the pipelines and other components of a single effect distillation column for rouge remediation and passivation. The procedures will not be described again here.

10.4.2 Pharmaceutical Water Distribution Systems

Because a WFI storage and distribution system generally has circulation pumps and heat exchangers, it is comparatively easy to perform the rouge remediation and re-passivation project for a WFI system. And the rouges are usually mainly class Ⅱ rouges. So the cleaning and rouge remediation effects can be generally satisfactory and clean surfaces can be provided for the subsequent passivation steps.

a. Centrifuge impellers. Fig 10.20 shows the endoscopic images of the internal chamber of the centrifuge pump of the WFI distribution system of a large volume parenteral manufacturer before and after rouge remediation. The comparison of the images obviously shows that the centrifuge pump impellers are completely covered with class Ⅱ rouges before rouge remediation and the attached rouges have been completely removed, the metal luster of the stainless steel impellers has been recovered after effective pickling, rouge remediation and passivation. The rouge remediation effects are very satisfactory.

b. User point loops. Fig 10.21 shows the endoscopic images of the internal walls of the user point pipelines of the WFI storage and distribution system of an API facility of a pharmaceutical enterprise before

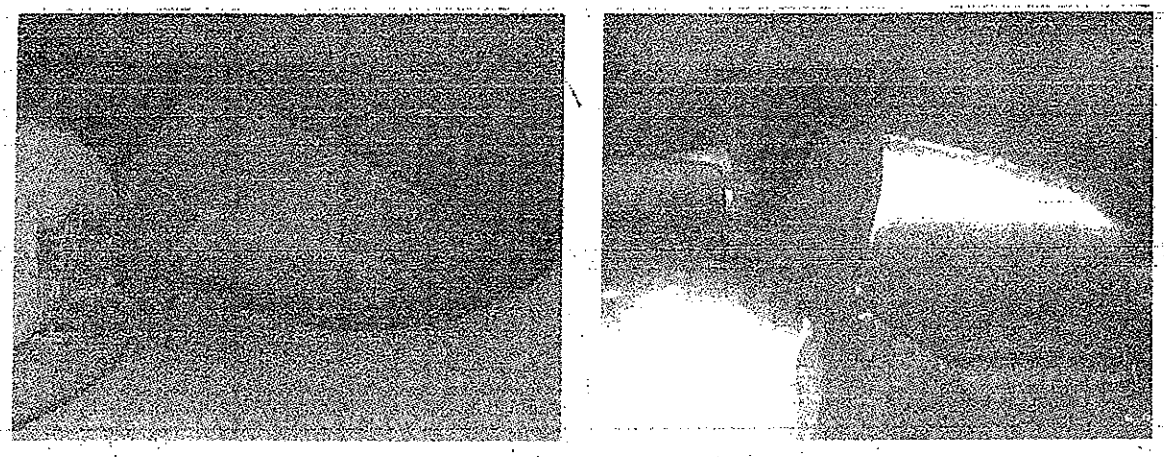


Fig 10.20 Centrifuge pump chamber rouge remediation effects (water system) (see the color pages behind)

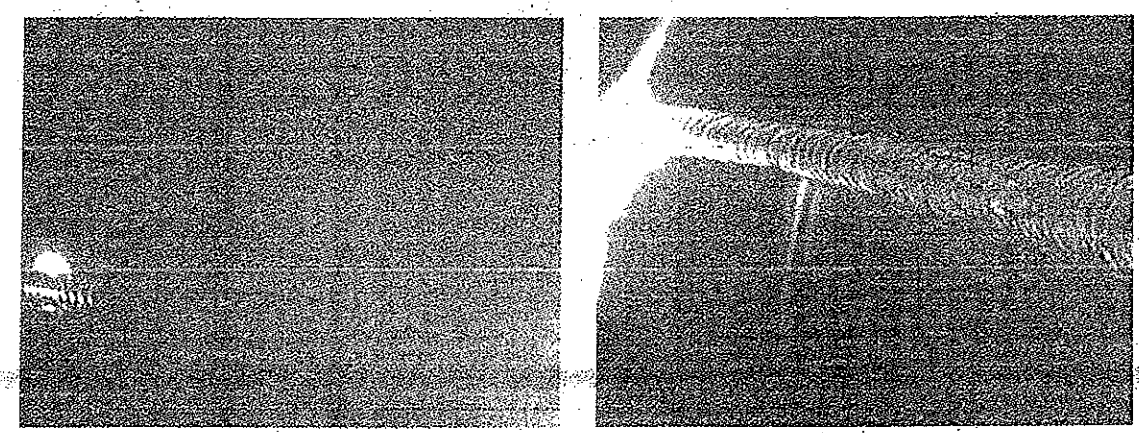


Fig 10.21 User point loop rouge remediation effects (API facility) (see the color pages behind)

and after rouge remediation. Before the cleaning and rouge remediation activities for the pipelines were performed, the welding seams, the heat affected areas and the entire internal wall of the pipeline were covered with rouges. There are more severe rouges at the welding seams and the heat affected areas, which is because the butted areas of the pipelines were welded when the system pipelines were installed and weld pools were formed at high temperature before the welding seams were formed. The weld pools were cooled and re-solidified from the molten state within a short period of time. The micro-structures of the welding seam areas underwent a melting and re-crystallization process. Because the cooling was very rapid, the crystalline grains did not have sufficient time to develop, the original austenite structures were damaged and a type of new and loose micro-structure was formed, causing the significant reduction of the corrosion resistance capability of the welding areas and the heat affected areas. Comparing the images we can see that after the rouge remediation and re-passivation processes for the WFI system, the rouges on the welding seams have been completely washed away, there are no obvious attached rouges at the heat affected areas, and the entire pipeline surface has recovered the original metal luster.

Fig 10.22 shows the endoscopic images of the internal walls of the user point pipelines of the WFI storage and distribution system of a blood product facility of a pharmaceutical enterprise before and after rouge remediation. The endoscopic images show that the entire internal wall of the WFI user point pipeline were covered with rouge and the accumulation of rouge colloidal particles can be seen on the pipe wall at some local areas. This imposed high risks to the quality of the final products, because the accumulated rouge particles on the stainless steel surface are very easily drop into the WFI circulation flow, can decompose to free ferric under the impact from the WFI at a high flow rate. If a very small amount of the fine particles go through the final filter, they will be introduced into the final product, causing serious product quality failures. Huge losses can result. It should also be noted in the images that the gaps at the mechanical connections of the pipelines are also high risk areas for rouge. This is because there is a very thin water film in the very small gaps between the cross section of the pipes and the gaskets. In the environment with dissolved oxygen, there will be a galvanic battery reaction between the internal stainless steel wall covered by the water film and the stainless steel matrix, resulting in damages to the passivation film on the stainless steel surface, thus causing the development of rouge at some local areas. At the same time, the rouges will be closely attached to the pipe seal gaskets because of electrostatic attraction, as shown on the images before rouge remediation. After sufficient rouge remediation and re-passivation for the user point pipelines, the rouges have been effectively removed from the pipeline internal walls and the gaskets. This indicates that when there is rather severe accumulation of rouges within a WFI system, the rouge remediation and re-passivation of the system in a timely manner by a professional team can effectively solve such severe rouge corrosion problems. This case also shows that when the rouges develop to a certain level in a WFI system, the product quality will face extremely high risks. So the periodic rouge remediation and re-passivation of the system has great significance for a pharmaceutical enterprise.

c. Diaphragm valve diaphragms. Fig 10.23 shows the comparative images of the diaphragm valve diaphragms at the user points of a WFI storage and distri-

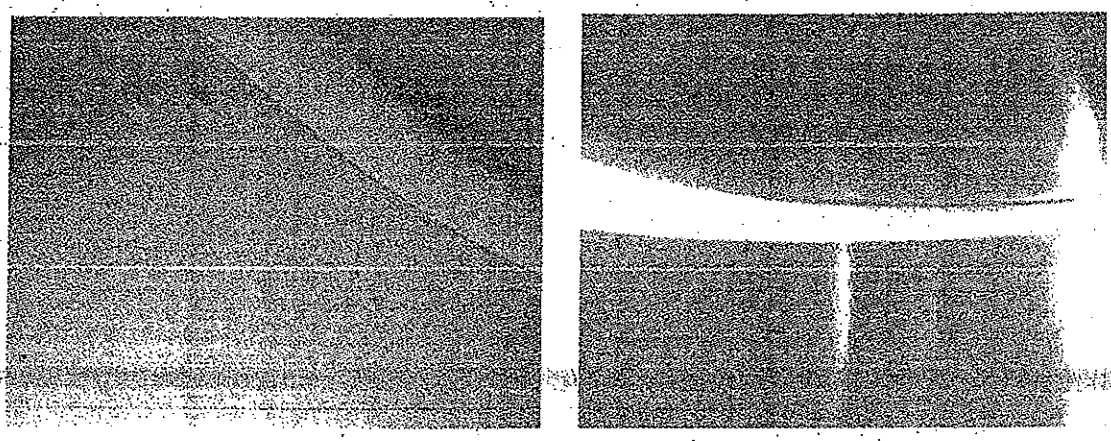


Fig 10.22 User point loop rouge remediation effects (blood product facility) (see the color pages behind)

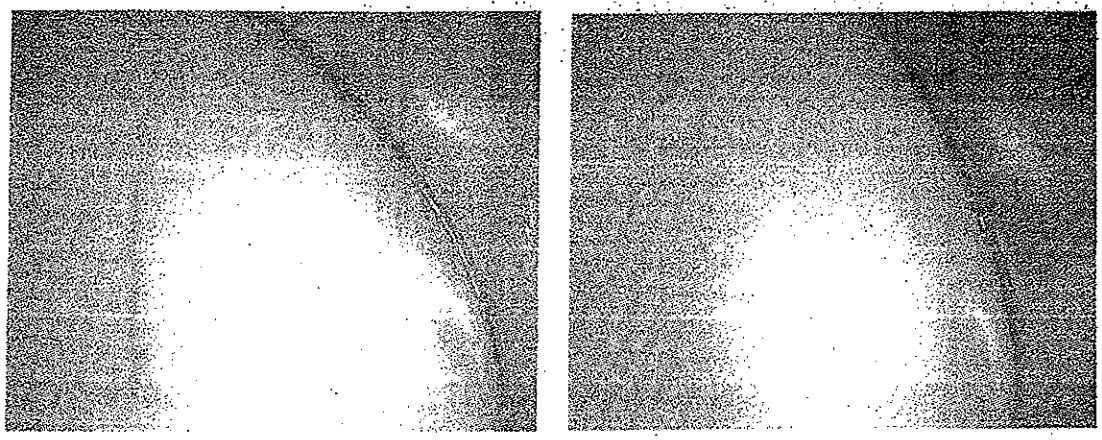


Fig 10.23 Diaphragm valve diaphragm rouge remediation images (see the color pages behind)

bution system of a Traditional Chinese Medicine Facility of a pharmaceutical enterprise before and after rouge remediation and re-passivation. Rouge remediation and re-passivation have never been performed for this WFI system. So there are rouges attached even to the diaphragm valve diaphragms. It is easier for the rouges on the diaphragm valve diaphragms to migrate than for those attached on stainless steel pipe surfaces. If the user point is connected to a piece of product related process equipment, it is highly possible that the rouges migrate to the equipment together with the WFI, come into direct contact with the product, and cause disastrous consequences. It is worth noticing that the material of a diaphragm is usually poly tetra fluoro ethylene (PTFE). The routine rouge remediation reagents are usually unable to effectively wash away the rouges attached on the diaphragms during the circulated cleaning cycles of the system. So many pharmaceutical enterprises would disassemble the diaphragms from the system when rouges are observed on the diaphragms and such measures as manual swabbing would be used to remove the rouges on the diaphragm surfaces by strong mechanical forces. This method is both time and energy consuming. Some professional formulated rouge remediation reagents can effectively remove the rouges attached on the diaphragms while the stainless steel pipelines are washed in circulation. During the cleaning and the maintenance of the WFI system of the above pharmaceutical enterprises, the rouge remediation service provider used a type of professional formulated rouge remediation reagent to carry out the rouge remediation for the system pipelines and the diaphragm valve diaphragms at the same time. From the images we can see that the rouges on the diaphragm valve diaphragms have been completely removed. The internal surface of the diaphragm valve chamber also shows metal luster. This shows the continuous development of the rouge remediation services in the pharmaceutical industry through technical innovations.

d. Heat exchangers. Heat exchangers are important parts of a WFI storage and distribution system. The heat exchanging capacity can directly affect the stability of the operation temperature of the WFI system. However, because of the complex internal structures of the equipment and the uneven distribution of the temperature gradients, it is easier for rouges to develop within a heat exchanger than in the circulation pipeline. So there are usually more severe rouges within a heat exchanger than in the system pipelines. Fig 10.24 shows the comparative images of the heat exchangers of a WFI system of a pharmaceutical enterprise before and after rouge remediation. The internal walls of the water distribution chambers of the pipelines within the heat exchanger shown in the drawing are covered with rouges. The rouges are scarlet in color and are severe class Ⅱ rouges. Severe rouge attachments can also be observed on the pipe internal walls. Because the diameters of the pipes are small, the surface roughness of the internal walls can be significantly affected if severe rouges are developed on the internal walls and even pipe blockages can result, which can greatly affect the heat exchange efficiency of the heat exchanger and hinder the normal running of the WFI system. Through the comparison of the images it can be intuitively seen that after the rouge remediation and passivation of the heat exchanger, the internal stainless steel surfaces of the water distribution chambers are shinny and without any attached rouges. And the rouges within the pipelines are also effectively removed. This to some extent ensures and even improves the heat exchange efficiency of the heat ex-

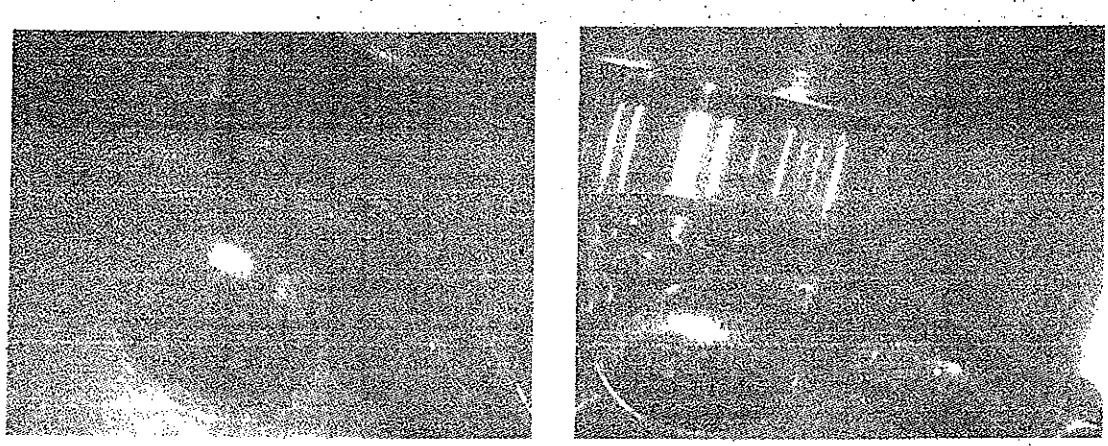


Fig 10.24 Heat exchanger rouge remediation images (see the color pages behind)

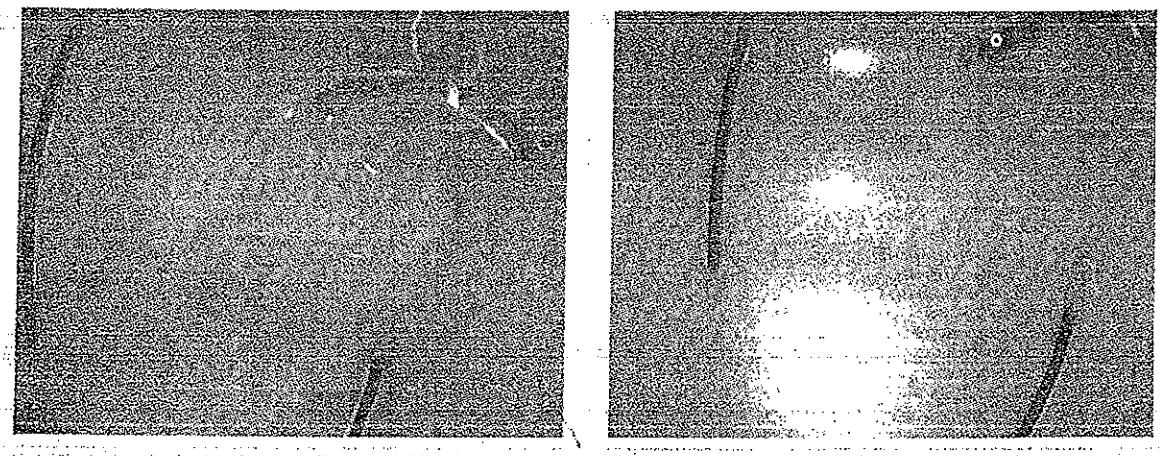


Fig 10.25 Sprayer rouge remediation images (see the color pages behind)

changer. From this we can see that the rouge remediation and passivation services can provide significant economic benefits to the production facility and the enterprise that cannot be ignored.

e. Sprayers. The formation and the development of rouges within the spray balls of a storage tank are very complicated because of the uneven distribution of the pressure gradient and the long term humid and hot environment within the storage tank. The corrosion at a spray ball body is more severe than that in any other parts of the WFI system because the spray ball is under pressure for a long period of time. Its surface roughness can also be adversely affected to some extent, which can affect the spraying efficacy and result in severe overall corrosion of the WFI storage unit including the storage tank. Fig 10.25 shows images of the rouges on the tangent spray balls of the WFI storage and distribution system of a large multinational pharmaceutical enterprise and the rouge remediation effects. In the images obtained by endoscope before rouge remediation we can see that there are rather severe rouges within the spray balls and the surface finish of the internal surface has been damaged to some extent. There are some rouges developed because of local galvanic corrosion around the spraying nozzles. The overall corrosion of the spray ball is rather severe. After rouge remediation and re-passivation, it can be seen that the rouges on the internal stainless steel surfaces of the spray ball have been completely removed. There is no visible adherence of rouges on the internal walls around the spraying nozzle and the surrounding areas. The overall cleaning effects are satisfactory. However, the surface roughness of the stainless steel surfaces has been greatly degraded because of the stress corrosion or other factors. This is a type of irreversible destructive corrosion. Such severe surface damages cannot be recovered by such stainless steel surface restoration methods as chemical rouge remediation and re-passivation.

10.4.3 Pure Steam Distribution Systems

Different from the WFI system, the pure steam system is a single direction non-circulated system. The system operation temperature is usually very high. Different amounts of condensate can exist in the pipeline

of a pure steam system according to the different process design concepts. These characteristics make the pure steam system very vulnerable to the generation of corrosion products that are very common in a high temperature oxidation environment, class Ⅲ rouges. Because the composition of class Ⅲ rouge is very complicated and includes Fe oxides with ferroferric oxide as the major component, nickel chrome oxides and complicated carbide, no effective cleaning reagents have been developed for class Ⅲ rouges in the metal corrosion study area up to now. Soaking is the traditional method for the cleaning and rouge remediation for a pure steam distribution system because the system itself cannot be circulated. When soaking the system with the reagent solution, the reagent can only react with such substances attached on the pipeline surface as the rouge Fe oxides, using the chemical properties of the reagent solution. The rouge remediation mechanism is complex and the dissolved rouge cannot be sufficiently removed from the system. And the rouges of the system are mainly the difficult to remove class Ⅲ rouges. So the rouge remediation for a pure steam system has always been a difficult task for rouge remediation technologies. An external pipeline can be connected to temporarily change the pure steam system into a completely circulated or partially circulated loop, for the circulation of the rouge remediation reagent solution within the pure steam system. This allows the rouge remediation reagent solution to fully take its effect and at the same time the significant mechanical scouring action of the turbulent flow of the reagent solution can effectively take the free iron dissolved in the solution out of the system so that the original clean status of the system can be restored to provide a good and clean surface for the subsequent passivation treatment.

a. Soaking method. Fig 10. 26 shows a comparison of the endoscopic images of the pure steam distribution system of the formulation facility of a pharmaceutical company in China before and after passivation using the soaking method. The images were taken from the outlet pipeline of the pure steam generator of the pure steam system. From the images we can see that there are significant rouges at the welding seams and the heat affected areas of the pipeline. A layer of saffron yellow rouge is attached at the welding seam, which is suspected to be class Ⅱ rouge. The entire internal pipeline surface is also covered with rouge and the rouge is dark violet in color. This is typical class Ⅲ rouge in a pure steam system. The pure steam system is treated by a professional rouge remediation service team. The soaking method is used for the washing, rouge remediation and re-passivation activities. After the rouge remediation and passivation activities have been completed, it was found through endoscopic inspection that the rouges have been completely removed and the welding seam is with shining metal luster. The surface layer of dark purple rouge at the heat affected area has disappeared. The base of the pipe wall shows dark red color. This is similar with the mechanism of formation of class Ⅲ rouges and passivation films. The only difference is that iron, instead of chromium, effused from the base to the surface. So class Ⅲ rouge is a type of corrosive oxidation film of multiple layers closed attached to the matrix. There are no significant changes in the original dark purple rouge layer. It is pointed out in ASME BPE that the rouges formed on a stainless steel surface that is satisfactorily treated are more difficult to be removed than those formed on a stainless steel surface that is not satisfactorily treated. This implies that the crystalline grains at the heat affected areas around the

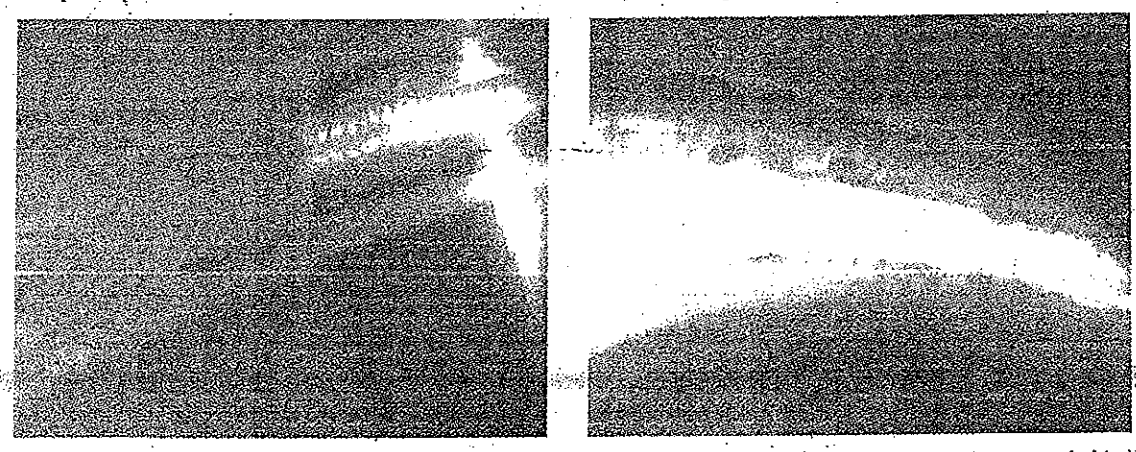


Fig 10. 26 Images of rouge remediation by the soaking method (pure steam system) (see the color pages behind)

welding seams of a pipeline have the tendency to grow further under the heat. However, the fast cooling process makes the density of the instable crystalline grain structure to decrease, so the crystalline structure at that area will no longer be that of austenite crystalline structure. The matrix of the rouges formed at this area has a far less dense structure than that of the pipeline surface. So it is comparatively easier to remove the rouges at this area. Generally speaking, the soaking method has certain rouge remediation effects. However, the rouge remediation effects are not very satisfactory.

b. Routine circulation method. Fig 10.27 shows a comparison of the endoscopic images of the pure steam distribution system of a pharmaceutical company before and after passivation using the circulation method. The images show the pure steam user point pipelines of the formulation room of a powder for injection production plant of a pharmaceutical company. From the images we can see that the internal surfaces of the user point pipelines have been completely covered by rouges. The rouges are dark red in color and are early phase class Ⅲ rouges. The areas severely affected by rouges are the heat affected areas around the welding seams and the pipe wall extensions areas. The rouges at these areas are dark in color and are more difficult to remove. When performing the rouge remediation and re-passivation for this pure steam system, the rouge remediation team used external sanitary flexible hoses to build locally circulated loops according to the distribution of the pure steam loop user points that can be in direct contact with the materials. Rouge remediation reagents with higher causticity as nitric acid and hydrofluoric acid are used for circulated cleaning and pickling. After the rouge remediation and re-passivation have been completed, it was found through endoscopic inspection that the rouges at the welding seam and the heat affected areas have been removed. However, the entire pipeline is without metal luster, the surface is rough at the heat affected areas, and there are obvious traces of corrosion. This is caused because the high causticity and penetrability of hydrofluoric acid eroded both the rouge layer and the stainless steel base. From this we can see that when the circulated method is used for the cleaning and rouge remediation of a non-circulated pure steam pipeline, the rouge remediation effects are significantly better than those by the soaking method. However, the rouge remediation reagents that can be selected for use are rather limited because class Ⅲ rouges are very difficult to be removed. The combination of nitric acid and hydrofluoric acid is often used by many rouge remediation service providers and engineering departments of pharmaceutical companies. The rouge remediation effect can be assured when this type of combination is used with circulation. However, this combination can also corrode the stainless steel surface, which is no less than the rouge corrosion. And if the combination proportion or the cleaning parameters are not selected properly, it can also cause severe damages to the surface roughness of the stainless steel pipelines. If the surface roughness is too high, it will be very difficult for the compact passivation layer to be formed on the stainless steel surface and the risk of accumulation of microbes will also be very high. So the rouge remediation effect achieved by highly corrosive acidic reagents for class Ⅲ rouges can only be temporary. Rouges will come back soon and there is a very high quality risk of out of specification microbial parameters.

c. Whole loop circulation method. Fig 10.28 shows a comparison of the images for the rouge remediation of a pure steam distribution system of a foreign-owned pharmaceutical enterprise. This pharmaceutical enterprise asked the rouge remediation service provider

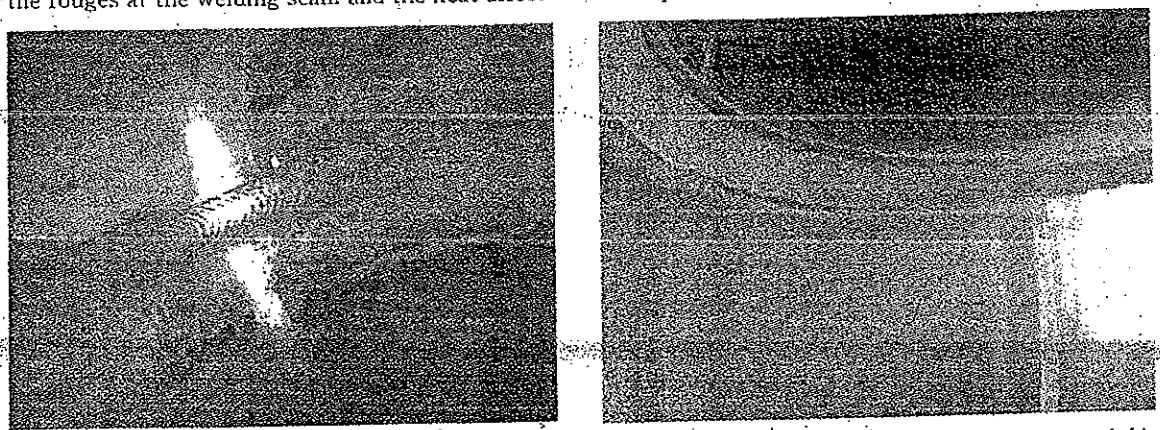


Fig 10.27 Images of rouge remediation by the common circulation method (pure steam system) (see the color pages behind)

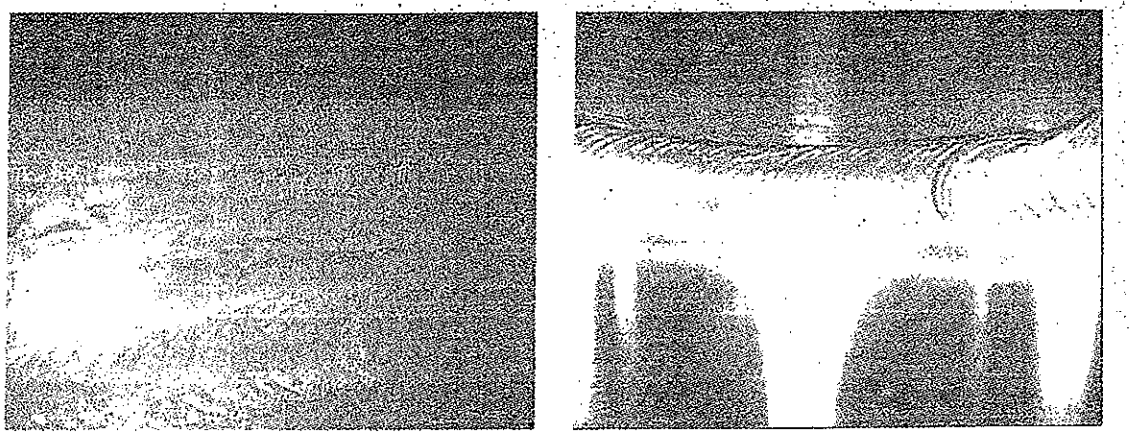


Fig 10.28 Images of rouge remediation using the whole loop circulation method (pure steam system) (see the color pages behind)

to perform the rouge remediation activities using the whole loop circulation method for the pure steam distribution system. The whole loop circulation is a rather complicated small project for a pure steam distribution system. This requires that the rouge remediation service team should have rather high professional skills, a thorough understanding of the system at the site, a sufficient reserve of multiple materials and a strong execution capability. After the system is modified and reconnected through various types of pipes and fittings, the whole pure steam distribution system can be recirculated. The system was recirculated for washing, rouge remediation and re-passivation. The reagents used were special formulated basic cleaning reagents and acidic rouge remediation and passivation reagents. The figure above shows the images before and after rouge remediation of the reference parts at the outlet of the pure steam generator. From the images it can be clearly seen that there were rather severe class Ⅲ rouges inside the pipes at the outlet of the pure steam generator before the rouge remediation. After the circulated cleaning and rouge remediation, it can be seen from the image at the right side that all the rouges attached on the pipe wall have been substantially removed and the pipe wall shows metal luster, except for some irreversible material degradation at the local heat affected areas. Compared with the method using the combination of nitric acid and hydrofluoric acid used in the example above, the special formulated rouge remediation reagents achieved a significantly better rouge remediation effect during the rouge remediation process than those achieved by the above described highly corrosive acidic rouge remediation reagents. This shows that the rouge remediation mechanisms of special formulated rouge remediation reagents are fundamentally different from those using the high acidity and the high penetrability of highly corrosive acids. At the same time, the recovery of the metal luster indicates that after the cleaning and the rouge remediation with special formulated reagents, the pipe wall was thoroughly and effectively cleaned, which provided a very good environment for the re-passivation by special formulated reagents.

From the analysis of the above rouge remediation and re-passivation cases for pure steam distribution systems, it can be seen that the circulated method is far better than the soaking method for the rouge remediation and re-passivation of pure steam distribution systems. This is because when a fluid flows in a pipeline in a turbulent flow, a very strong scouring force can be generated onto the pipe wall surface, which can timely remove any of the rouge iron ions dissolved by the chemical effect of the rouge remediation reagent away from the reaction site, and ensure that the iron ions will be kept in a free state without resettling onto the surface throughout the flowing process. And the reagents in a turbulent flow can also be attached onto the surface of the rouge corrosion layer by mechanical force, which can exert a type of physical decomposition effect. With partial or whole distribution loop circulation of a pure steam distribution system, the use of highly efficient special formulated rouge remediation reagents can achieve far better rouge remediation and re-passivation effects than those achieved by such highly corrosive acidic rouge remediation reagents as the combination of nitric acid and hydrofluoric acid. The targeted enveloping action of special formulated reagents on Fe, the major element in rouge, and the promotion of the development of the chromium rich layer on a stainless steel surface are much better than the ordinary rouge remediation reagents.

10.5 Rouge Prevention

Pharmaceutical water systems are major sites for the development of rouges. The development of rouges can be caused by adverse factors during any phases of the life cycle of the system. So interventions at the design phase, the construction phase and the operation phase of a pharmaceutical water system can facilitate the prevention of rouges.

10.5.1 Prevention during Design Phase

The core design concepts for clean fluid process systems include three aspects, Quality by Design, particulate contamination prevention and microbial contamination prevention. Any deviation in a pharmaceutical water system can be traced back to an inappropriate design, an installation error or a "microbial contamination" or "particulate contamination" resulted from improper operations. For example, the development of rouge can cause particulate contamination of the system.

The development of rouges in a clean fluid system depends to a large extent on the design. The development of rouges can be greatly slowed down by a rational design of the clean fluid system. Rouges mainly occur within a piece of equipment under high temperatures. And the introduction of exogenous Fe ions is also a possible cause of the development of rouges. In order to slow down the development of rouges, high temperature environments and the introduction of exogenous Fe ions should be avoided from the design. In this book we are going to elaborate in detail how the development of rouges can be slowed down, and discuss design calculations, the operation temperature, the polish, the pH, the microbial contamination prevention measures, the particulate contamination prevention measures and the equipment selection.

a. Design calculation. The GMP requirement is that the operation capacity of a water system should not exceed its design capacity. There is a saying that Quality by Design is Design by Calculation. Calculation is one of the important steps for the design of a pharmaceutical water system. A set of reliable calculation methods for a pharmaceutical water system can provide the optional theoretical base and references for the selection of a pharmaceutical water equipment and system, and it can also ensure the rational design of the water system and ensure the slowing down of the rouge development rate from the source. The calculations includes the calculations of the capacity of the water generation equipment, the storage tank volume, the time of use at each of the user points of the plant, the peak flow and pressure, the loop length and diameter, the pump flow rate and lift, and the heat exchanger capacity.

First, for the water generation equipment, the storage tank volume, and the water consumption at each of the user points of the plant, should be calculated for optimization using an equipment selection software considering the total investment, to identify the best combination of these three parameters. Second, the pump flow rate and lift and the loop diameter should be calculated for optimization using a pharmaceutical water system pump and loop selection software based on the positions and the parameters of all the user points, the time of use of the user points, the peak flow rate and pressure, the operation temperature, the return water spraying ball opening pressure, the viscosity of the fluid, the loop length, the return flow rate, and the number of pipes and fittings.

A water system with an optimized design should ensure that the system has a turbulent flow to prevent the formation of bio-films and a positive pressure should be maintained within the system to prevent any siphoning that may contaminate the water quality. The requirements described above are the basic requirements for a pharmaceutical water system. In order to slow down the development of rouge within the system, it should be considered to avoid allowing the pumps to run at high lifts for long periods of time when optimizing the design of the pump capacity and the loop length. For a centrifuge pump, the high pressure and the pressure variations within the pump chamber can accelerate the corrosion of the metal by the small amount of oxygen dissolved in the water, which can cause the development of rouges. So the loop of a pharmaceutical water system should be kept as short as possible, the number of bends should be reduced to the minimum, the sequence of the user points should be reasonably arranged, the peak water consumption time should be arranged in an optimized way, the loop diameter and the return water flow rate should be reasonably selected, and the resistance within the loop of the water systems should be reduced as much as possible. The centrifuge pump should be operated through variable frequency converters. On one hand this can

save energy and on the other hand the pump supply capacity can be adjusted continuously and the changes can be slow, to avoid the pump running at a high lift for a long period of time.

For a water system, the cavitation of the circulation pump cannot be ignored, especially for a WFI system that is running at a high temperature. The very large instant impact force generated by cavitation, and the chemical corrosion of the metal by the small amount of dissolved oxygen in the water can cause black spots and cracks on the surfaces of the impellers and the pump shells after a period of time, which can result in the shedding of Fe ions and the subsequent development of rouges and contamination of the entire system. For the prevention of cavitation, the design of the pump suction pipe plays a critical role. The effective cavitation allowance of the pump suction pipeline should be at least 1.3 times of the cavitation allowed required by the pump. Otherwise, the pump will not be able to work properly. This is especially true for a high temperature WFI system using over-heated water for sterilization and a purified water system using pasteurization. Valves with lower resistances should be used for the valves before the pump. The valve diameter can be smaller than the pipe diameter, but no less than the pump inlet pipe diameter. The length of the pump inlet pipe should be reduced as much as possible and the number of bends should be reduced. The diameter should be 1 to 2 levels higher than the pump inlet pipe diameter to reduce the resistance. Cavitation can result at the pump suction system because of the accumulation of air. So no air traps should be formed within the suction pipe. During installation, eccentric reducers are often required because of the different diameters. The installation of reducers at the pump suction pipeline should be able to prevent the accumulation of non-condensable gases.

b. Water temperature settings. When designing a water system, microbial growth prevention measures are often considered. The microbial growth prevention measures used for a PW system include ozone sanitization, UV disinfection and low temperature storage (about 20 ℃). The microbial growth inhibition measures for a WFI system include the storage and operation at 70 ℃ and low temperature distribution and operation (below 15 ℃). No matter what type of microbial growth inhibition measures are used, the risk of particulate contamination caused by rouges should be considered during design.

Temperature is one of the important influencing factors for microbial growth. The microbial vegetation will stop growing when the temperature is above 60 ℃. Most of the pathogenic bacteria stop growing when the temperature reaches 50 to 60 ℃. Most thermophilic bacteria stop growing when the temperature reaches 73 ℃. When the temperature reaches 80 ℃, only spores and some extremely thermophilic bacteria can survive. So both the Chinese GMP and the EU GMP recommend that *"WFI can be circulated at a temperature of above* 70 ℃." For a PW system, it is generally recommended to use a lower temperature (such as 18 to 20 ℃) during the routine operation to inhibit the rapid growth of microbes. When discussing the development of rouges in the last chapter, it was mentioned that the lower the operation temperature of a pharmaceutical water system, the better we can postpone the development of rouges. For a WFI system circulated at a temperature of above 70 ℃, although it has very low risks

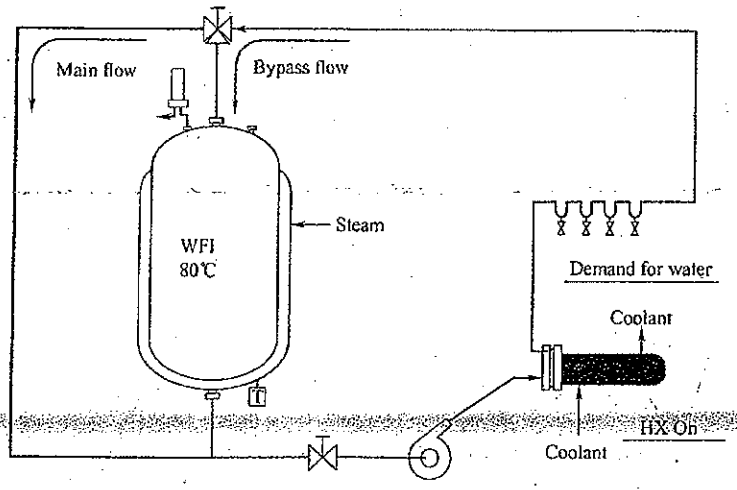


Fig 10.29 Working mode of hot storage and bypass cold circulation

of microbial contamination, the risk of rouge development is very high. When designing a WFI system, the operation temperature is often designed to be 80 to 85 ℃, and even as high as 90 ℃ in some cases. Reducing the design operation temperature while ensuring the compliance with the GMP requirements, can help slowing down the development of rouge.

At present, the design concept of high temperature storage and cold bypass circulation has been widely applied and promoted for WFI distribution systems (Fig 10.29). This type of systems eliminated the problem of sudden heating and cooling at the ambient temperature WFI user points. It has excellent performances in all such areas as the initial investment, energy saving, WFI utilization, microbial control and rouge inhibition.

c. pH value settings. The pH value is also called the hydrogen ion exponent. It indicates the degree of acidity and alkalinity, i.e. the negative log of the hydrogen concentration of a solution. pH is one of the most important parameters of water or water solutions.

The *Chinese Pharmacopoeia* (2015 Version) specifies that the pH of WFI should be 5 to 7. The lower the pH value, the higher the $[H^+]$ concentration. When the pH is less than 7, the speed of uniform corrosion, electrochemical corrosion, crevice corrosion and pitting corrosion of the stainless steel surfaces will be increased with the increase of the $[H^+]$ concentration in the water. After the passivation layer on the stainless steel surface is damaged, the oxygen in the water can slowly react with the iron released from the metal to form loose ferric oxides, i.e. rouges. So the pH value should be strictly controlled.

d. Finish level. The surface roughness of a stainless steel refers to the microscopic geometrical irregularities caused by small gaps, peaks and valleys on such processed surfaces as stainless steel pipe internal surfaces or equipment internal surfaces. Surface finish is another term for surface roughness. The surface roughness can significantly affect the performances of a pipeline or a piece of equipment. The corrosion resistance can also be significantly different. For a coarse internal surface, it is very easy for the fluid to penetrate through the passivation layer through the microscopic valleys on the surface to the metal layer, which can cause corrosion and the development of rouges. It can also cause the accumulation of microbes and the formation of a bio-film, which can not only speed up the corrosion of the pipeline but also contaminate the entire system.

In order to reduce the surface roughness of a stainless steel surface, it is generally required to polish it. ISPE recommends that the surface finish *Ra* should be no more than 0.76 μm for pharmaceutical water systems. The ASME BPE recommends that the surface finish *Ra* should be no more than 0.6 μm for the pipelines of pharmaceutical water systems and it also recommends electro-polishing should be used for WFI systems. For solution preparation tanks, electro-polishing is also recommended and the surface finish *Ra* is recommended to be less than 0.4 μm. Although electro-polishing can achieve better microbial control and corrosion resistance compared with the other two polishing methods, it is more expensive. An enterprise can select the appropriate method according to its own conditions.

Although better rouge prevention performances can be obtained using electro-polishing than using mechanical polishing, standard pipes need to be cut and welded during the installation phase, welding and passivation around the welding seams are more influential to the development of rouges. So how the welding and the pickling and passivation can be better performed is a critical problem every stainless steel pipe and fitting processing company faces.

e. Microbial contamination prevention. If there is any microbial contamination in a pharmaceutical water system or a solution preparation system, the sterilization or sanitization process needs to be repeated. And the sterilization or sanitization can promote the development of rouge within the system. So, microbial contamination should be prevented during the running of a pharmaceutical system or a solution preparation system, to prolong the sterilization or sanitization cycle of the entire system, thus slowing down the development of rouges. In some enterprises in certain countries, a strictly validated WFI storage and distribution system can be sterilized only once a year.

The microbial contaminations of a water system can be divided into exogenous microbial contaminations and endogenous microbial contaminations. The raw water is the most important source of exogenous microbial contaminations of a water system. The unit operations are the major sources of the endogenous microbial contaminations. After microbial contaminations

occur, the microbes can form colonies on the pipe walls, valves and other areas, and proliferate to form a bio-film. And the bio-film can become a continuous source of microbial contaminations. So, microbial contaminations should be prevented in the following areas during the design, selection, installation and operation phases of the entire water system.

• The system connections should meet the installation requirements specified in the ASME BPE. Sanitary connections should be used.

• Dual pipe design should be used at the outlet pipes of the PW storage tank to prevent any deadleg.

• No intermediate water tanks should be used for the PW generator or an intermediate tank with sanitization measures should be used.

• System deadleg should be strictly controlled.

• System slopes should be strictly controlled.

• The flow rate within the system must be strictly controlled. It should be calculated rationally to prevent any microbial growth because of a too low flow rate.

• The water temperature should be strictly controlled to avoid the temperature suitable for microbial reproduction.

• The surface finish should be strictly controlled for the components of the system to control microbial growth.

• Sanitization measures should be designed for the vent filters.

• Microbial inhibition measures should be included when designing the water system.

• Non-sanitary valves should be forbidden.

• The degree of automation should be improved. PAT should be used to analyze the data trends for alarms and actions.

• Filters, which can cause rapid microbial growth, should be forbidden in the system loop.

f. Particulate microbial contamination. Because the water storage and distribution system does not have a purification function, once there is a particulate contamination, the system needs to be cleaned and sanitized (sterilized) again. So the following areas should be considered for particulate contamination prevention during the design, selection, installation and operation of the entire water system.

• Materials and system components with reliable quality should be used to avoid failure of meeting the design quality requirements.

• A positive pressure should be strictly maintained within the system and calculations should be performed rationally to prevent any back suction at the user point loop.

• It is forbidden to install any filters in the main loop of a water system to prevent any external contamination caused by a broken filter element.

• Deadleg should be strictly controlled to prevent any out of specification residues caused by failure of sufficient cleaning.

• The slopes should be strictly controlled to prevent any failure of self emptying of the system.

• The surface finish should be strictly controlled for the components of the system to prevent any out of specification residues.

• The cleaning and passivation procedures should be strictly executed.

• The welding operations should be controlled strictly to prevent any corrosion around the welding seams.

• The degree of automation should be improved to prevent any risks of contamination caused by manual operations.

• After system sanitization or sterilization, re-contamination of the system can be caused if any contaminated air is sucked into the system when the system is emptied.

g. Selection of equipment components. The equipment selection for a water system should meet the process requirements and the selected equipment and components should have reliable quality to prevent the introduction of any particulate contamination or microbial contamination.

Spray balls are usually installed at the top of a tank to ensure that the entire tank internal surface is kept wet during the entire self cleaning process, and ensure a uniform temperature throughout the system during pasteurization or over heated water sterilization. The spray balls usually used in a water system include rotary spray balls and fixed spray balls. Compared with fixed spray balls, rotary spray balls can save cleaning water and can ensure 360° spraying thanks to the water lubricating effect. However, for rouges, no dry friction should be allowed at the rotary spray balls. Otherwise iron can be shed into the water and form rouges. In a solution preparation system, the clean gas inlet to the tank should be kept away from a rotary spray ball to prevent any dry friction at the spray ball

when it is rotating rapidly forced by the high pressure gas.

The tank instrument connections can usually be divided into two types, clamp connections and NA connections. When clamp connections are used, and the installation position is below the liquid surface, a deadleg will be created, which can hinder the flow of the fluid within and the cleaning of the connections and microbial growth can be easily caused. So NA clamp connections are recommended. The NA clamp connection is a new type of connector for tanks. It can achieve the deadleg free connection of auxiliaries to a tank and can effectively eliminate any risks of microbial growth at the connections.

A centrifuge pump is the source of power for the running of an entire water system and it is also an area often affected by rouge. The design of the centrifuge pump must meet the production process requirements, must not contaminate the pharmaceutical water system, should have a self-draining port at the bottom of the pump shell, and it should also be ensured that there are no volumetric air gaps at the upper part of the pump chamber. In order to slow down the development of rouges within the pump chamber, it is recommended to electro-polish the internal wall of the pump chamber, the pump lift should be no more than 70 m, an inducer should be added at the pump inlet if the system is sterilized or sanitized at a high temperature, and internationally established brands should be selected if possible to ensure the quality of the centrifuge pump. A non-sanitary centrifuge should not be used.

A heat exchanger is used to maintain the water temperature and for the periodic sanitization and sterilization of the system. So it is also a high risk area for rouge development. The *Inspection Guide for High Purity Water* of the US FDA suggests that double plate heat exchangers or heat exchangers with a higher pressure at the clean side than that at the non-clean side should always be used for pharmaceutical water systems. The double tube plate design is now considered mainstream for heat exchangers used in pharmaceutical water systems. For a heat exchanger with a double tube plate design, there are mainly two types of connections between the inner and outer tube plates, expansion and welding. At present most of the enterprises in China use expansion for the inner tube plate and welding for the outer tube plate. However, corrosion is likely to occur at the welding seam and the nearby areas on the outer tube plate, and this is the reason why heat exchangers are high risk areas for rouges. So in order to slow down the development of rouges, it is recommended that expansion joints should be used for both the inner tube plate and the outer tube plate for the heat exchangers. Such heat exchangers that cannot be self-emptied as single plate heat exchangers and double plate heat exchangers should not be used for pharmaceutical water systems.

An ozone generator is often used to generate ozone in a PW system that uses ozone for microbe inhibition or sanitization. There are ozone generators using water as the source material and ozone generators using gases as the source material. The first type of ozone generators use PW as the source material and generate ozone through electrolysis and the generated ozone is introduced into the water system in the form of a type of ozone water. The second class of ozone generators are further divided into those using air as the source material and those using oxygen as the source material. A discharge is used to turn the oxygen in the gases into ozone and the generated ozone is introduced into the water system through a jet aerator. From the point of view of particulate contamination prevention, particles can be carried in the ozone for an ozone generator using gases as the source material. And it cal also release some cancerogenic substances, so this type of ozone generator is not recommended.

The storage and distribution system of a water system does not have any water purification function. The particulates and the microbes of the feed water should meet the pharmacopoeia requirements. That is to say, the quality of the water generated by the water generator should meet the pharmacopoeia requirements. At present, the water generation systems on the market are of varying quality. Water generation systems of reliable and high quality that can be run stably should be selected to prevent any particulate contaminations and microbial contaminations of the storage and distribution system caused by the instable running of the water generation systems.

h. Design qualification. The Design Qualification is performed before the installation of the system/equipment. So the completeness and the quality of the Design Qualification have fundamental influences on the subsequent operation of the system/equipment. Taking a pharmaceutical water system as an example, the Design Qualification test items include:

• Design document review. To verify that all the design documents (URS, FDS, PID, calculation sheet, equipment list, instrumentation list, etc.) for the generation and distribution systems are integrate and approved. The test cases related to rouges include the verification of the URS requirements on the material of construction of the components in direct contact with the product, the verification of whether the materials listed in the mechanical component list are consistent with those specified in the URS, and the verification of whether any deadleg will be formed by the components listed in the mechanical component list.

• Generation system processing capacity review. To verify the selection of the generation system, the material balance calculation sheet, whether acceptable PW, WFI or pure steam can be generated with the supply water of certain quality, and whether the output can meet the requirements.

• Storage and distribution system circulation capacity review. To verify the technical parameters of the pumps and the calculation sheet of the distribution loop to see whether the requirements at the points of use for such parameters as the flow rate, pressure and temperature can be met, and whether the running of the distribution system can prevent any microbial growth. The rouge related test cases include the verification of whether cavitation can be easily caused at the selected pump, and whether a turbulent flow can be ensured by the system flow rate.

• Equipment and component review. To verify whether the structures and the materials of the equipment and components used in the generation and distribution systems can meet the GMP requirements. Examples of such requirements include whether the material and the surface roughness of the metal parts in direct contact with water can meet the URS requirements, whether the RO membrane can tolerate pasteurization, whether the vent filter of the storage tank is a hydrophobic filter, and whether the material of the valve gaskets can meet the GMP or FDA requirements.

• Instrument and component verification. To verify whether sanitary connections are used for the critical instruments of the generation and distribution systems, whether the material, precision and error can meet the URS and the GMP requirements, and whether calibration certificates and quality certificates can be provided upon delivery. The test cases related to rouges include the verification of whether clean connections are used for the connections of the instruments and components.

• Pipeline installation verification. To verify whether the material and the surface roughness of the pipeline of the generation and the distribution systems can meet the URS requirements, whether sanitary connections are used, whether the system slope can ensure the emptying of the system, whether there are any deadlegs, whether an inspection plan has been prepared for welding, and whether the steam trap of the pure steam distribution loop is acceptable. The test cases related to rouges include the verification of whether the material of construction and the surface roughness of the pipelines can meet the URS requirements, whether the steam trap design is acceptable (i. e. it is not easy to generate any condensate that can be accumulated within a pure steam system for a long period of time), and whether the system can be completely emptied (to prevent any corrosions cause by residues).

• Sanitization method verification. To verify the sanitization method used for the system, whether it can ensure the sanitization of the entire system, including the storage tank, the components and the pipeline, and how the sanitization effect is ensured. The test cases related to rouges include whether the sanitization frequency is too high, and whether the design sanitization temperature is too high.

• Control system verification. To verify whether the design of the control system can meet the URS requirements, such as whether the access control is reasonable, whether the critical parameters are with alarms, whether the system operation requirements can be realized through the automation system, and whether the critical data can be stored.

10.5.2 Prevention during Construction Phase

When installing a new pharmaceutical fluid system, the user should select a competent constructor with sufficient qualifications, experience with higher level construction and a good reputation in this industry. The supplier should be required to select the pipeline fittings and components following the relevant requirements. The user should perform the quantitative tests for the purchased materials on the material and such parameters as the construction elements or entrust a third party. For pharmaceutical fluid systems with dif-

ferent process requirements, the supplier should select mechanically polished or electrically polished stainless steel pipes based on the relevant requirements for the installation. During the installation process, the supplier should arrange welding operations with a competent team with high level welding skills and complete the equipment positioning and erection activities. Appropriate welding processes and parameters should be selected based on the pipe material and the environment at the site. The inflation protection time and the air consumption should be strictly controlled. The welding quality can directly affect the formation of rouge during system operation. If such parameters as the current and the inflation time are set inappropriately, such welding quality problems as welding misalignments, fusion failures and heavy temper can result. If these problems are not identified and rectified in time, rouge can develop around the welded area first during the running of the system. If welding seam oxidation occurs during the welding process and the oxidized welding seams are not cut from the system, iron oxides (rouge) can be left in the system. This means that the rouging process has been started before the system is put into use. The welding seam oxidation is a type of irreversible damage to the stainless steel pipeline. This type of welding quality deviation is not acceptable for clean pipeline installations. After installation, the new system should be cleaned, pickled and passivated in time and the records should be filed into the as-built documentation. For a renovation project on an existing pharmaceutical fluid process system, besides following the requirements described above when installing any newly added pipes, the supplier should also assess the rouge in the existing system and perform the necessary rouge remediation and passivation operations.

a. Material selection. For the production of biopharmaceuticals or other life science products, the optimal construction material for the fluid process pipeline components is 316L stainless steel (UNS S31603). This type of material usually contains about 65% to 70% iron (Fe). The 316L stainless steel can meet the requirements of almost all the authoritative manufacturing specifications and standards. It should be noted that now 316L stainless steel is widely used in the pipes and fittings of pharmaceutical fluid process systems. However, the composition can be somewhat different for the 316L stainless steel materials provided by different suppliers as a result of their different manufacturing processes and technical standards used. Table 10.10 summarizes the ranges of the compositions in 316L stainless steel. Almost all the compositions of the 316L stainless steel materials used in the pharmaceutical industry are listed in the table below.

Table 10.10 Comparison of chemical compositions of 316L stainless steel pipes

Element	Content(wt)/%				
	ASTM A270	DIN 17457	BS316S12	EN DIN 1.4404	EN DIN 1.4435
Carbon	0.035(Maximum)	0.03(Maximum)	0.03(Maximum)	0.03(Maximum)	0.03(Maximum)
Chromium	16.0-20.0	16.5-18.0	16.5-18.5	16.5-18.5	17.0-19.0
Manganese	2.0(Maximum)	2.0(Maximum)	0.50-2.0(Maximum)	2.0(Maximum)	2.0(Maximum)
Molybdenum	2.0-3.0	2.5-3.0	2.25-3.00	2.0-2.5	2.5-3.0
Nickel	10.0-14.0	12.5-15.0	11.0-14.0	10.0-13.0	12.5-15.0
Phosphorous	0.045(Maximum)	0.04(Maximum)	0.045(Maximum)	0.045(Maximum)	0.045(Maximum)
Silicon	1.0(Maximum)	0.75(Maximum)	0.20-1.0(Maximum)	1.0(Maximum)	1.0(Maximum)
Sulphur	0.005-0.017	0.03(Maximum)	0.03(Maximum)	0.015(Maximum)	0.015(Maximum)
Nitrogen				0.11(Maximum)	0.11(Maximum)
Iron	Relative average	Relative average	Relative average	Relative average	Relative average

The content of each of the major elements in 316L stainless steel can affect the development of rouges in a pharmaceutical system. This can be explained taking carbon as an example. From the table we can see that the maximum content of carbon in 316L stainless steel should be no more than 0.035%. This is because carbides will be released at the crystal boundary when a stainless steel pipe is welded. These crystal boundary carbides can cause the intergranular corrosion of the alloy. Reducing the carbon content can reduce the possibility of releasing crystal boundary carbides and thus making the stainless steel more resistant to intergranular corrosion. Let's take chromium as another example. Chromium is the most important element for the inhibition of corrosion and rouge development for stainless steel. The existence of chromium results in the formation of a complex chromium oxide rich layer on the surface of stainless steel, i.e. the so-called passivation layer. Although manganese plays an important role in stabilizing the major microscopic austenite crystalline grain structure in 316L stainless steel, it is also the important reason for the occurrence of the tempering color during the welding process. Molybdenum can enhance the resistance of an alloy to pitting corrosion, especially the pitting corrosion caused by chloride solutions. In addition, scientific studies have found that molybdenum can work in synergy with nitrogen during the development of the passivation layer. If the contents of sulfur or phosphorous in an alloy are too high, a tendency of separation will be caused on the microscopic crystal boundary of stainless steel. According to scientific studies, when the combined content of phosphorous and sulfur exceeds 0.04%, welding cracks caused by the separation of crystal boundary occur, which can facilitate the development of rouges. And the places where there are large sulphide inclusions (such as welding seams) are often also places where corrosion can likely occur. Silicon can increase the resistance of austenitic stainless steel to cracks caused by stress corrosion in a chloride solution. However, the existence of silicon oxide is also one of the direct reasons for the development of the difficult to remove class Ⅲ rouges in a system operating at a high temperature (such as a steam system).

b. GMP compliance. Clean pipelines are important components of a pharmaceutical process. They are important conduits for the transfer of the various types of media during a pharmaceutical process. The ASME BPE, the GMP of various countries and the pharmaceutical processes all have very strict requirements on the design of the stainless steel clean pipelines of pharmaceutical fluid process systems. For example, *Chinese GMP* 2010 specifies that the PW and WFI generation, storage and distribution systems should be able to prevent microbial growth and contamination, and the construction materials of storage tanks and transferring pipelines should be non-toxic and corrosion resistant. Deadleg and blind pipes should be avoided for the design and the installation of a pipeline. The ASME BPE has detailed descriptions for the requirements on the dimension design and the installation specifications for the pipes and fittings, including the concepts of sterile systems, the component dimensions, the material joints, the surface roughness of product contact surfaces, the equipment sealing elements, the polymer materials and their acceptance criteria. These standards are generally accepted construction standards in the pharmaceutical industry in China. Each of the pharmaceutical engineering companies should modify the relevant specifications in the ASME BPE to the various standard construction procedures and quality management measures for their clean pipeline system installation projects based on their specific conditions to ensure the overall quality of the projects.

The surfaces of the pipelines of a pharmaceutical fluid process system in contact with the fluid media must be even and smooth. Generally the surface roughness (Ra) is recommended to be no more than 0.6 μm for the surfaces of such components as pipes, fittings and on-line monitoring instruments in contact with the fluid media to effectively reduce the risk of rouge development and microbial growth on the pipeline surface and other internal contaminations of the system. At the same time, it must be ensured that there is no deadleg in the pipeline through the design of the clean pipeline of a pharmaceutical fluid process system to reduce the risk of microbial growth and rouge development at the deadleg. The 3D principle should be followed for the design of the system for deadleg control. When designing a clean pipeline system, the system emptying capability at the time of system cleaning or maintenance must be considered. That is to say, slopes must be designed during the installation of the pipelines to ensure that each of the components and instruments of the system can be self emptied, and the self emptying capability should also be considered when designing the

relevant tanks and other process equipment, to prevent any stagnant water that cannot be emptied from the pipeline or equipment, which can cause higher risks of rouges at these parts. In addition, a reasonable spatial layout should be considered from the drainage pipe connected to a drain and the water pipeline of a pure steam system to prevent any waste water from being sucked back through siphoning and the accumulation of any stagnant water within the pipeline, which can cause pipeline corrosion and the development of rouges.

c. Installation and processing. Although in some cases the rouges in a pharmaceutical fluid process system may have been caused by a material problem, the cases where the rouge development is caused solely by the material problem are uncommon. Compared with the risk of system material, the risk of the system installation quality on rouge development is even higher. During the installation of a pipeline, the first task is to provide high quality, safe and reliable pipeline welding connections and reasonably and effectively control the welding quality throughout the whole welding process to better control the project quality and provide acceptable products.

Austenitic stainless steel has satisfactory corrosion resistance in both oxidative media and reductive media because of the addition of chromium and nickel, which have excellent passivation performances. So it is widely used in clean pipeline installation projects for pharmaceutical fluid process systems. The types of austenitic stainless steel include 316, 316L, 304, 304L, 321, 302, etc. So the clean pipelines of pharmaceutical fluid process systems are almost all austenitic stainless steel pipelines. At the time of welding, there will no phase changes, cold cracks or hardening tendency for this type of steel. However, there will be intercrystalline corrosion, hot cracks and crevice corrosion, which are the direct causes of rouge development. If the inert gas (such as argon) protection is not sufficient or there is no inert gas protection during the welding process, it is very likely to cause such severe quality issues such as welding seam oxidation. The major components of oxidation welding slag are ferric oxide, which is a type of rouge itself. And the oxidation welding slag can be easily shed into the fluid by the mechanical scouring force of the fluid when the system is running. The shed oxidation welding slag will be further decomposed into fine rouge particles. If they are not retained by the final filtration membrane, it will cause very severe detrimental effects to the enterprise and the public. So it is a fundamental rule to use inert gas protection at the time of welding for the clean pipelines of pharmaceutical fluid process systems.

At the time of welding, the temperature at the welded joint will generally be maintained at 450 to 850 ℃ for a certain period of time. In such a case it is very likely for austenitic stainless steel to release $Cr_{23}C_6$ at the crystal boundary, thus resulting in intercrystalline corrosion at the layer that is poor in chromium around the crystal boundary. When there is intercrystalline corrosion, there are no visible traces at the surface. However, there can be crystal boundary fractures once the stainless steel is stressed and its strength will be lost almost completely. This is also the most dangerous damage that can happen to austenitic stainless steel. At the same time, it will be easier for the iron in the stainless steel to be oxidized because of the loss of chromium. The development of rouges will also begin during intercrystalline corrosion. There will be a rather high tensile stress at the time of welding because of the low heat conductivity coefficient and the high coefficient of linear expansion of austenitic stainless steel. At the same time, melting-point eutectics can result at the crystal boundary, which can cause hot cracks at the time of welding. Similar with intercrystalline corrosion, the chromium content at the crystal boundary will be reduced because of the eutetics, which can accelerate the formation of ferric oxides and the subsequent development of rouges. From this we can see that the welding seams and the heat affected areas are the high risk areas in clean stainless steel pipelines for rouge development.

If the root of the joint is not completely penetrated or the welding seam depth is not sufficient at the time of welding, welding seams lack of penetration or not fused will result. This is mainly because the welding current is set too low, the welding pin movement speed is too high or the welding pin is not located at the center of the welding seam. Besides lack of penetration or infusion, welding misalignment can also result because the welding pin is not located at the center of the welding seam or the current is not set correctly. All these welding quality issues caused by operation errors can cause the partial of complete exposure of the welding seams, which can result in crevice corrosion at these areas. Crevice corrosion is a type of electrochemical corrosion. It is a type of local corrosion at the metal

surface due to the close vicinity or contact between the metal base and another type of substance or the exposure of the base metal because some of the protection layer is damaged. For a welding seam with exposed areas because of poor penetration or fusion, it is sufficiently wide to allow the media with corrosion sources to enter it and it is sufficiently narrow to trap the corrosion media inside it. A large amount of rouge can develop within such crevices and spread outwards from the crevice. At the end the entire internal surface of the stainless steel pipe can be covered with rouges, which can potentially cause some quality events. Besides the development of rouges caused by poor welding quality, any inappropriate operations during the pretreatment of the pipe joints before welding can also cause scratches on the stainless steel surface, thus damaging the passivation layer on the stainless steel surface and accelerate the development of rouges.

In order to obtain acceptable welding, the installation service provider should make sufficient preparations before performing the welding operations of the clean pipelines to meet various welding requirements. A welding operator with the relevant qualification certificates should be selected according to the relevant specifications in the clean pipe and fitting welding procedures during the preparation phase for the welding activities. And the preparation should be made in all such areas as the welding process, the welding equipment, the welding materials and the welding operation environment according to the characteristics of the construction activities for clean pipelines of pharmaceutical fluid process systems. The preparations implementation should be effectively controlled.

Because of the characteristics of the materials and the industry requirements for clean pipelines, standard operation procedures for the welding of clean pipes and fittings must be established before any welding activities to provide guidance to the welding operations and assurance of the welding quality. If the pipe wall is rough or there are any dead ends in the pipeline, it will be very likely for the microbes to form a bio-film, based on these favorable conditions. This can bring great dangers and troubles to the running and the routine management of the media being transferred. In order to ensure satisfactory welding quality, tungsten electrode inert gas protection should be used for the welding of clean pipelines of pharmaceutical fluid process systems.

During the clean pipeline installation process, manual argon arc welding and automatic argon arc welding are often used. These two types of welding methods should be selected based on the importance of the clean pipeline, the welding forming requirements, and the project economics. Automatic argon arc welding is usually selected because of its better welding stability, welding seam appearance and surface roughness. It must be used for the welding of such important clean pipelines as those of WFI systems, pure steam systems and those in direct contact with the drug product or its production components or packaging materials. Manual argon arc welding can be used for pipelines of pharmaceutical raw water pipelines and drainage pipelines.

Besides qualified welding operators, reasonable welding process and acceptable welding equipment, the welding environment must also be controlled. The cleanness and tidiness, the temperature and the humidity at the installation and construction environment of clean pipelines can all affect the welding process. The installation of clean pipelines of a new pharmaceutical fluid process system is often accompanied by some civil construction activities of the relevant infrastructures. So there are often such problems as dusts and sundries at the installation site of clean pipelines. If the environment around the site for the welding is not cleaned and controlled in time, foreign matters that can adversely affect the welding quality in the airborne dusts can settle down on the internal side of the pipelines and even on the welding seams of the pipeline joints. If these foreign matters are infused into the welding seams during the welding operations, adverse impacts on the welding quality will be caused. And the welding seams themselves are high risk areas for rouge development. There can be traces of rouge at the welding seams with poor welding quality even before the system is put into use.

If the temperature and the humidity of the environment at the clean pipeline installation site are too high, there is a large amount of moisture in the air and it is very easy for condensate to form on the pipe internal wall, including the welding seams at the joints. The presence of water during the welding process can greatly increase the chances of the welding seam to be oxidized. If the welding seam is oxidized, the oxidation welding slag can soon develop into rouges. If any oxidized welding slag drops off when the system is running, the product quality can be greatly endangered and severe quality issues can occur. If the temperature

at the welding site is too low, such welding equipment as automatic welding machines cannot operate normally. The project progress can be affected and the equipment can also be damaged. Unpredictable failures or instable performances of the equipment can result during the welding process, which can cause an increase in the rate of welding quality issues.

Furthermore, it should be avoided to perform any welding operations in an environment with a high air flow. A strong air flow can affect the protection of argon on the weld pool, causing such welding quality issues as oxidation and bubbles. And there should be sufficient illumination at the site to avoid any problems during the welding activities due to insufficient lighting. The control of the environment of the welding site is a very important factor that can affect the welding quality.

Before starting the welding of clean pipelines, the control of the pretreatment of the pipes must be enhanced according to the installation procedures, which can also effectively avoid the formation of hot cracks and bubbles. After the lines and the materials have been prepared for the clean pipelines according to their layout, the welding joints must be well polished to avoid any carryover of sundries. After the surface has been mechanically polished, the pipeline must be degreased to remove any oil stains on the surface. And pipe covers must be used to cover the ends of the pipes to be welded after completing the degreasing operations. It is generally required that the length of the joints to be welded covered by the pipe cover should be no less than 20 mm to maintain the cleanness of the degreased pipes. This can ensure the cleanness of the welding workpieces and avoid any secondary contamination of the clean pipes.

The clean pipes need to be assembled before either manual welding or automatic welding of the clean pipeline welding joints. This includes the butting of the welding joints and the positioning welding. First, the correct gap and the alignment of the joints must be ensured when connecting the clean pipe joints to be welded. If the gap is incorrect or the joint butting is not aligned, such welding defects as arc burns, poor welding seams and insufficient penetration can result. In order to ensure that there is no mis-alignment at the joints to be welded, contact patterns can be used to inspect the joints. Second, positioning welding should be performed after it has been verified that the butting is correct to prevent any mis-alignment at the welded joints caused by such reasons as the buckling deformation of the welded parts during the welding process. When performing the positioning welding for clean pipelines of a piece of pharmaceutical fluid process equipment, the cross spot welding method should be used for 4 ~ 12 symmetric point welding. The size of the spot welding can be approximately determined according to the following formula.

$$d = \delta + 1 \text{ or } d = 2\sqrt{\delta} \qquad (10.3)$$

in which, d is the diameter of the weld nugget and δ is the pipe wall thickness.

Stainless steel has a high coefficient of linear expansion and a high welding deformation, so the space between different welding spots for positioning welding should be small. The space should be determined mainly based on the pipe wall thickness. Table 10.11 can be referenced for the selection of the specific parameters.

Table 10.11 Relationship between pipe wall thickness and space between positioning welding spots

Pipe wall thickness (δ)/mm	Space between positioning welding spots(d)/mm
1.2	10 to 30
$3 \leqslant \delta \leqslant 4$	40 to 80

The most important sector for welding is the control of the welding process parameters, including the welding current, the welding voltage, the welding speed, the argon flow rate, the tungsten needle and its shape, and the quality tests.

• Welding current. The welding current is the major parameter that determines the welding seam penetration for TIG (tungsten inert gas) welding. From the point of view of the material of the welding object, it is ideal to use a straight polarity direct current welding method for the clean stainless steel pipelines, and the second best option is using an alternating current power supply for the welding. The current is mainly based on the pipe thickness, the welding position and the type of joints used. From the above welding defect analysis we can see that the higher the current, the higher the weld penetration and weld width and the severer welding seam surface defects. Such defects as burning through and undercuts can result when the current is too high, and insufficient penetration can result when the current is too low. A trial

welding can be performed based on the actual conditions to determine the welding parameters. The welding current for the same type of pipes can be determined based on the welding quality of the trial welding.

• Welding voltage. Generally the welding voltage for TIG welding is within the range of 10 to 20 V. If the welding voltage becomes higher, the welding width will also be increased, but the penetration and the surface indentation at the welding seam will be decreased. When the welding voltage is too high, such defects as insufficient penetration and poor protection can also result. So the arc length should be reduced as much as possible during welding as long as there is no short circuit of the arc.

• Welding speed. The welding speed is to be selected mainly based on the clean pipe wall thickness and in combination with the selection of the welding current. When welding a clean pipe, the welding speed should not be too high in order to ensure the effective protection of the welding by argon. If the speed is too high, the argon supply flow can be left significantly behind, so the tungsten electrode, the arc column and the weld pool can be exposed to the air. In order to avoid and reduce intercrystalline corrosion during the welding process, rapid welding with a small current within certain ranges can be used. This can facilitates the prevention of hot cracks. In order to avoid any adverse influences caused by the rapid welding with a small current, such measures as increasing the argon flow and reducing the welding gun anteversion angle to obtain good protection effects.

• Argon flow. There is an optimal ratio between the argon flow and the spray nozzle size for the optimal protection effect and the largest protection area of the parts to be welded. Although the flow can be controlled based on the theoretical parameters, the welding spot test method is usually used at the site to inspect and verify the argon protection effect and range. The specific method is as described below. A TIG welding spot test is usually performed on the surface of a stainless steel material. The arc is stricken under the specified welding process parameters and maintained for about 5 to 6 seconds before the power is cut. In this way a welding spot area will be formed on the stainless steel surface. The areas under argon protection within this area will be in shinny silver color, and the areas beyond the argon protection within this area will be in a dark color.

• Tungsten needle and its shape. Cerium-tungsten needles are usually used for the tungsten needles because cerium-tungsten needles are superior to thorium-tungsten needles in such areas as process performances and allowable current and with lower radioactivity. There are many types of shapes for the tungsten needle ends used for welding. Tungsten needles with smaller diameters are usually used for small current welding and the ends are ground to an angle of about 20° to facilitate the ignition induction and the stabilization of the electric arc. And they can also be made with an obtuse angle of more than 90° or a flat-topped cone to avoid the overheated melting of the ends and reduce the loss of the ends. At the same time it can ensure a stable cathode spot and homogeneous welding seam appearances. Furthermore, the influences on the penetration and the weld width should also be considered when selecting the tungsten needle ends. The sharper the angle, the deeper the penetration and the narrower the weld width will be.

• Welding quality inspection. After completing the welding of the clean pipe joints, the welding should be inspected against the drawings and the welding process requirements to see whether the welding can meet the design specification requirements. And the relevant welding records and welding quality inspection records should be well kept and archived into the as-built documentation. The welding quality inspection should include the inspection of the welding seams and the re-tests after a welding defect is treated. Two inspection methods, visual inspection and instrument inspection, are used for the inspection of welding quality. When visual inspection is not possible for the clean pipe to be inspected, professional instruments can be considered for the inspection of the welding quality. Considering the cleanness requirements of the pharmaceutical fluid process system pipelines, it is recommended to use an advanced industrial endoscope to inspect the quality of the welding seams. If any welding quality issues such as weld misalignments, insufficient penetration or infusion failure are identified, the welding operator should be informed in time to make rectifications for the welding or repeat the welding. If it is found that the welding seam has been oxidized, the welding seam should be cut and the welding should be repeated after the pipe joints have been pre-treated.

Generally speaking, the welding quality control for the clean pipelines of a pharmaceutical fluid process sys-

tem is a systematic activity and involves a large scope of factors and there are many influencing factors for the welding defects. The process control methods should be used during the entire process to control the welding quality, reduce the risks of the development of rouge development in the clean pipelines because of any welding quality defects and provide assurance for the drug quality in the early phase.

d. Pickling and passivation. After completing the installation of the clean pipelines of a pharmaceutical fluid process equipment, the system should be pickled and passivated in time. Although the stainless steel components may be clean and with intact passivation layers before installation, the passivation layer may have been damaged at the welded areas and the heat affected areas, which may cause the early development of rouges. The distribution of such elements as chromium, iron and oxygen may have been changed during the metal melting process and the passivation layer reforming process at the welded areas and the heat affected areas. The level of iron may have been increased and the level of chromium may have been decreased. Correct and effective pickling and passivation can recover or enhance the chromium-rich chemically inert surface, i.e. the passivation film, of the system. The passivation layer is a product of the interaction between the stainless steel base material and the relevant fluid. Its thickness and composition usually depend on the solution used and generally cannot be predicted or calculated. So in order to obtain an ideal passivation layer, especially before a new system is put into use, standard procedures of pickling and passivation pertinent to the actual conditions of the system must be developed based on the relevant standards and regulations. And the pickling and passivation of the system should be performed following the established procedures to improve the corrosion resistance of the clean pipelines of the system and slow down the development of rouges in the system.

During the installation of the clean pipelines of a pharmaceutical fluid process system, the effective control of the construction material of the clean pipelines, the construction quality of the pipeline installation and welding processes, and the passivation of the installed system, can be used to improve the corrosion resistance of the system before it is put into operation. This can in some degree inhibit the rapid development of rouges and provide assurance of the satisfactory product quality for the pharmaceutical enterprise.

e. Installation qualification. IQ is used to verify that the major components of the equipment or system are correctly installed and are in compliance with the design requirements (such as standard specifications, the contract and the tender data package). The relevant supporting documents should be available and the instruments required for validation should be calibrated.

Taking a pharmaceutical water system as an example, IQ is generally performed separately for the generation system and the distribution system of a pharmaceutical water system. The documents to be verified during IQ include:

- The IQ protocol approved by the quality department;
- As-built documentation package. Process flow diagrams, pipe and instrument diagrams, component list, electric design documents, parameter manual, wiring diagrams, material certificates, necessary surface finish certificates, welding documents, pressure test records, cleaning and passivation records, etc.;
- Technical parameters and calibration records of critical instruments;
- Calibration certificates and quality certificates of the instruments to be used during IQ;
- System operation and maintenance manual;
- System commissioning records, such as FAT and SAT records.

The test items of IQ are as described below:

• Verification of the as-built process flow diagrams, the pipe and instrument diagrams: to verify whether the components shown on these drawings have been correctly installed and identified, and whether their positions, installation directions, the positions of the sampling valves, the positions of the on line instruments, the air gap to drain, etc. are correct. These drawings are very important for achieving and maintaining the water quality and any subsequent system renovations. And the isometric drawings of the system can help determine whether the system can be emptied. If necessary, they should also be inspected. The test cases related to rouge include the verification of whether the actual installation is consistent with the design, the verification of whether welding connections or clamp connections are used, and the verification of the low point drainage.

• Component verification. To verify whether the

models, the installation positions and the installation methods for the components are as specified in the design drawings and the installation instructions during IQ. For example, it should be verified to see whether the installation method of the heat changer of a distribution system, the model and the installation method of the RO units, the installation positions of the sampling valves, and the installation angles of the diaphragms valves are consistent with the instructions, whether the integrity test before shipment from the factory is acceptable for the vent filter of the storage tank, and whether the installation position of the steam trap of the pure steam system is correct. The test cases related to rouges include the verification of the selection of spray balls, the full coverage, and the cavitation of pumps.

• Calibration of instruments. To verify whether the critical instruments of the system and the instruments to be used for IQ are within their respective calibration due dates, and to verify the calibration of the non-critical instruments during IQ, if not verified and documented during commissioning. The test cases related to rouge include the verification of the calibration of the level meters and the thermometers. The spray ball can be soaked if the level is too high and cavitation can result if the level is too low.

• Component and pipe material and surface roughness. The test cases related to rouge include the verification of whether the construction materials and the surface roughness of the critical components can meet the design requirements. The construction materials and the surface roughness of the critical components should be traceable to the supplier, the product batch No., the serial No., the heat No., etc. The heat No. of the pipe material certificate and the welding logbook should be consistent with each other. The heat No., the serial No., the quantity and the component list and the actual installation should also be consistent for the valves. A pressure vessel certificate should be available for a pressure vessel.

• Documents on welding and other connection methods. The test cases related to rouges include the verification of the welding records, the welding point drawings, the welder qualifications, the endoscopic inspection data, any third party welding inspectors, the welding pieces, and the argon certificates, the standard operation procedures, the welder qualification certificates, the welding inspection protocols and reports, the welding point drawings, and the welding records.

• Pipeline pressurization test and cleaning and passivation verification. The pressurization test and the cleaning and passivation need to be performed during the commissioning. During IQ, it needs to be verified whether these activities have been completed and documented following the standard operation procedures. The test cases related to rouge include the verification of the cleaning and passivation methods, the passivation reagent used, the reagent concentration, and the reaction time. The blue point test should be witnessed by Party A personnel.

• System slope and deadleg verification. The slope of the distribution loop should ensure that the system can be emptied at the lowest point, any deadleg should meet the $3D$ or higher criteria to ensure that there is no cleaning deadleg (please refer to the GEP related specifications for the deadleg of the pure steam system and the clean process air system). Both deadleg inspection and slope inspection are related to the development of rouges.

• Utility verification. To verify the utility systems, including the power connections, the compressed air, the nitrogen, the plant steam, the cooling water, and the supply water systems, have been correctly connected and their parameters can meet the design requirements.

• Automation system verification. To verify the installation of the automation system, which generally include the hardware inspection, the wiring diagram inspection, the input and output test, the HMI operation picture inspection, the software version inspection, etc.

10.5.3 Prevention during Operation Phase

The developed rouges can be effectively controlled and even completely removed through appropriate methods. However, rouges can be regenerated and can occur repeatedly. There are many factors that are related to the recurring speed of rouges during the equipment or system running process. So, in order to keep the risk of rouges of the entire system low, the enterprise should also standardize the management of the relevant operations or parameters during the routine maintenance sector using the quality matrix concept and establish reasonable rouge prevention procedures considering the conditions of the enterprise, besides satisfactorily cleaning the system.

a. Recycled water temperature. Article 99 of the *Chinese Good Manufacturing Practices* (2010 *Verision*) specifies that the PW and WFI generation, storage and distribution systems should be able to prevent microbial growth. The PW can be recirculated and WFI can be recirculated at a temperature of more than 70 ℃. Considering the microbial inhibition requirements for WFI in GMP, it is recommended to maintain a high temperature of 75 to 85 ℃ for the storage and the distribution of WFI. This temperature range can effectively inhibit both microbial growth and rouge development. If the temperature is too high, it will be likely for cavitation to occur in the pump and cause pitting corrosion. In such a case a large amount of rouges can be developed within the pump chamber and they can spread all over the system.

A high temperature storage and distribution system refers to 6. 2. 4.

During the operation phase, high temperature and low temperature alarms should be set and they should be interlinked with the thermometer after the heat exchanger. PID regulation valves should be used to control the flow of the plant steam or the cooling water/chilled water. In this way the temperature of the main loop can be maintained within a reasonable range. At the same time, a cooling heat exchanger installed at the main loop can also be used to control the too high a temperature of the product water of the water still. Once the temperature is too high, the heat exchanger can be used to lower the temperature to the set temperature.

b. Product water temperature. The product water temperature of a water still should be set within a reasonable range. The WFI temperature is considered to be too high if it is above 100 ℃. Its microscopic state is similar to a high pressure pure steam system. It can decompose H^+ (protons). The protons are in a fluid state and the electrochemical corrosion effect is very severe. Its volume is very small and can easily penetrate through the dense passivation film of stainless steel and damage it. As long as the WFI quality conforms to the internal control criteria of an enterprise, the WFI outlet temperature should be controlled as low as possible to prevent the WFI with a too high temperature from entering into the storage and distribution system. If the temperature is too high it can bring a high stress to the cooling capacity of the heat exchanger of the storage and distribution system and a high risk of rouges. And it can also cause an increase in the power consumption for the enterprise.

c. Pure steam flow rate. Pure steam systems are often with the most severe rouges among all the fluid process systems because of their high temperature and flow rate. Plant steam is usually used as the heat source for the pure steam generation equipment on the market. Heat exchangers and evaporation columns are used for the exchange of heat to generate steam, and the pure steam is obtained after effective gas-liquid separation. The heat exchangers using plant steam as the heating source include double tube plate heat exchangers recommended for evaporation columns. This type of structural design can prevent the pure steam from being contaminated by the heating media.

The condensate of the pure steam used for moist heat sterilization must conform to the pharmacopoeia quality criteria for WFI. And the endotoxin level is a very important parameter. In the pure steam generator, the mechanism used to remove endotoxins uses the non-volatility of endotoxins. The higher the steam and water separation efficiency, the purer and the more stable the generated steam. If there are any liquid drops carried over in the steam, the endotoxins in the carried over liquid drops will contaminate the pure steam. Special care should be taken to the removal of any liquid drops carried over in the steam for the design of a pure steam generator. The pharmacopoeia requirement on the endotoxins in WFI is that it should be less than 0. 25 EU/ml. A pure steam generator can reduce the endotoxins in the raw water by 3 to 4 orders of magnitude. For example, for the condensate of the pure steam generated by the external spiral separation technology, the endotoxins of its condensate can be as low as 0. 01 EU/ml. It can very satisfactorily prevent any risks of for sterile injections posed by the endotoxins in the pure steam.

Pure steam sterilization is a type of moist heat sterilization method. It is a very common type of sterilization method used in pharmaceutical companies. It uses high temperature and high pressure steam for sterilization. The penetration capacity of pure steam is very high. Such substances as protein and protoplasm colloids can be easily solidified under moist heat conditions, and the enzyme system can be easily damaged. The steam can penetrate into the cells and turn into condensate, during which process the latent heat is released and the temperature is increased. This further improves

the sterilization capacity.

During pure steam sterilization, the temperature only needs to be above 121 ℃ and the flow rate is usually set from 15 to 25 m/s. Considering the heat loss during the transferring process, the temperature of the pure steam generated by the pure steam generator can be increased appropriately. However, if the temperature and the flow rate are too high, severe rouges can be caused. Once rouges develop in a pure steam distribution loop, the downstream equipment (such as solution preparation tanks and autoclaves) can be easily contaminated. The risk of particulate contamination is very high after a system is sterilized on line. So an enterprise should reasonably control the temperature and the flow rate of the pure steam according to their actual requirements and relevant rouge remediation and maintenance procedures should be established.

d. Sanitization and sterilization cycles. The commonly used sanitization and sterilization methods for water systems include chemical sanitization, UV sanitization, pasteurization, ozone sanitization, circulating steam sanitization, over heated water sterilization and pure steam sterilization. The sanitization and sterilization cycles for water systems should be strictly verified through PQ. Some enterprises would like to increase the frequency of system sanitization and sterilization in order to ensure absolute safety. However, the sudden changes in the environment of the water system (in temperature and humidity) can cause alternating overloads to the system and the corrosion fatigue of the passivation layer is increased, thus causing the deterioration of the physical strength and the microscopic compactness of the passivation layer. The passivation layer can be damaged by external mechanical actions and chemical actions, and the rapid development of rouges will result at the end.

For a system that uses hot sanitization/hot sterilization, the alternating loads of the system can also be easily increased if the sanitization/sterilization frequency is too high. The frequent changes in the temperature are not favorable to the stabilization of the passivation layer. So it is recommended that the enterprises should establish reasonable sanitization and sterilization cycles while ensuring a safe microbial load to avoid over sanitization or over sterilization.

e. System shut down. If the production schedule is not very tight for an enterprise, and the production is to be stopped for a period of time for energy saving, the following measures can be taken to prevent the development of rouges. Before stopping production, any bio-films, organic films and rouges within the system must be removed, and the stainless steel surface should be recovered, to ensure that there will be no these risks during the production stop period. After the water is completely drained, dry compressed air is to be used to blow the system and the system should be kept dry as much as possible. After blowing, check whether there is residual water at each of the user points, pump chambers, tank bottoms and other local lowest points. After the first blowing, blow the system with compressed air for a second time after 24 hours, and check again after another 24 hours, until it is completely dry. At the end of the shutdown period and before the formal use, the bio-film, organic film and Rouge Remediation activities should be performed again for the system to prevent any of these risk sources from developing during the shutdown.

In order to reduce the rouge development speed at each of the pure steam user points as much as possible, it is recommended to standardize the procedures to be followed before use. First, any condensate should be drained to reduce the environmental corrosions. If a user point is not used very often, it should be specified in the SOP for the pure steam distribution system that the condensate draining operation should be performed periodically at this user point. A periodic maintenance inspection system should be established for the pure steam distribution system and emphasis should be put on the inspection of the steam trap capacities.

f. Tank level control. Severe rouges can be caused if the tank level is over the spray balls. So the tank level should not be too high and the spray balls should not be soaked in water. In this case the spray ball cannot perform its functions. It is recommended that the calibration of the level meter should be checked periodically. The high level limit should be controlled at 80%. Once the high level limit is reached, the water supply valve should be closed and an audio and visual alarm should be initiated. The management should establish an annual maintenance plan and the entire system should be tested again by professional personnel (similar to re-validation activities). And the test cases should include the testing of the automation system.

The factors that can cause the rapid development of rouges during the running of the system are not lim-

ited to only those described above. The management of the enterprise and the system operators can establish the relevant standard operation procedures and optimize the operation parameters considering their own conditions so that the equipment and system can be running in a satisfactory environment to ensure the water quality, the product quality, slow down the development of rouges and prolong the service life of the system.

10.6 On-line Analytical Technologies

During recent years, the Process Analytical Technology (PAT) has drawn more and more attention from the pharmaceutical industry. Such authorities including the US FDA are actively promoting PAT to ensure QbD. The FDA believes that product quality is endowed by design, not the testing of the final products. PAT has become an optimal effective tool for the standardization of the production processes to ensure the product quality of large scale production. It can improve the production efficiency as well as reduce quality risks.

The PAT technologies have been widely used in the pharmaceutical water systems. For example, temperature sensors, pressure sensors, flow sensors, ozone sensors, conductivity sensors and TOC sensors are often installed in pharmaceutical water systems to monitor the water quality and the operation statuses of the systems.

In recent years, breakthroughs have been made in the research and development of on-line microbe monitoring and corrosion monitoring instruments. They have been put into use in the modern industry. The real time corrosion speed and corrosion accumulation data provided by an on-line corrosion monitoring instrument provide effective scientific references and real time assessment data for the determination of the rouge remediation and passivation frequencies. An on-line corrosion monitoring instrument (Fig 10.30) includes a sensor at the front, a transmitter, a remote display, a data recorder, and an analog transmission unit. The analog transmission unit is directly connected to the DCS, SCADA, BMS and process control systems. The data recorder can record the data independently and the data can be transferred to a computer. The display unit provides power supply and RS485 signals to the sensors and the transmitters. The effective distance from the sensor is 4,000 feet (1.2 km).

10.6.1 Principles of On-line Testing

Rouge is a corrosion product. Corrosion is a type of electrochemical reaction. Iron reacts with oxygen in an environment with water to generate iron ions and hydroxide ions, and the iron ions are further oxidized to generate ferric hydroxide. The entire corrosion process can be divided into 2 steps. In the first step, iron releases electrons at the anode to generate iron ions. Then in the second step the ions released act as the corrosion current (i_{corr}) and move to the neighboring cathode area, where the cathode reaction occurs. Although reaction occurs at the cathode, there is no loss of metal at the cathode. If the corrosion current i_{corr} can be measured, the amount of the metal ions can be measured using Faraday's law and then determine the corrosion speed. In reality, this type of current must be measured indirectly. The specific method is to provide a small electric potential (ΔE) and then measure the current between the two electrodes (i_{meas}). The increase

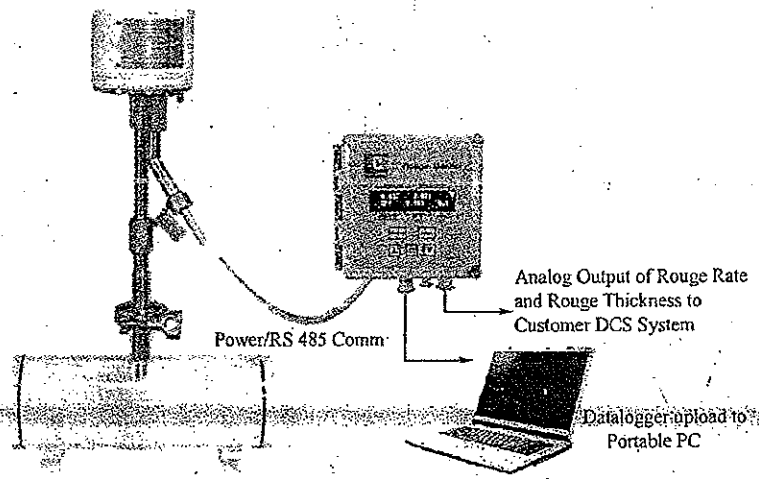


Fig 10.30 On-line corrosion monitoring instrument

in imeas is the increase in the corrosion speed.

The relationship among the externally measured current (i_{meas}), the corrosion current (i_{corr}) and the external electric potential provided through a single interface (ΔE) was proposed by Stern and Geary for the first time in the *Journal of Electrochemical Society* published in February, 1957.

$$i_{corr}=\frac{b_a b_c}{2.303(b_a+b_c)}\frac{i_{meas}}{\Delta E}=\frac{b_a b_c}{2.303(b_a+b_c)}\frac{1}{R_p} \tag{10.4}$$

Including, b_a = anodic tafel slope; b_c = cathodic tafel slope; R_p = linear polarization resistance.

Based on the above principles, the industrial application of dual-electrode rouge sensors (Fig 10.31) has been realized by modern technologies, which enables the PAT for rouges.

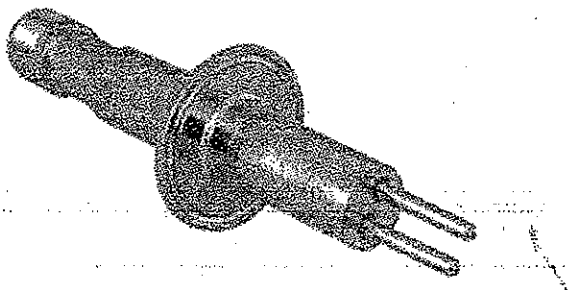


Fig 10.31 Dual-electrode rouge monitoring sensors

Rouges are developed in a water system on alloy materials under corrosion. Over the last 50 years standard electrochemical methods have been used for the detection of corrosion speed in most of the industrial water systems. These water systems include cooling water systems, production water systems, drinking water systems, boiler water systems and water phase chemical processes, food processes, paper pulp and paper making processes. Of course, the environments of these applications are different from that of the pharmaceutical industry. The water used in the pharmaceutical industry is mostly highly pure water that is low in corrosion and conductivity. This type of electrochemical technology, including its principles, applications, limitation and interfering factors, has been well described in the *Guideline on Corrosion Monitoring for Plant Equipment (Electric and Electrochemical Methods)* published by the American Society of Testing and Material (ASTM) G96—1990 (2008). The computerized data handling methods for the electrochemical measurement of the corrosion speed are described in the *Corrosion Speed Calculation and the Electrochemical Measurement* published by American Society of Testing and Material (ASTM) G102—1989 (2010).

The variation in the current detected between the metal and water interface is converted to corrosion speed. The continuous test based detection values are obtained following the criteria described above, which is called the Tafel slope. The Tafel slope depends on the ion movement between the metal and water interface, such as the transfer of electric charges, the diffusion control, and the movement of the metal ions to the oxidation film. Generally, the Tafel slope is determined based on experience. The relevant corrosion speed data can be obtained by comparing the loss of metal within a certain period of time at the monitoring electrodes or coupons of similar materials. Because the highly pure water used in the pharmaceutical industry only has very low corrosion speed and conductivity, the Tafel slope is very low and even not detectable. The change in the corrosion speed and the loss of metal are about several nanometers in several months. This is also difficult to detect. The detectability, the stability of the corrosion and the applicability of the detection instrument can be increased only by the monitoring of more sensitive ions.

The corrosion speed of a type of low corrosion speed water measured by a very low conductivity is different from its actual corrosions speed. And the Tafel slope is usually constant certain operation conditions. So, if the measured corrosion speed is doubled the actual corrosion speed would also be likely to be doubled. Generally, the change in the corrosion speed is far more important that the absolute value of the corrosion speed. The purpose of this test is to determine the range of the high and low corrosion speed under the same operation conditions, to determine and shorten the duration of the environment that can cause a high corrosion speed, and prolong the duration of the environment that can cause a low corrosion speed. Under these environmental conditions, the loss of metal and the corrosion products can significantly affect the rouge development speed in a pharmaceutical water system.

The ASTM Guideline G966 indicates the use of an equivalent circuit as the typical electrochemical probe for the corrosion surface of metal in a water environment. If the water resistance of a type of stainless steel in a highly pure water environment is 4.65 mΩ/cm, the corrosion will be 10 nm every month. Please see Fig

10.32 for the components of the circuit.

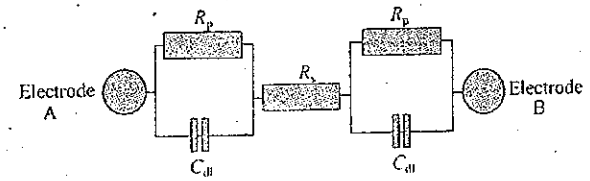


Fig 10.32 Components of equipment circuit

In this example, R_p is 1 mΩ, R_s is 511 kΩ and C_{dl} is the standard 100 mV. Theoretically speaking the maximum potential between the two electrodes should be 20 mV for effective testing. A corrosion of 1 nm a month is equivalent to 800 pA. This is a very small measured value to be applied to the site environment.

In order to detect very small current changes, a high resistance must be maintained to prevent any current leakages. And a special type of measurement is required to deduct the solution resistance value R_s from all the resistances to obtain the required R_p value. The R_p value is inversely proportional to the corrosion speed and the rouge development speed. High speed corrosions (such as 400 nm/month) are difficult to measure, because the R_p value is very small compared with the R_s value. However, in the pharmaceutical water systems, the corrosion speed is actually about several nanometers per months in most of the cases and it generally will not be more than several tens of nanometers per month.

A high performance instrument should be able to measure the very low corrosion and corrosion speed in a stainless steel high purity water system. The data obtained at the labs and at the site can further prove the performances of the instrument. And these data can be studied to predict the causes of any change in the corrosion speed in the highly pure water systems or ultra pure water systems.

10.6.2 Application of On-line Monitoring

Because a very small amount of rouge in the water will not cause any significant influences to the conductivity of the water, conductivity alone cannot be used to accurately detect the development of rouges. The existence of other substances in the water, such as gases, can cause significant changes in the conductivity until a balance is reached.

Because of the lack of precise testing methods and technologies, the rouge remediation and passivation frequency is determined based on the duration or the visual inspection of the pipes and containers. The interval can be half a year, one year, two years, depending on the production suspension plan, etc. Although the accuracy of this type of method cannot be ensured, it has been widely used as the routine prevention method by the enterprises to meet the SOP requirements.

Precise corrosion speed measurement methods can help determining the rouge remediation and passivation operation progresses and can provide better methods for the observation of the rouge development process. Measuring the rouge speed can help enterprises determine their corrosion level and determine the concentration of rouges that can possibly exist in their final products.

Complete automation and computerization have been achieved for modern pharmaceutical water systems. Some on-line instruments have been used to replace or enhance lab tests. The on-line instruments can be used to realize the real time release of the pharmaceutical water. The integration of rouge monitoring instruments, the available water system instruments and the computer systems can better analyze the data and determine their relevance to other process data. This can also be in compliance with GMP 21CFR Part11 requirements.

The unit of the corrosion speed is nm/month or μm/month. The unit for corrosion accumulation or metal loss is nm or μm. The corrosion and the corrosion speed are not at a steady speed. Early studies show that the major areas of corrosion include the pumps and the spray balls. At these areas the passivation layer is damaged because of the too high flow speed of the medium. It is very easy for the metal parts to be corroded without the protection of the passivation layer.

The corrosion monitoring instruments should be installed starting from the pumps and the first instrument should be placed near the downstream part of the system as much as possible. Places with very high turbulent flows should be selected, for they are often areas with severe corrosions. The second corrosion monitoring instrument should be installed on the loop before WFI goes in and out of the storage tank. Please see Fig 10.33 for the structure and the position of the corrosion monitoring instruments.

Through the measurement and the analysis of the corrosion speed through on-line corrosion monitoring it has been found that the changes in the corrosion speed can be caused by the following reasons: changes in the fluid statuses in the pipeline, the locations of the user

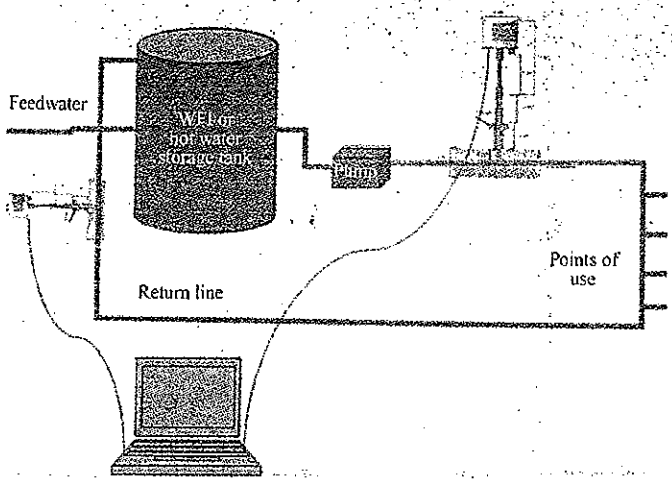


Fig 10.33 Recommended installation positions of corrosion probes in water systems

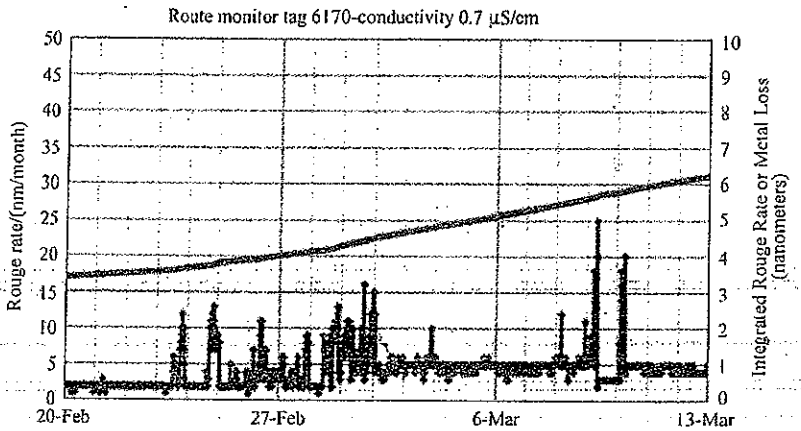


Fig 10.34 Rouge development speed increase curve

points, the variations in pressure, the water consumption, the circulation volume and the structure. There are also such factors as the minor differences in the 316L stainless steel, such as the temperature, the ratios of chromium, molybdenum and nickel, the differences in the carbon dioxide saturation, and other possible factors. All these factors make the corrosion speed optimization process very complicated.

From Fig 10.34 we can see that from mid February to mid March, there is a significant fluctuation in the corrosion speed. It increased to 20 to 25 nm/month between February 20 and March 13. After analysis it was found that the data changes are significantly related to the process changes.

Some problems that cannot be solved now can be solved through on-line real time monitoring. These problems include how the corrosion speed can be determined, what are the acceptable criteria for the corrosion accumulation, when rouges will precipitate, how the corrosion speed and the corrosion accumulation data and the establishment of their corresponding limits can help an enterprise make decisions on the rouge remediation or passivation activities, etc. If the corrosion speed is 3 to 5 nm/month, the rouge accumulation is 20 nm, it may take several years to reach the rouge remediation and passivation action limit (such as 50 nm) designated by the user. If according to the previously established procedures the rouge remediation and passivation need to be performed once a year, the present maintenance schedule can be postponed for two to three

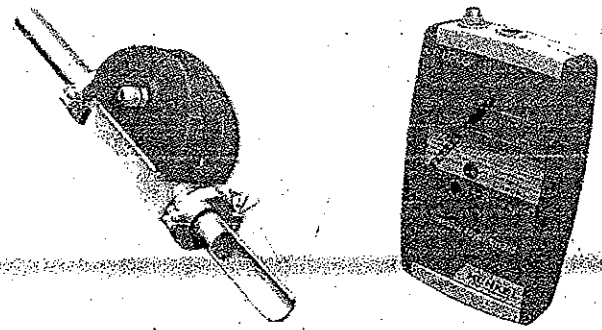


Fig 10.35 On-line rouge monitor with alarm lamps

years.

The monitoring instruments can be used to ensure the quality of the final products through the 24/7 continuous monitoring data. The system can provide early warning of rouge development to the user through alarms (Fig 10.35). These long-term monitoring data can help determining the feasibility of the monitoring systems in monitoring the passivation, the passivation persistence, the rouge remediation frequency and the actual cost saving values.

The use of on-line monitoring can evaluate the actual corrosion speed and the metal loss during any period of time, allowing the user to determine the corrosion speed and the metal loss limits based on experience. In this way the rouge remediation and passivation cycles can be determined based on the user defined limits, not any subjective decisions made by QC/QA. The corrosion speed can help determine the possible level of rouge in the final product. More importantly, the rouge remediation and passivation frequencies can be optimized based on these scientific data, which can save a lot every year for the enterprises.

Chapter 11

Quality Management

Quality management refers to all activities and management functions, which define quality policy, objectives and responsibility, achieved by quality planning, quality control, quality assurance and quality improvement included in the quality system.

The framework of quality management established and implemented effectively in a pharmaceutical enterprise is of critical importance for product quality assurance. Meeting the requirements of the ISO 9001 international quality management system is only meeting the minimum requirements of quality management, while to set up advanced quality concepts, conduct strict quality control, carry quality management through to the end, make "Quality First" enjoy wide support, provide products of high quality and gain customer trust, ensures the enterprise can remain invincible in the intense market competition.

11.1 Quality Control

The operation techniques and activities undertaken to meet quality requirements are referred to as quality control. Quality control refers to various operation techniques and activities undertaken to meet quality requirements and obtain economic benefits by monitoring the quality of the process and eliminating the factors causing unacceptable or unsatisfactory effect at each phase. At the enterprise level, quality control activities are mainly the production site management within the enterprise, and the activities involving the technical and management control measures necessary to maintain the quality. Quality inspection subordinates to quality control, it is an important activity of quality control.

Quality control is of vital importance during the implementation of the pharmaceutical water systems. The correct understanding of quality by design, quality control model, total quality management and good engineering practice contributes to the effective control of the comprehensive quality of the pharmaceutical systems, among which, the control of welding and passivation quality is the most critical aspect in the operation of the whole pharmaceutical water system. This chapter will put emphasis on it.

11.1.1 Quality by Design

Quality is the source of enterprise development, while the quality reliability of a pharmaceutical water system is the stepping stone for product quality assurance in the pharmaceutical enterprise. With the incoming implementation of international strategies by more and more Chinese pharmaceutical enterprises, as a direct impact system in the construction of whole facilities, the design, installation and validation of pharmaceutical water systems have been the key point for renovated and new projects in domestic pharmaceutical enterprises. Taking the pharmaceutical water system as an example, the whole system is composed of multiple independent units such as the generation unit, storage unit, distribution unit and point of use pipeline unit. According to the "Barrel Theory" (Fig 11.1) in quality management, the final quality of pharmaceutical water systems is determined by the "weakest link" unit in the whole system.

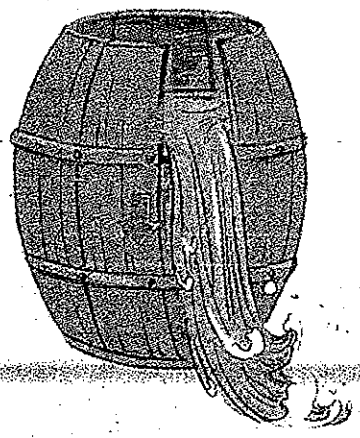


Fig 11.1 Barrel theory

Quality by design (QbD) stresses the final quality of products and services depends crucially on the design, not the manufacturing and service process. QbD is the basic part of the FDA cGMP. It is a new pharmaceutical quality assessment system established on the basis of scientific understanding of products and processes using the principle of QbD, the new system will put an emphasis on the scientific understanding of the manufacturing process itself rather than traditional compliance with regulations, which result in the change of evaluation key points by FDA.

The objective of the QbD implementation is to ensure the product quality at a high level, at the same time saving investment and operating costs and improving efficiency for pharmaceutical enterprises. The high quality product originates from design and development, and the design process is the source of quality control. If the design has defects at an early stage, even when making great efforts for subsequent activities, it is difficult to manufacture a pharmaceutical water system of high quality, even causing difficulties for following activities such as material preparation, processing, assembly, inspection, commissioning, etc.. There is no doubt that having adequate quality control points at each stage during the design process is a significant step in the system construction for ensuring the high quality of design of a pharmaceutical water system.

The concept of QbD applies throughout the implementation of pharmaceutical water system. The design of a pharmaceutical water system is mainly taking the quality requirements, process selection, installation requirements, operation requirements, validation requirements, and other factors into consideration. A pharmaceutical water system is taken as an example. First the usage of pharmaceutical water is defined, and then the specification it needs to conform to is determined, e. g. a Chinese GMP compliant water for injection system. The process selection mainly verifies which method is adopted to generate, store and transfer the pharmaceutical water. Installation requirements mainly consist of compliance with the GEP and ASME BPE requirements for installations of high quality. Operating requirements should take comprehensive consideration of the production, maintenance and GMP requirements. Validation requirements are to verify the document contents and standards based on the registered project. Therefore, only if full understanding of the process requirements and strict control at each step of pharmaceutical water system, can "the most important raw material" in the pharmaceutical industry consistently comply with the quality requirements.

Calculation is an important part in the design of a pharmaceutical water system. As an example, one set of reliable calculation methods for a pharmaceutical water system can provide the scientific theoretical basis and accurate investment estimation for the pharmaceutical water equipment and system selection of the enterprise. The calculation of a pharmaceutical water system mainly include the calculation of the output of the water generation equipment, volume of the storage tank, pump flow and lift, pipe diameter of pipelines, area of heat exchanger, etc. Both the Chinese GMP and the European GMP require that the operation of a water system must not exceed its designed capacity. Usually, improper calculation will result in the pump cavitation phenomenon, no water available at the point of use valve at the end of the circulating pipelines, system flow and pressure alarms, even the system being in a state of negative pressure; all of these will have direct impact on the normal production of the enterprise. This may happen for the following reasons, inappropriate model selection of the water generator, volume of storage tank too small, not enough centrifuge power or the pipe diameter of pipelines too small.

With the completion of the plant equipment layout and equipment selection, the enterprise and design unit should start investigating the actual water demand of each process water point of use, and write a detailed water consumption investigation list (Fig 11.2), each process water point of use should have the following four parameters established.

- Usage time. It is usually divided into 0-24 hours, 24 time periods in total.
- Consumption in corresponding time period by the point of use. Unit is L or m^3.
- Instantaneous flow of the point of use once the valve is opened in corresponding time period. Unit is L/h or m^3/h.
- Temperature and pressure required by the process for the point of use.

a. Calculation of water generation equipment and storage tank. The productivity of the water generation equipment and volume of the storage tank are determined by "usage time" and "consumption of corresponding time period of the point of use" of each point

User Points	1		2		3		4		Total	
Location(Room numberand Room Name)										
Use for(or Name of the Equipment)										
Daytime	Consumption	Flow	Consumption	Flow	Consumption	Flow	Consumption	Flow	Cons peak/hour	Flow peak/hour
0:00-1:00									0	0
1:00-2:00									0	0
2:00-3:00									0	0
3:00-4:00									0	0
4:00-5:00									0	0
5:00-6:00									0	0
6:00-7:00									0	0
7:00-8:00									0	0
8:00-9:00									0	0
9:00-10:00									0	0
10:00-11:00									0	0
11:00-12:00									0	0
12:00-13:00									0	0
13:00-14:00									0	0
14:00-15:00									0	0
15:00-16:00									0	0
16:00-17:00									0	0
17:00-18:00									0	0
18:00-19:00									0	0
19:00-20:00									0	0
20:00-21:00									0	0
21:00-22:00									0	0
22:00-23:00									0	0
23:00-24:00									0	0
Sum	0		0		0		0		0	
Peak Value(L/M)										

Parameter 1 Usage time
Parameter 2 Consumption of single point of use
Parameter 3 Flow of single point of use
Parameter 4 Pressure and temperature

Fig 11.2 Water consumption investigation list

of use; it has no direct relation to instantaneous flow, temperature, pressure and other parameters. We can accurately simulate the optimal combination of the productivity of the water generation equipment and volume of the storage tank with the equipment selection software for the pharmaceutical water systems (Fig 11.3), using the principle of comprehensive investment assessment.

b. Calculation of centrifuge flow and pipe diameter. The actual consumption per unit time is the result of usage time multiplied by instantaneous flow, centrifuge flow/lift and pipe diameter are determined by "usage time" and "instantaneous flow once the valve opened in the corresponding time period of the point of use" of each point of use; it has no direct relation to the actual consumption, temperature, pressure and other parameters. The position and parameters of all points of use of a pharmaceutical water system are determined which include the quantity of pipe fittings, fluid viscosity, fluid temperature, vertical additional height, opening pressure of the spray ball for return water, equilibrium pressure of the cold point of use, and other parameters. The water consumption investigation list will provide the maximum system peak flow for the designer. Generally, the pump flow is the sum of maximum peak flow and minimum flow, the minimum flow can be converted to the flow of 1 m/s. The actual required value of pump flow/lift and pipe diameter can be simulated accurately using the pump and pipe diameter selection software of the pharmaceutical water system (Fig 11.4). For a more accurate selection of the pump parameters and pipe diameter, the "Pipeline subsection method" is usually adopted to calculate system resistance by simulation.

c. Calculation of heat exchanger. In a pharmaceutical water storage and distribution system, the heat exchanger has mainly the following two functions: ①realize the pasteurization or superheated water sterilization for the storage and distribution pipeline; ②Conduct instantaneous cooling for the cold point of use of the water for injection pipeline. The calculation of the heat exchanger is done using the law of conservation of energy, $Q=c\cdot m\cdot (T_2-T_1)=K\cdot A\cdot \Delta T_m$, the formula is the basic calculation method of energy conservation in "Principles of Chemical Industry", it is not described in detail here. The special calculation sheet for the heat exchanger is usually provided by the supplier of the heat exchanger. The calculation of the heat

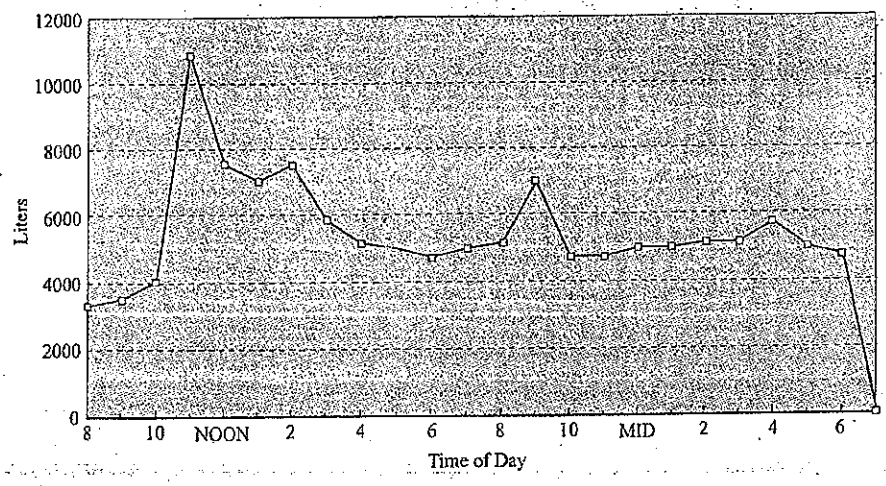


Fig 11.3 Equipment selection software of the pharmaceutical water systems

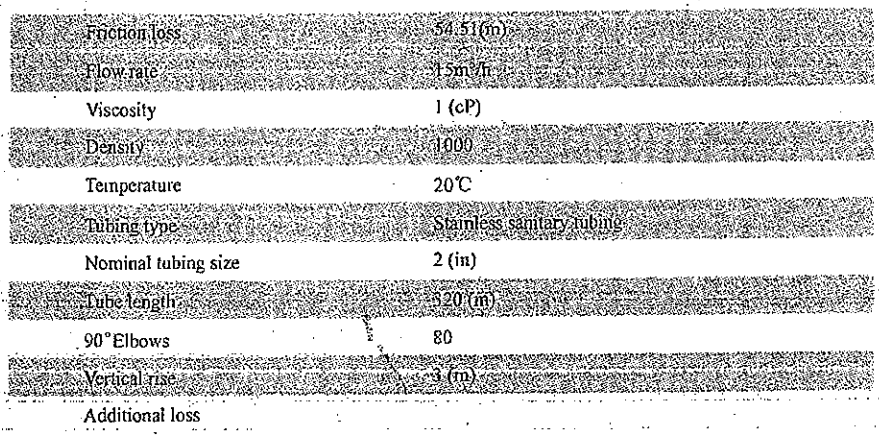


Fig 11.4 Centrifuge and pipe diameter selection software

exchanger for pasteurization system is illustrated in Fig 11.5.

11.1.2 Quality Control Model

The V model (Fig 11.6) is a very effective quality control model used for a pharmaceutical water system. It can effectively control the quality at the phase of design, installation, construction, commissioning, validation, after-sales service of purified water, water for injection, pure steam and other systems.

The user requirement specification (URS) refers to the customer requirements for an equipment or system. It mainly includes the requirements for process, unit operation, process condition, productivity, GMP regulations, document traceability and other requirements (such as location, packaging and transportation), etc. URS is a very important document for ordering a system or equipment, and PQ is to verify whether the URS is completely satisfied. The URS is the basis of the entire project, a precise URS and contract is the good basis for future inspection.

The Quality and project plan (QPP) is one of the very important documents for the whole project management. The main purpose is to outline the quality control requirements at different phases of the product execution. QPP is usually prepared and then executed by the supplier after being submitted for customer's approval. The quality management procedure is an important part in QPP, a good quality management procedure mainly includes the project management, process and mechanical design, automation design, purchasing management, warehouse and logistics management, installation management, field tests, training, etc. among which, the project management includes the key information such as project organization structure, responsibilities and authorizations, and the project schedule Gantt chart (Fig 11.7).

A project change is a frequently occurred activity during a project's execution, a process change in the project can be done using the change procedure, and the change notice must include the description of the system change reason and change protocol, the impact

Working conditions:

		Tubeside		*Shellside*	
		In	Out	In	Out
Medium		PW	PW	Steam	Condensate
Working pressure	(bar/a)	6,00	5,66	3,00	3,00
Temperature	(°C)	46,4	58,6	144,0	140,0
Flowrate	(kg/h)	7500	7500	180	180
Design conditions:					
min.pressure	(bar/a)	0,0		0,0	
max.pressure	(bar/a)	10,0		10,0	
min.temperature	(°C)	-10		-10	
max.temperature	(°C)	140		200	
Material		1.4435/BN2		1.4571/1.4541	
Gasket		EPDM(FDA)			
Test pressure	(bar/a)	15,0		15,0	
Dimensions:					
Heating tube	(mm)	12×1			
Lenght	(mm)	1500			
No.of heating tubes		14			
Shell pipe	(mm)			76,1×2,9	
Volume	(litre)	3,2		3,4	
Weight	(kg)	125/135			
Calculation:					
Velocity	(m/s)	3*		10,1*	
Log.temp.diff.	(K)	65,5			
Exchange surface	(m²)	0,663*			
K-value	(W/m²K)	3150			
No.of passes		1		1	
No.of baffles		0		2	
Heating transfer	(kW)	435			
Reserve capacity	(%)	9,2			

Fig 11.5 Calculation sheet of heat exchanger for pasteurization

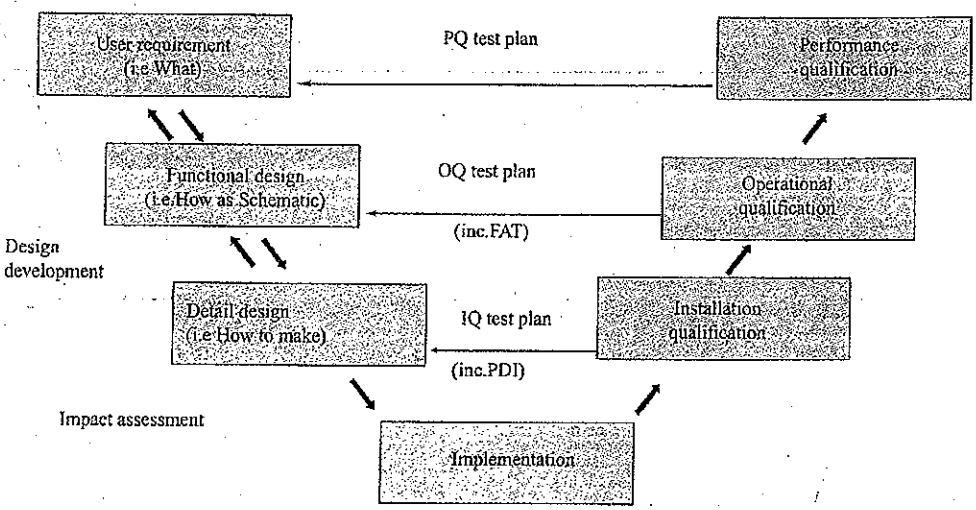


Fig 11.6 V Model of a pharmaceutical water system

on the system after the change, tests to be done, and documents to be updated.

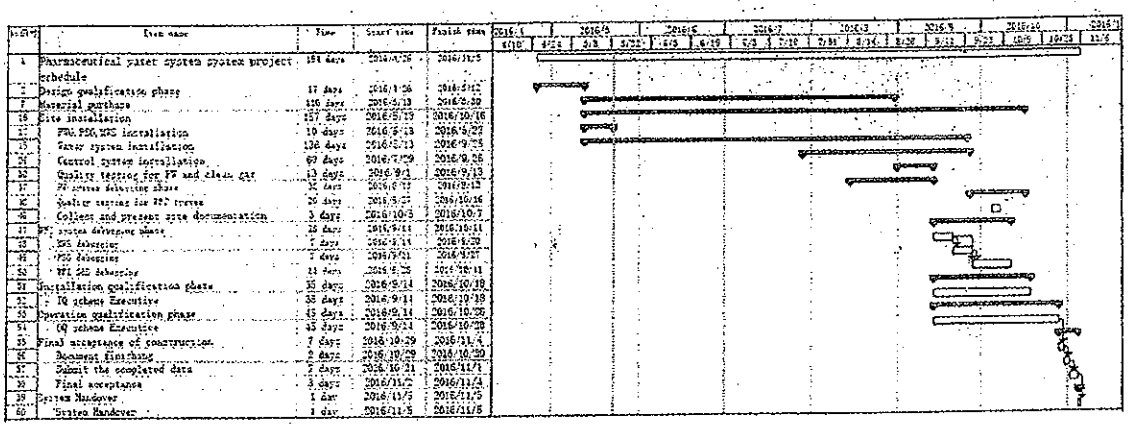


Fig 11.7 Project schedule Gantt chart

The quality of materials has a direct impact on the function realization of a system after installation, and can even cause adverse effect on products; therefore, the construction unit should not only conduct quality audits and control of downstream suppliers, but also comply with the quality management requirements of the project owner. The project owner will designate his inspectors or delegate a third party company (usually as a supervision company) to conduct management. After receiving materials, the construction unit should inform the supervision company and owner representative to jointly conduct an appearance inspection for incoming materials, if re-inspection is required, the supervision company and construction unit will take samples together and submit them for testing. The materials cannot be used before the issuance of the test report, and the materials are subjected to an acceptance inspection after obtaining the test report. The documents to be submitted to the supervision company include the list of materials, self-inspection records, documentary evidence for quality (certificate of quality, test report).

Austenitic stainless steel refers to stainless steel containing chromium of more than 18%, nickel of about 8% and small percentages of molybdenum, titanium and nitrogen. It has a good overall performance, and resists corrosion of multiple media. The commonly used grades are 1Cr18Ni9、0Cr19Ni9, etc. 0Cr19Ni9 steel has a high Ni and Cr content, and it is in the austenite phase at room temperature. This type of steel has good plasticity, tenacity, weldability and corrosion resisting properties. Its corrosion resistance is good in oxidizing and reducing media, it is usually used to make sanitary equipment, pipelines and pipe fittings, etc. In a pharmaceutical water system, the issue of highest concern for the project owner is whether the materials of items such as pipelines and pipe fittings can meet the requirements stipulated for the 316L stainless steel. If an inspection requirement is made by the project owner, personnel from the project owner and construction unit should take samples for pipelines or pipe fittings together, seal the samples and send them to the quality supervision and inspection unit for testing. The materials can be used after the test results are qualified. A portable alloy analyzer (Fig 11.8) is able to analyze the elementary composition, content, grade and other information of the tested metal in a short time. It is widely used for the material tests in pharmaceutical industry at present. It should be noted that this type of alloy analyzer cannot analyze carbon, therefore, it can only analyze 316 stainless steel, but cannot analyze 316L stainless steel, even so, a portable alloy analyzer still has positive significance on material analysis.

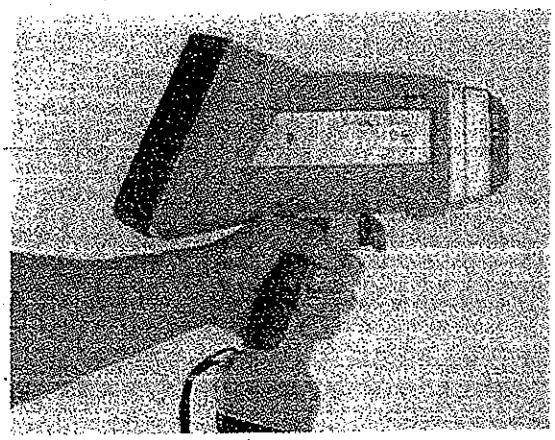


Fig 11.8 Portable alloy analyzer

In-warehouse and ex-warehouse inspections must be conducted on all raw materials. Only qualified raw materials can ensure the overall quality of the system. The in-warehouse inspection results are recorded in the material in-warehouse inspection sheet, and the materials should be at least inspected for material grades,

identification, damage, size, surface roughness, documents, etc. and it must be ensured that unqualified materials are not warehoused. All types of raw materials in a pharmaceutical water system must be managed and classified uniformly in strict accordance with the material grade (Table 11.1). Generally, the materials coming in direct contact with pharmaceutical water must meet the standard of 3.1, while materials not coming in direct contact with pharmaceutical water must meet the standard 2.2.

Table 11.1 List of material grades

Standard designation	What it means for us
2.1	A certificate of conformity. The certificate should state that the delivered part/component are made of the material quality that was ordered from the purchaser
2.2	Same as 2.1 + a non batch specific material analysis/specification of the delivered/ordered material
2.3	Same as 2.2 but the material analysis has to be done on the specific batch/material batch that is used for the part/component
3.1.A	Same as 2.3 but the certificate has to be issued and validated by an inspector designated by the official regulations e.g. Tüv
3.1.B	Same as 2.3 but the certificate has to be issued by an inspector independent of the manufacturing department e.g. the quality department
3.1.C	Same as 2.3 but the certificate has to be issued and validated by an authorized representative of the purchaser
3.2	Same as 2.3 but the certificate has to be validated by an authorized representative of the purchaser and an inspector independent of the manufacturing department

The design phase mainly includes the process design, mechanical design and electrical design. The design documents include the P&ID, function specification, component list, hardware design specification, software design specification, circuit diagrams, function logic, modular design, etc. All documents at the design phase will be verified by design qualification.

The function specification (FS) and function logic (FL) are documents that define how to operate the system, and how to perform logic control, including programs and alarms, instruments and meters, program steps, conversion and logic. FS is a document for process description, while FL is a document derived from FS, the functional description of the system in digital format. FS will be tested and verified at the phase of following commissioning or operational qualification. Hardware design specification (HDS) describes the necessary hardware design and system automation level of the electrical system. Software design specification (SDS) describes the programming software program and HMI interface.

The installation mainly refers to installation and construction according to the design documents. The basic documents at the installation phase include the *Standard Operating Procedure for Clean Pipeline and Fitting Welding*, *Standard Operating Procedure for Hydrostatic Testing*, *Standard Operating Procedure for Cleaning*, *Standard Operating Procedure for Pickling and Passivation*, *Standard Operating Procedure for Dead Leg Check*, *Standard Operating Procedure for Slope Check*, *Standard Operating Procedure for Endoscopy*, *Standard Operating Procedure for Modularized Assembly*, etc. All documents for installation will be verified at the phase of installation qualification.

Operation phase mainly refers to the commissioning and trial run of the system. After the completion of the internal testing and commissioning, the supplier will notify the user to jointly participate in the factory acceptance test (FAT) and site acceptance test (SAT). Generally, FAT and SAT include four main parts: mechanical and document inspection, hardware acceptance test, software acceptance test and operation test.

The requirements traceability matrix (RTM) is a documentation process that describes the user requirements for the system, and validates the relationship between the outcomes of these requirements. For a pharmaceutical water system, the supplier should make sure that the contents of relevant documents during the design, construction and commissioning correspond to the descriptions of actual user requirements one by one, in the form of a matrix, and form traceable documents, in order to ensure the design process corresponds to actual user requirements.

The ISPE guide recommended that the FAT and SAT test reports of a pharmaceutical water system can be referred to the phase of IQ/OQ directly (Fig 11.9), which requires the whole system to have as far as possible a modularized design so as to implement FAT and SAT for each constituent part of pharmaceu-

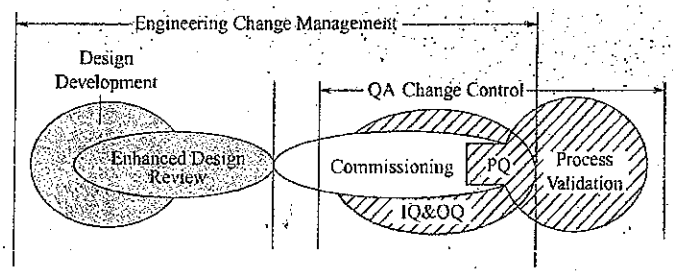


Fig 11.9 Relationship of commissioning and qualification

tical water system more comprehensively.

11.1.3 Total Quality Management

The PDCA cycle is also referred to as Deming circle (Fig 11.10), which was proposed by Dr. Deming, an American quality management expert. It is a scientific procedure followed by total quality management. The process of total quality management activities is to run the cycle comprehensively in the order of the four phases: plan, do, check and act, which are relative, and with no obvious boundaries between phases. The quality will be gradually improved accompanying the completion of a cycle.

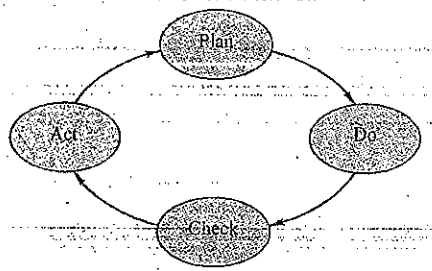


Fig 11.10 PDCA cycle

a. Plan. The pharmaceutical enterprises establish EHS management system according to relevant national laws and regulations, combined with ISO 9001, ISO 14001, OHSASI 8001 and GMP management system, and taking into consideration of their own technical conditions and resources business conditions.

• Establishing the management policies, targets, indicators and management protocols. Policy is the main goal leading to the advancement of the enterprise quality, and the guiding principle for implementing the EHS system. Targets and indicators should be established according to relevant national laws and regulations as well as the conditions of the enterprise itself, which shall be practicable. The management protocol is the specific implementation plan and protocol of the EHS targets and indicators. The objective of the EHS management system implemented by the pharmaceutical enterprise includes: reducing personnel injuries, accidents, contaminants, waste, operating costs and potential adverse factors; promoting the production reliability, economic benefits, enterprise reputation and credibility. The production management and EHS management are combined together at an early stage of the process research, facility design, construction, production schedule and business planning to drive the objectives of production and EHS with an emphasis on the efficiency of the whole process, and enhancing the long-term benefits provides by the EHS performance and management level.

• Establishing risk identification and evaluation mechanism. Risk includes unsafe conditions originated from objects, unsafe behavior originated from humans, management defects and environmental factors. It is required to identify sources of danger and hazardous environmental factors during the establishment of the plan. Multiple qualitative and quantitative evaluation methods can be used during risk assessment, including the analogy method, operating condition risk evaluation (LEC), fault tree analysis (FAT), event tree analysis (ETA), preliminary hazard analysis (PHA), failure mode effects analysis (FMEA), failure mode, effects and criticality analysis (FMECA), hazard operability analysis (HAZOP), safety checklist analysis (SCA), risk rank (RR), what … if (WI), etc., among which, the commonly used safety evaluation methods are SCA, RR, PHA, WI, HAZOP and FMEA. Only if the risk is identified and evaluated correctly, can the EHS management personnel establish corresponding preventive and corrective measures with clarity. The objects of assessment include the process, equipment, facility, environment, personnel, management, etc.

• Establishing relevant standards and operating procedures. Corresponding preventive and corrective measures should be adopted and relevant standards and operating procedures, including standard management

procedure (SMP) and standard operating procedure (SOP) should be established, after the completion of risk assessment. The procedures should be established in considering the conditions in different plants, processes and posts respectively with good operability and systemization.

b. Do. The enterprise should configure relevant resources and strictly control the execution process in accordance with the EHS after the establishment of the EHS management documents.

• Configuring relevant hardware facilities. Configuring safety and fire protection related facilities: identification facilities for escaping, electricity guarding, theft guarding, fireproofing, falls preventing, explosion proofing and relevant potential sources of danger; warehousing and management facilities for hazardous materials, flammable and combustible materials and poisonous materials; environmental pollution sources identification, testing and handling facilities; waste gas, liquid waste and solid waste treatment facilities; emergency handling facilities for sudden environmental events; personnel labor protection, emergency treatment and protective facilities, etc. The abovementioned hardware facilities should be managed uniformly and effectively, and utilized comprehensively.

• Deploying relevant organization and personnel. Establishing an independent EHS department at the same level as the production department and quality department to ensure the EHS operation efficiency and quality. The EHS management system is an effective structured operation mechanism and internal management tool for continuous development of the enterprise, its implementation requires the participation of all staff, from executive level, middle level to operators at the basic level. It requires all staff at each post to realize the importance of EHS, know their responsibilities, and understand how to implement and comply with the requirements of the EHS system. It requires the enterprise to conduct systemized, effective and repeated training and guidance for the staff to improve their professional quality and cognitive level. Only if the staff implements the specific requirements of EHS in practical production operations, can they really be involved in the EHS system.

• Controlling the executing process strictly. The EHS system is not a compulsory standard, and totally different from the GMP management system. No authority or regulation can force the enterprise to implement it at present. The establishment and implementation of the EHS system completely depend on the understanding of the enterprise. Only if the enterprise realizes the necessity of implementing EHS thoroughly, can it implement EHS system consciously and positively in its practices. During the implementation of the EHS system, attention should be paid to communication with the staff; collect EHS information, conduct overall control, dynamic management and timely disposal of the information, realize the reminding and early warning of the staff, control possible and potential environmental risks, reduce or eradicate the occurrence of environmental pollution, industrial accidents and occupational diseases to a maximum.

c. Check. The enterprise checks the actual implementation effect in accordance with the established plan and inspection schedule to verify whether it has reached the expected purpose. The check results can be analyzed and validated by means of histograms, displacement diagrams, control charts and system diagrams. The check results should be obtained according to the stipulated purpose in the EHS implementation measures. The result should be practical and realistic with no exaggerating or narrowing of the facts. It should analyze the objective to be achieved and improve the method, conduct compliance inspection to EHS policies, strategies, documents and solutions, eliminate or improve incompliant systems, documents and measures.

d. Act. Continuous improvement is the common requirement of the GMP and EHS systems. The enterprise should conduct internal audits of the implementation of the EHS system regularly on the basis of check results. The procedures of the internal audit should include audit scope, frequency, method and capacity, as well as responsibilities and requirements for conducting the audit and reporting the result. The internal audit should be performed and organized with a plan and method following a certain procedure to identify the important, special and critical processes of the audit for planning and execution, identify the problems that exist in the system operation, actively take corrective and preventive actions, improve the effectiveness of the system operation, and enhance the ability of risk resistance and accident prevention of the enterprise. The audit schedule, checklist, non-conformity report, audit record, audit report, etc. should be retained to ensure the traceability of the process. These accumulated experiences will enhance the analysis and decision-making

ability of the enterprise. The completion of the internal audit is not the end of the system operation; it is the start of the next operation process. The new objective, indicators and management protocol result from the internal audit, and identified hazards and influencing factors are controlled and managed to promote the continuous improvement of new cycle. The enterprise EHS management system is improved and promoted continuously in a PDCA cycle.

11.1.4 Good Engineering Practice

A project is an organized temporary endeavor which outputs a unique and predefined product, service or result by using predetermined resources within the pre-confirmed time period. The project is characterized by one-time, uniqueness, definiteness of objective, temporality and openness of organization and irrevocability of consequences. Project management are activities with respect to planning, organization, leadership and control carried out for meeting or exceeding the requirements and expectations of project related parties by using various relevant knowledge, skills, methods and tools.

11.1.4.1 Introduction

GEP is the abbreviation of good engineering practice. It is the solution for obtaining appropriate economic benefits by implementing definite engineering methods and standards during the project cycle. In the US and EU, GEP has been successfully applied in the projects of the biopharmaceutical and other relevant industries, and GEP has gained a certain credibility with the pharmaceutical industry after being used by GMP consulting companies and engineering consulting companies with technical strength and rich experience in numerous GMP projects. In December of 2008, ISPE incorporated GEP into the Good Practice Guide, and prepared and issued the GEP Guide, meanwhile, it is introduced to the engineering consulting companies of the global pharmaceutical industry and other relevant fields. Fig 11.11 shows a typical GEP project management lifecycle flow diagram.

The GEP is usually used to describe the engineering management system expected for a regulated pharmaceutical enterprise. During the lifecycle of a new or renovated project, it is ensured that each stage of the engineering construction conforms to the general engineering practice, GMP related facilities, equipment or systems comply with GMP regulations, each aspect of the project satisfies the user requirements by implementing defined engineering methods and standards, and providing effective solutions with appropriate costs, so as to achieve the balance between progress, cost, quality, benefits and risks, and maximize the project value.

The GEP is composed of the following parts: professional and competent project management (process, flow and personnel); professional and competent design, purchasing, construction and pilot run; relevant safety, health, environmental regulations, operation and maintenance requirements, recognized industrial standards and guidelines are taken into consideration; appropriate records are available so that the operation and maintenance can meet the regulatory requirements.

The GEP is not a mandatory requirement of the GxP system, but it can ensure the project is reasonably, economically and effectively implemented. This is the basis of the GMP validation activities. The GEP

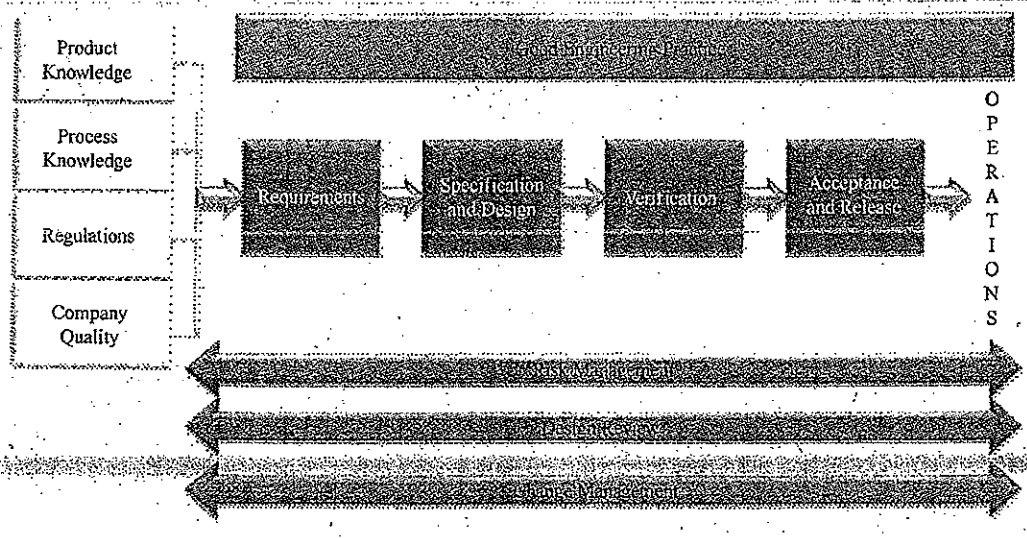


Fig 11.11 GEP project management lifecycle flow diagram

system, as an important supplementation of the GMP system, is to ensure that drug manufacturing enterprises are in final compliance with the GXP. The whole scope of pharmaceutical engineering activities defines the critical attributes of GEP, including how to correlate the GEP and GxP. The GEP covers the whole product cycle from concept design to the completion of the project. The GEP also provides basic requirements for the pharmaceutical industry and other fields (e.g. GxP, construction, etc.) (Fig 11.12). The GEP project management refers to dynamic management, which follows GEP concepts and methods, complies with the GxP standards for controlling the project progress, cost and quality (including engineering quality and GxP quality).

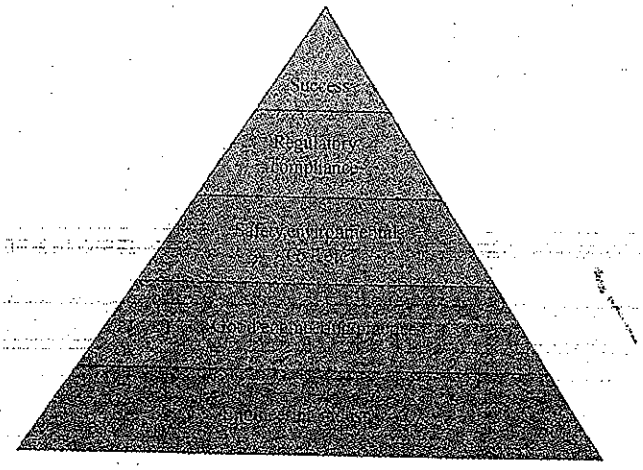


Fig 11.12 Relative position of GEP in relation to GxP

The GEP related facilities, equipment and utilities have the following characteristics: ①The design and installation of a project should take full consideration of current Good Manufacturing Practice, safety, health, environment, ergonomics, operation, maintenance accepted industrial codes and regulatory requirements; the project is comprehensively controlled from engineering quality to drug quality. ②Specialized and competent personnel with corresponding project management qualifications is responsible for project management, and controlling the delivery of design, procurement, construction, installation and commissioning. ③Reasonable filing and records are required for documentation, including the design concept, design blueprints (construction drawings), test records, maintenance and operation manuals, statutory certificate of inspection, etc.

The following issues should be clarified if GEP is actually implemented.

- GEP provides the overview of each project phase and sequence from start, commissioning, qualification to system operation.
- GEP management scope and relevant management concepts need to be defined.
- Description of the activities related to GEP and corresponding documentation need to be provided.
- Establishment of an effective project team concept and organization, and outline of the roles and responsibilities.
- Establishment of an effective project management process, specifying its contents be means of documentation.
- When GEP is applied to the whole project process, it will define the means of achieving the effective qualification basis.

A typical GEP project should include project engineering, common practices as well as operation and maintenance (Fig 11.13). Project engineering refers to the activities performed together with configuration capital and other resources, focused on significant equipment changes or new equipment. Common practice is generally related to project engineering and routine operation and maintenance. The operation and maintenance of the equipment and facilities used in the production process need to be performed in compliance with specified requirements.

11.1.4.2 Risk Management

Risk management is the core component of the GEP activities, e.g. balancing of the risk and benefits. The system risk must be controlled at an acceptable level during the actual system operation. The specific contents of risk management include:

a. Defining/Identifying risk. A regulated company should be able to define the major risks which constitute threats to production activities, and evaluate the risk levels.

b. Evaluating risk. Appropriate evaluation methods should be used to define whether the effect of risk is long-term or short-term; meanwhile, a specialized assessment team should be responsible for evaluating the grade of risk and providing the corresponding risk definition. The evaluation process should take the probability of occurrence, severity of consequence and de-

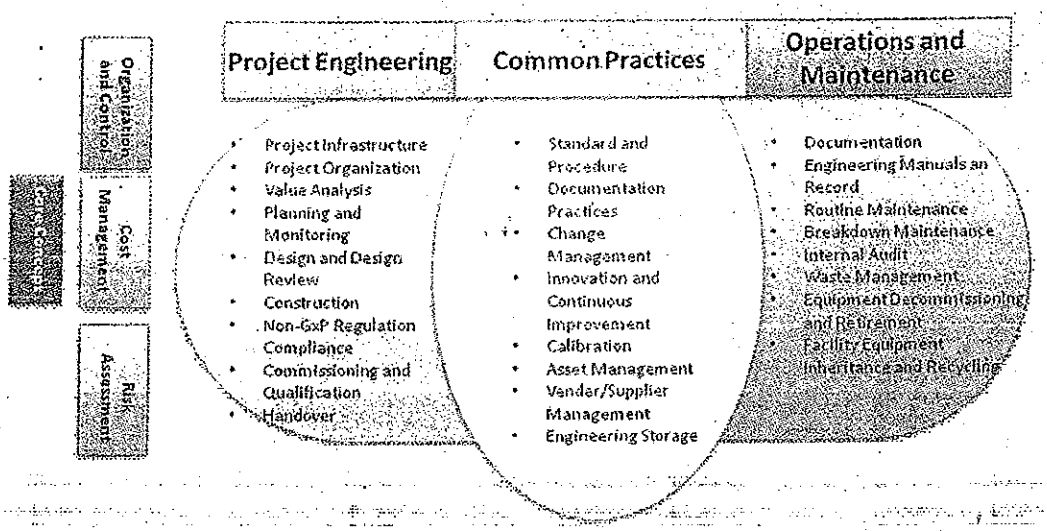


Fig 11.13 The contents of the GEP project

tectability of risk into consideration. The risk should be regarded as a part of all production activities, and a certain amount of risk needs to be accepted during the actual production or construction process. Risk assessment should be undertaken by appropriate technicians, usually, they include technicians from each area exposed to risk, quality personnel and third party assessment teams (if necessary).

c. Documents. For risk management, the documents above a certain level (refers to policy documents to be evaluated or discussed) should be determined by a logical process of thinking, discussing and communicating among team members from an appropriate team, including the prospection of risk and harm. Critical risks with impact on commercial goals should be documented in detail. Only if it is possible to have impact on the process of establishing assessment and evaluating logic, shall the assessment be adopted.

d. Mitigation strategy. Risk management should also include backup strategies, contingency plans and risk mitigation. The commonly used risk mitigation measures include backup of the critical computer system and data, backup electricity generation, redundancy of steam/air and gas systems, backup pumps, special protection for parts with high risk, safety systems/automatic power off systems, etc.

11.1.4.3 Cost Management

Cost management is a critical part of the GEP. The impact of any activity in the project on cost (including returns of these activities) should be evaluated and managed. The returned value of input cost is a critical parameter for balancing cost, quality and schedule. Cost management should ensure that each aspect of the project with impact on cost is understood, evaluated and managed, and returns maximum value for the company. The value here refers to balancing the engineering cost, quality and schedule. Cost management includes:

a. Initial estimate. A company should have an established systematic process to calculate the expense budget for a given project and to evaluate its feasibility. The cost budget should trace and predict the final cost and project sustainability, and be subject to updates at any time as the project progresses.

b. Planning. The relationship between schedule and cost should be understood and optimized to obtain maximum return on investment.

c. Return on investment. The relationship between the activity cost and the return on investment should be analyzed, and recommendations provided at each phase of the project development.

d. Front end loading. More resources that are allocated for the project planning and design phases can improve the level of design and the definition of the stages, and help reduce the risks of over-spending and running behind schedule, however, it may slow the project during subsequent stages.

e. Packet policy. The return on investment should be subject to company regulations; an acceptable payback period for the investment and long-term business strategies should be determined.

f. Cost of ownership. The cost of ownership (acquisition cost), including the operating and closing costs should be reflected in the investment decision.

g. Cost control. Cost control measures should be established in an appropriate manner to ensure the impact on

costs and schedule is controlled before they are approved.

11.1.4.4 Organization and Control

Organization and control is another important part of the GEP activities. Organization should ensure the maximum efficiency, and an acceptable input-output ratio. The organization of the internal control mechanism should monitor the performance and progress of assigned activities, and a clear organization and control structure should allow for an effective response to changing market demands. Organization and control should include:

a. Clear structure. In a mature company business hierarchy, reporting relationships and responsibilities should be clearly understood and documented. Matrix management used in specific activities can redefine or revise the hierarchy; such changes should be clearly defined.

b. Review. A regulated company should review the organization structure periodically to ensure maximum efficiency and the overhead rate is acceptable when comparing with similar companies.

c. Supervision. The control mechanism in the company should supervise the performance and progress of assigned activities.

11.2 Welding Quality Control

Welding is one of the most common and important processes in a stainless steel system. It is found in many pharmaceutical water engineering projects; unacceptable welding quality is the primary cause for rapidly appearing rouge in the system or for the water quality index not complying with requirements.

For welding of sanitary stainless steel pipelines, fittings and other process components, it is mandatory to perform trace welding. If trace welding is not possible at certain locations manual welding can be performed if approved by the owner or third party management company. The welded junctions of manual welding should be subject to strict quality control measures. The control of the welding quality is an important factor for determining whether the pharmaceutical water system can meet the process design requirements, therefore, the requirements for welding equipment, argon quality, weld forming, color of weld joint, finish of weld joint, gradient, dead leg, etc. are very strict. The control of the welding quality requires the construction unit to allocate substantial human and material resources, and the project owner shave have a specially assigned person to supervise and inspect the welding quality.

11.2.1 Basic Elements of Welding

It is a must to seta dedicated clean pre-treatment room complying with requirements for storing clean pipeline materials and welding pre-treatment of the pipelines. All appliances used for cutting and surface treatment of stainless steel should be dedicated to process 316L stainless steel, and separated from appliances for cutting other materials. The procedure of pipeline cutting should not introduce impurities (e.g. dust, oil, grease, etc.), damage or deform the pipeline, etc. It requires the construction unit to train or hire well qualified workers and acquire machines and tools, e.g. GF dicing saw, tungsten needle grinding machine, butt clamp, clean gas tube, chamferer, stainless steel scraper, mouth machine, stainless steel file (or alloy file), universal bevel protractor (for controlling the installation angle of diaphragm valve), special industrial endoscope, special automatic stainless steel welder, etc.

The welders must be trained and qualified by the relevant labor department and should have a certificate of special operation for welding, especially for the workers involved in automatic welding, who need to have a comprehensive understanding of automatic welding equipment, they should undergo special technical and quality training specific to pharmaceutical water systems of different cleanliness grades. Due to the lack of a qualification evaluation system for workers engaged in welding with automatic welding equipment in China, the training is usually conducted by the welding equipment manufacturer or organized by construction unit. It is recommended for construction units to establish job level evaluation mechanism for welders, including workers involved in manual and automatic welding; evaluate the competence of welders annually, and prohibit unqualified welders to conduct welding.

The welding of materials made of 316L stainless steel should use argon-shielded welding, both the inside and outside of the welding materials need to be completely covered by argon and isolated from air for welding protection. The argon used during the welding process must be provided with complete quality certifi-

cate, including oxygen content, water content and purity. A protection gas of high purity is an important factor in the success of the welding operation. The purity of argon for protection is required to be not lower than 99.99%, it is recommended to use argon with purity of above 99.999%; it is suggested to use a gas filter to avoid the effect of particles in argon. The purity of argon can be verified by making welded samples, and the optimal protection effect of argon indicated by no change in color of the weld joint and the heat-affected zone of the internal wall of the welded sample after welding.

The welding quality should be strictly controlled during welding. After the pipeline is cut, the burrs in the pipe orifice must be processed with a special file, and the internal and external walls of the welded junction should be cleaned (it is better to wipe with a lint free cloth dipped in ethanol), and then the butt joint is made. The deviation of the welded junction should be within the standard requirements, and the deviation of the internal and external walls should not be more than 15% of the thickness of the pipeline wall (Fig 11.14).

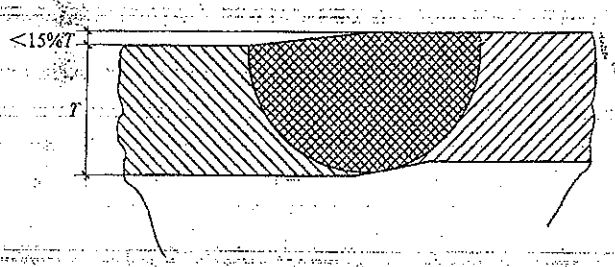


Fig 11.14 Test standard of deviation of welded junction

The welding spot formed by spot welding in the welded junction should be as small as possible and no continuous spot welding apparent. Spot welding should use an as low as possible fusing point, and the diameter should be not more than 2.0 mm (Fig 11.15). For a pipeline with the diameter of less than 4 inches, it is suggested that the number of temporary welding spots is not more than 6. Automatic welding cannot be conducted for weld joint; manual welding can be performed by an excellent welder with the agreement of the customer and welding engineers. The manual welder should be subject to skill assessment (employment with certificate) and verification by making welded samples before the welding operation.

Welding of the samples for verification must be done in an environment equivalent to the one actually used in construction. After the weld joint of the sample is tested and qualified, the welding process parameters

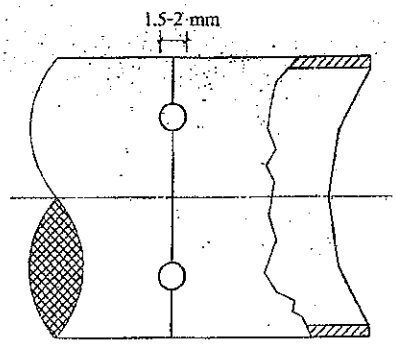


Fig 11.15 Requirements of spot welding

can be used in the normal welding, meanwhile, the welded sample should be stored in proper conditions and handed over to the customer after the completion of construction (Fig 11.16). The welding parameters used for the welded sample must be consistent with that for site operation. The formal welding is performed after the abovementioned activities are completed, after that, the completed weld joint should be cleaned by coating with acid unguent on the exterior of the weld joint and scrubbing with a scouring pad and fresh water (chloride content should be less than 25 ppm).

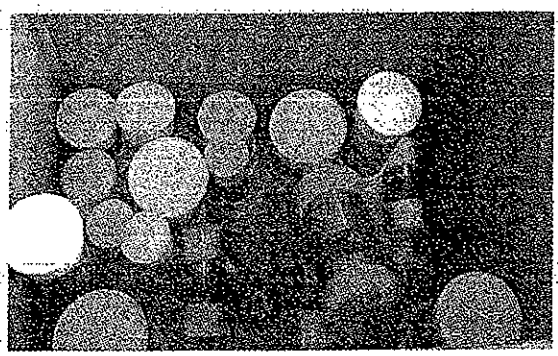


Fig 11.16 Management of welded sample

After welding, the welder should conduct self-inspection on 100% of the welded junctions, and relevant personnel are required to conduct mutual inspections.

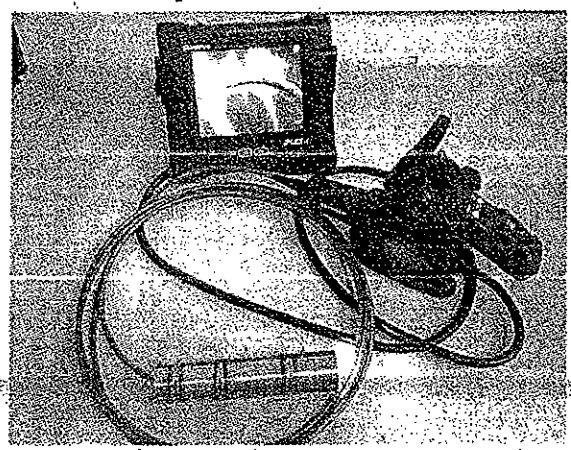


Fig 11.17 Endoscope detector

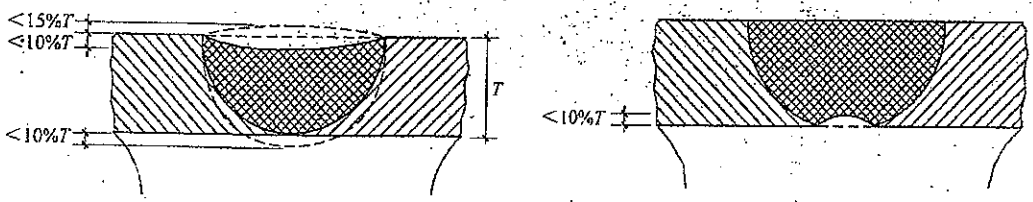


Fig 11.18 Requirements for weld joint concave-convex irregularities

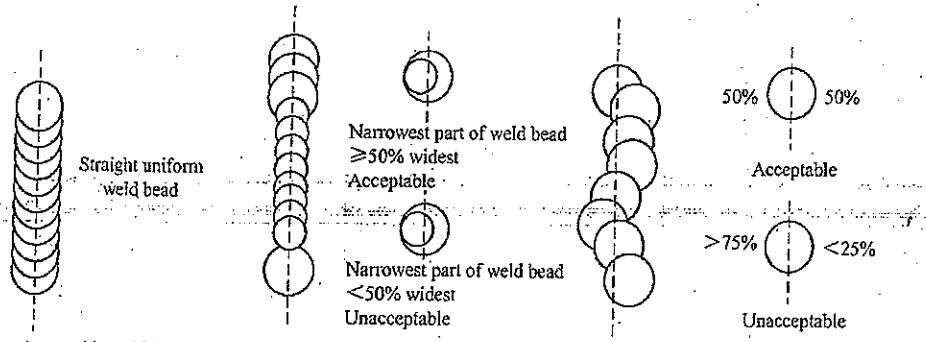


Fig 11.19 Requirements of weld joint molding

Welded junctions that are found to have problems must be timely repaired and corresponding corrective actions taken. The release of welding quality requires endoscopy (Fig 11.17), and the proportion of endoscopy sampling is stipulated as not less than 20% sampling ratio of automatic welding, and 100% inspection for manual welding.

No visible concave or convex irregularities should be observed during the visual inspection (Fig 11.18), no serious molding non-uniformity (Fig 11.19), no erosion, pinholes, corrosion, tack weld joint, etc.

11.2.2 Common Weld Defects

During welding, the defects such as weld porosity, incomplete penetration and fusion, solid inclusion, welding deformation and shrinkage, surface tearing and polishing scratching should be effectively controlled. Please refer to 9.4.1.

11.3 Passivation Quality Control

The chapter about passivation of clean stainless steel piping system in *ASME BPE* 2014 gives a specific description of the design, executive standard and acceptance method. It contains the preparation for and implementation of such procedures as initial water flushing, chemical cleaning, degreasing, passivation and final rinse after the installation, location or renovation of special equipment and BPE equipment, and it also stipulates the examination method of the passivation process for production systems and components coming in direct contact with biological pharmaceutical engineering products and personal-care supplies, meanwhile, it provides some information on passivation procedures and verification methods for the surface passivation effect after the completion of various passivation processes. The contents are especially applicable to 316L stainless steel and alloy materials with higher standards.

Passivation is the optimal choice, and also a necessary procedure for improving the corrosion resistance of stainless steel of standard grade, but for stainless steel with higher requirements for corrosion resistance (such as the content of molybdenum reaching 6%), passivation is not enough. Passivation is used by the equipment user to reduce the iron content and increase the chromium content in the system. It should be noted that optimal passivation or other surface treatment can only make the corrosion resistance of the metal itself reach its maximum in a specific environment. In other words, passivation can only maximize the corrosion resistance of the metal itself, but not grant additional corrosion resistance to the metal. Therefore, under certain circumstances, passivation cannot replace other additional substances to promote extra corrosion properties.

Although stainless steel assemblies may be clean and the surface passive film complete, welding damages the passive film in the weld joint and the thermal effect areas. The initial element distribution (chromium, iron, oxygen) present in the weld joint and thermal effect areas is disorganized due to metal melting, and thus the iron content is increased, while the chromium content, which is originally higher than the iron content, is decreased.

In addition, during the processing of the system pipe fitting, the occurrence of heat tint and introduction of impurities (especially iron) will weaken the corrosion resistance of the alloy to some extent. Passivation after welding helps recovering the damaged passive film by removing free iron, but it cannot remove heat tint. The removal of heat tint requires the use of an acid with stronger chemical corrosion properties than commonly used acids, such as nitric acid and citric acid used for passivation.

The alloy parts may be contaminated during processing, cutting and bending by contaminants such as iron introduced during processing, and residues generated by the heat tint and welding process, or contamination caused by arcing, and marks made on the surface of the alloy, etc. therefore, the corrosion resistance of the alloy will be reduced. If the stainless steel has direct contact with carbon steel or iron parts, it significantly influences the corrosion resistance of the stainless steel. Passivation is helpful in removing contaminants, especially the iron, and recovering the passive film damaged by processing on the surface of alloy, its importance is obvious.

11.3.1 The Principle of Passivation

Passivation is a method of making the metal surface not easily oxidized to delay the corrosion of metal. The effect of passivation, including passivation depth and optimizing the distribution of metallic elements on the surface [e.g., chromium-to-iron (Cr/Fe) ratio], will determine the corrosion resistance and corrosion rate after the metal is passivated. Passivation is a spontaneous phenomenon when there is oxygen in contact with the clean surface, which can generate a passive film on the surface of the stainless steel. The passive film on the stainless steel surface can be strengthened to some extent by chemical treatment. A prerequisite of passivation is a cleaning procedure of the surface. The mentioned cleaning procedure should include the removal of all contaminants on the surface (grease, granules, etc.) to ensure the optimal corrosion resistance of the metal surface, protect the products from being contaminated and meet the requirements for appearance of the alloy surface. The ultimate purpose of chemical passivation is to ensure there is no elemental iron and other impurities on the alloy surface to achieve the optimal corrosion resistance.

Passivation is divided into spontaneous passivation, chemical passivation and electrochemical passivation. Spontaneous passivation refers to a passive film generated on the surface of stainless steel, a spontaneous phenomenon due to oxygen existing on the clean surface of stainless steel. The passive film on the stainless steel surface can be strengthened to some extent by chemical and electrochemical treatments. The metal passivation caused by some passivators (chemicals) is called chemical passivation; oxidants such as concentrated HNO_3, concentrated H_2SO_4, $HClO_3$, $K_2Cr_2O_7$ and $KMnO_4$ can make the metal passivated. After the metal is passivated, its electrode potential is moved in the positive direction, and makes it lose its original properties, e.g., the passivated iron cannot displace the copper in the cupric salt. The potential of $Fe \rightarrow Fe^{2+}$ is -0.44 V, but it is changed to $+0.5$-1 V after passivation. Moreover, the metal can be passivated by electrochemical methods, e.g., placing Fe into a H_2SO_4 solution as anode, polarize the anode with impressed current, rise the potential of iron, then Fe is passivated. The metal passivation caused by anodic polarization is called anodic passivation or electrochemical passivation.

The formation of the passive film on the metal surface corresponds to two different theoretical models, the oxide-film theory and adsorption theory respectively.

a. The oxide-film theory states that the passivated metal will form a compact and well-covered solid substance on the surface when dissolving. This substance forms an independent phase, which is called passive film or oxide film. The film separates the metal surface and solution mechanically to make the dissolution rate of metal slow down greatly and passivates the metal. The experimental evidence shows the oxide film can be seen on the surfaces of some passivated metals, and its thickness and composition can be measured using methods such as XPS. If some reagent, which can dissolve the metal but have no reaction with the oxidation film, is used, the metal is dissolved and removed carefully out of the film, so as to separate the visible

passive film.

When the metal is dissolved as the anode of an electrochemical reaction, its surrounding solution layer is changed. On the one hand, the dissolved metal ions are accumulated due to the low diffusion rate, on the other hand, hydrogen ions on the interfacial layer migrate to the cathode, and anions (including OH^-) in the solution migrate to the anode, as a result, the OH^- ion and other anions concentrations are increased near the anode. Accompanying the electrolytic reaction, the electrolyte concentration may become saturated or hypersaturated in the solution layer closely near the anode interface, therefore, the metal hydroxide with low solubility or some salt will be deposited on the metal surface and form an insoluble film. This film is usually too loose to cause passivation of the metal, while it can impede the dissolution of metal; however, the electrode surface is covered by it, the contact area of the solution and metal is largely shrunk, therefore, the current density of the electrode will be increased and the potential of the electrode will be changed to positive. It may cause the OH^- ion to discharge on the electrode, it will react with metal ions on the electrode surface to form a passive film. It is known from analysis that most of the passive film is composed of metal oxide, but a portion is composed of hydroxide, chromate, phosphate, silicate, slightly soluble sulfate and chloride.

b. Adsorption theory states that effective passivation on the metal surface does not require the formation of a solid film, it is enough to achieve passivation by forming an adsorption layer made by oxygen or particles containing oxygen (e.g., O^{2-} or OH^-, more people think it is oxygen atoms). Although the adsorption layer only has a monolayer thickness, due to the adsorption of oxygen on the metal surface, an oxygen atom is combined with the outermost atom of the metal for chemical adsorption, that makes the chemical binding force on the metal surface saturated, changes the structure of the metal and solution interface, and greatly improve the activation energy of the anode reaction. The main experimental basis of the theory is measuring the interfacial capacitance and electric quantity required by the passivation of some metals. The experimental results indicate that some metals can be passivated without requiring the formation of an oxide film.

The two passivation theories explain part of the experimental facts, but they have advantages and disadvantages when considered at the atomic level. The metal passive film does have the structure of an oxide film, meanwhile, it has a monolayer adsorption film, and it is not clear what conditions can form an oxide film and what conditions can form an adsorption film. Direct experimental evidence to combine the two theories is lacking, therefore, the passivation theory needs to be further studied.

11.3.2 Passivation Process Procedure

The best opportunity for passivation is after the installation activities such as the welding process or after the new pipe fitting is welded to the existing system. Before passivation, the passivation provider should select welded and non-welded pipe fittings as specimens for final acceptance inspection. The specimens should undergo passivation with various methods (e.g., circulation, spot, bath) to prove the passivation method is capable of providing the required surface characteristics, namely, cleanliness, surface chemistry, and corrosion resistance.

The passivation technical protocol and qualification documents should be timely reviewed by the customer. The customer has the responsibility to review and verify that the passivation protocol can be used to deal with the system and specimens. The passivation technical protocol should ensure the reasonability of each parameter used in the passivation process to achieve the effective removal of free ions in the system to be treated, and make the specimens for acceptance inspection of the passivation effect meet the requirements of each item in Table 11.2.

Table 11.2 Passivation effect test standard

Material of specimen	Test method	Cr/Fe ratio	Layer depth of passive film /Å
316L stainless steel	Auger electron spectroscopy analysis	1.0 or above	≥15
316L stainless steel	Glow-discharge optical emission spectroscopy analysis	1.0 or above	≥15
316L stainless steel	X-ray photoelectron spectroscopy analysis	1.3 or above	≥15

The protocol evaluation should at least include the following items:

a. Process description. It should include but not limited to the following steps (refer to Table 11.3)

- Site investigation and preparation before passivation;
- System rinse;
- System cleaning;
- Passivation;
- Final rinse;
- System acceptance.

b. Important parameters. The following important parameters should be considered in the design.

- Passivation time;
- Temperature of passivation reagent in the process;
- Basic chemical index of passivation reagent;
- Passivation completion verification;
- Conductivity of final deionized water.

c. Passivation effect verification by sample test.

- The test result of the qualification sample obtained by electron spectroscopy for chemical analysis (ESCA)/X-ray photoelectron spectroscopy (XPS), auger electron spectroscopy (AES) or glow-discharge optical emission spectrometry (GD-OES);
- Due to the fact that the above mentioned passivation effect involves significant costs for the user, it is possible to use easier and more economic site verification methods for the passivation effect acceptance inspection, such as the blue point test.

At present, many norms and regulations give detailed descriptions of the passivation process, this book excerpted the relevant stipulations on the passivation process in such literature as *Drug Manufacturing Validation Guide*, SJ 20893—2003 *Stainless Steel Pickling and Passivation Practices*, *ASTM A967 and ASME BPE*.

a. Drug GMP Guideline. The passivation process described in the chapter *Facilities and Equipment* in the Chinese *Drug GMP Guideline* 2010 is the following:

6.2 Passivation

Passivation is the process of consolidating the steel surface by chemical reagents with strong oxidizing properties such as nitric acid. The acid can reduce the acid soluble material on the steel surface and make the chromium with high reactivity on the surface stay in the form of composite oxide.

After the chromium nickel stainless steel system is established, the welding will damage the existing passive film and decrease the corrosion resistance of the material. Passivation can restore the integrity of the surface of damaged corrosion-resistant materials.

It is very important to form a passive film on the surface of chromium nickel stainless steel, it can maximize the corrosion resistance of the material.

Both chemical and electrochemical processing can be used to form the oxide film. The thickness of chromium oxide film is usually 0.5-5.0 nm, *with an average of* 2.0-3.0 nm.

6.2.1 Passivation procedure

There are many passivation procedures, but they have the same main steps:

- *Cleaning and degreasing (alkaline solvent is commonly used)*
- *Water flushing*
- *Acid wash (actual passivation step)*
- *Final water flushing*

6.2.2 Solvent in common use

Nitric acid is a strong oxidizing acid, it is the most commonly used acid for passivation. In addition to generating an iron free surface, it can provide the oxidation environment required for passivation. Nitric acid is a corrosive chemical reagent, it must be handled, stored and used with care.

Although nitric acid is the traditionally preferred acid for passivation, the application trend for passivation solutions is to reduce chemical corrosion, and take safety, cost and the environmental pollution of the liquid waste into consideration.

Citric acid and ammonium citrate (citric acid containing ammonium) are used as substitutes for nitric acid gradually replacing it. The safety provided for personnel and work environment by these chemical reagents is virtually ideal. The ASTM A380 (1996) categorized these acids as acids for cleaning but not acids for passivation. The reason for such distinction may be that these acids are not oxidizing agents like the nitric acid. The standard states that the treatment with citric acid-sodium nitrate has low risk when it is used to remove free iron and other metal contamination and light surface contaminants.

Phosphoric acid is a weak oxidizing acid and is sometimes used in specific passivation, however, no formal documentation indicate that phosphoric acid can be used as an acid for passivation.

Chelating agents, also known as release agents or coordination compounds, including all standard water softening compounds, e.g., sodium tripolyphosphate (STPP),

nitrilotriacetic acid (NTA) and ethylenediaminetetraacetic acid (EDTA) are compounded to acid passivation solutions to promote the leaching of metal ions.

6.2.3 Chemical reagents application methods

Passivation can be achieved by a series of application methods.

The best effect can be reached by stirring or striking during rinsing. The contact with the chemical reagents is usually sufficient during the pickling process. The preferred application method for the operation of passivation is circulation. Circulation can make it reach the standard flow rate (usually it is 5 feet/second, i.e. 1.5 m/s). The flow rate complying with operation requirements cannot be confused with particle removal. It is widely thought that high flow rate can remove particles, but it is wrong. The appropriate math equation for the number of total linear feet must be calculated for particle removal. A recirculating water system of 1000 feet (300 m) with a constant pipe diameter requires filtered circulation for 25 hours to remove the total number of particles.

6.2.4 Cleaning and passivation test

Many tests can be used to determine appropriate cleaning level. It requires verifying cleaning before the passivation operations. The tests conducted by cutting off the free surface of water, wiping or ultraviolet light are some of the test methods. These tests are only a preliminary inspection for cleaning as described in ASTM A380 (1996).

Once the passivation is completed, a test method should be chosen to prove or indicate the passivation operation is successful. The following methods are usually used for testing: copper sulfate titration test, potassium ferricyanide test (blue point test), etc.

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6.2.5 Improved passivation procedures

The passivation procedure can be improved to handle dirt, surface finish requirements and various conditions occurring in welding areas. The simplest method for improving a specific procedure is to adjust the contact time and solution temperature and concentration. Sometimes, a reagent for removing specific dirt can be added to change or modify the detergent or pickling chemical reagent. For example, the solution containing sodium hydrosulfite can be used to replace the detergent rinsing procedure for derouging. Citric acid and phosphoric acid can also be used, they can remove light rouge. Other example is using hydrofluoric acid, or more specific ammonium bifluoride to remove silicone dioxide dirt. The dirt removal step and its attached cleaning step require adding extra steps to the standard procedure.

It is important to conduct laboratory tests to determine the effect of procedures when developing a passivation procedure. If no preliminary laboratory tests are done, an educated guess should be made and the result may be not be satisfactory.

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6.2.6 System preparation for passivation

The first test for the system passivation preparation is the static pressure test. All newly constructed or renovated systems must have a pressure test conducted before executing any chemical operations. The second test before passivation is to check the compatibility of the system components and passivation solution, including on-line instruments, flow meters, regulating valves, UV light, pumps, pump seals, filter membranes, gaskets and sealing materials as well as other special on-line equipment. The equipment manufacturer or supplier should be consulted to confirm whether their equipment is compatible with the passivation solution. Any incompatible parts should be removed from the system and substituted by gaps, valves, pipes or temporary connecting hoses. Under some conditions, for on-line instruments, the possible chemical incompatibility is due to the effect on instrument calibration. The incompatible parts should be separated from the main system for separate treatment.

Once the system/chemical compatibility is established, the system to be passivated should be separated from the rest of the system, processing equipment, connected utilities, etc. In most cases, the on-line heat exchanger (excluding metal sheet and support) and the small filter frame (removable filter element) remain in the system and are passed through by the passivation solution. As long as appropriate air exhaust and drain capacity are available, it can be done.

The individual equipment requiring for passivation should be separated from the main system for treatment; unless otherwise specified, it can remain in the system and can be passed through by the passivation solution. All separation points must be controlled by valves to prevent the passivated system from becoming blind pipes.

It is critical to eliminate all blind pipes to ensure the contact of chemical reagents and complete rinse.

The exhaust port at the high level and drain point at the low level are used for the complete filling and draining of the system. For a distribution system without an exhaust port at high level, the high flow rate and flow rate restriction techniques can be adopted to ensure the complete filling of the system.

After the system has undergone the pressure test, compatibility verification, system isolation and it was ensured the blind pipes are controlled by valves, it must be checked whether all automatic control valves of the automatic control of the system are effective, whether the online temperature sensor can turn on the reversing valve when abnor-

mal temperature is detected, and whether it has ideal water flow channel.

The contractor for passivation usually provides temporary equipment, such as circulating pipes, pump heat exchangers, flow meters, filters, hoses, spray heads, accessories, special adapter or connector accessories and container for neutralization. All these equipment should be checked to ensure they can meet the expected use requirements.

6.2.7 Treatment of passivation chemical reagents

The treatment of liquid waste is an important issue. The chemical reagents used for cleaning and passivation are soluble and easy to neutralize. Except for the heavy metals dissolved in the pickling solution, the only criterion as to the harmfulness of the liquid waste is the pH being out of the range of 2~12.5. Heavy metals in the effused liquid waste can cause environment or treatment problems. It is found that the levels of two heavy metals of the thirteen metals with priority contamination detection are increased in the passivation liquid waste, they are chromium and nickel.

The discharged liquid must meet the requirement of discharging temperature at the site.

There are three methods used for treating the liquid waste generated by passivation:

They can be injected into the chemical reagent discharging equipment. This method can be adopted only when the discharging equipment is compatible and the treatment system is effective.

The liquid waste is neutralized in the equipment provided by the contractor, and discharged into the treatment system through the chemical reagent discharging equipment.

The last choice is to discharge far away from the site. The cost of this discharging method is the highest.

If there is no available liquid waste treatment system, the neutralized liquid waste can be drained to the sewer after being authorized by the municipality or owner of the privately operated sewer. Any form of liquid waste is not allowed to be discharged in the storm drain in any cases.

The documents confirming the liquid waste has been discharged appropriately should be received, which should include the shipping list or carrying list for hazardous waste, and the national standard compliance receipt issued by the treatment organization, indicating the place for transporting and treating the liquid waste. When the liquid waste is treated off the site, it is important to verify their certificates before accepting the service of carriers for liquid waste and arriving at final destination.

Finally, it is the responsibility of all participants to discharge the liquid waste in an appropriate and legal manner. The owner of the liquid waste generating facility, contractors, sub-contractors involved with the use of chemical reagents, the carrier and final waste treatment organization should be responsible for the reasonable discharge of the liquid waste.

6.2.8 Documentation

Complete and detailed documentation and records must be maintained according to the selected execution procedures. The concentration, temperature and contact time of chemical reagents, the quality of the supplied rinse water and the readings of effluent samples tests should be recorded.

Some contractors record work data in chronological order using a work logbook, including the details from the time contractor arrives at the site up to the time he leaves the site. In addition to the work logbook, the passivation logbook should also be filled. The detailed information should be recorded in the "fill in the blanks" forms provided by the passivation contractor, validation company or the owner. It is important to maintain exact and detailed documents no matter how the information is recorded. The following information can be submitted to the owner and combined to the final validation documents.

- *Passivation procedures;*
- *Relevant information of each aspect;*
- *Data generated by operation procedures;*
- *Test procedures and equipment;*
- *Passivation logbook;*
- *Batch information of chemical reagents;*
- *Identified systematic diagram, complete use point checklist or pipeline identification list.*

b. The descriptions of passivation in stainless steel pickling and passivation *practices*, *China* SJ 20893—2003 *Stainless Steel Pickling and Passivation Practices* are following:

3.3.1 Degreasing

The grease, dirt and other foreign materials on the surface of the stainless steel parts should be thoroughly removed before pickling or passivation. Cleaning methods such as reagent cleaning, alkaline solution chemical cleaning and electrochemical cleaning can be used when necessary to obtain a clean surface. The chosen method should have no effect on material performance.

Note: clean surface means the surface presents a uniform and continuous water film which does not break for 30s when spraying water on the base surface, and the surface has no other foreign matter or residue detrimental to the quality of the parts.

3.3.2 Pickling

The pickling of stainless steel parts usually uses a chemical method, the reagents used include dilute sulfuric acid, nitric acid and hydrofluoric acid. The mixture of

nitric acid and hydrofluoric acid has a good effect, but it is not suitable to use for austenitic stainless steel and martensitic stainless steel. For parts with welding and heat treatment residues, the surface has a layer of dense and slightly soluble oxidation film, which contains a large amount of chromic oxide and nickel oxide as well as very slightly soluble oxide iron and chromium ($FeO \cdot Cr_2O_3$), therefore, the treatment should usually be subject to several steps such as eliminating the oxidation film, etching and removing etching residues.

a) Eliminating the oxidation film: the solution contains 80-120 g/L of 66% nitric acid, the solution temperature is room temperature, and the treatment time is less than 60 min. Anode electrolysis can also be used: the solution contains 600-800 g/L of hydrogen sodium, the solution temperature is 140-150 ℃, anode current density is 5-10 A/dm², the operation continues until the oxidation film is eliminated.

b) Etching: the solution contains 200-250 g/L of 98% sulfuric acid and 80-120 g/L of 36% hydrochloric acid, the solution temperature is 40-60 ℃, the operation continues until the oxidation film is eliminated completely.

c) Removing etching residues: the solution contains 30-50 g/L of 66% nitric acid and 5-15 g/L of 30% hydrogen peroxide, the solution temperature is room temperature, and treatment duration is 10-60 s. Anode electrolysis can also be used: the solution contains 50-100 g/L sodium hydroxide, the solution temperature is 70-90 ℃, anode current density is 2-5 A/dm², and the duration is 5-15 min.

3.3.3 Passivation

3.3.3.1 Classification of passivation solutions

The stainless steel parts should be passivated only after thoroughly degreased and pickled, and the surface cleaned. The passivation solution for different types of parts has different process parameters. The parts should be completely immersed in the solution to prevent serious corrosion on the part above the liquid level. The passivation solutions are divided into four types (Table A.1).

type Ⅰ—medium temperature nitric acid-sodium dichromate solution;

type Ⅱ—low temperature nitric acid solution;

type Ⅲ—medium temperature nitric acid solution;

type Ⅳ—medium temperature high concentration nitric acid solution.

It should be noted that, the penetration surface of stainless steel parts cannot undergo passivation, for carbon and chromium will produce carbon-chromium compounds on the surface; stainless steel with nitrogen penetration cannot undergo passivation, for passivation will seriously corrode the parts with nitrogen penetration

Table A.1 Classification of passivation solutions

Type Ⅰ treatment solution	Type Ⅱ treatment solution	Type Ⅲ treatment solution	Type Ⅳ treatment solution
Y1Cr18Ni9			
Y1Cr18Ni9Se			
1Cr12			1Cr12
0Cr13			0Cr13
0Cr13Al			0Cr13Al
1Cr13			1Cr13
2Cr13			
3Cr13			
1Cr17Ni2			1Cr17Ni2
7Cr17			7Cr17
8Cr17			8Cr17
9Cr18			9Cr18
9Cr18Mo			9Cr18Mo
11Cr7			11Cr7
00Cr27Mo		00Cr27Mo	
	1Cr17Mn6Ni5N	1Cr17Mn6Ni5N	
	1Cr18Mn8Ni5	1Cr18Mn8Ni5	
	1Cr17Ni7	1Cr17Ni7	
	1Cr18Ni9	1Cr18Ni9	
	0Cr18Ni9	0Cr18Ni9	
	00Cr19Ni10	00Cr19Ni10	
	0Cr19Ni9N	0Cr19Ni9N	
	1Cr18Ni12	1Cr18Ni12	
	2Cr23Ni13	2Cr23Ni13	
	0Cr23Ni13	0Cr23Ni13	
	2Cr25Ni20	2Cr25Ni20	
	0Cr25Ni20	0Cr25Ni20	
	0Cr17Ni12	0Cr17Ni12	
	0Cr17Ni12Mo2N	0Cr17Ni12Mo2N	
	0Cr18Ni10Ti	0Cr18Ni10Ti	
	0Cr18Ni11Nb	0Cr18Ni11Nb	
	1Cr18Ni19Ti	1Cr17	
		2Cr25N	

3.3.3.2 Type Ⅰ

The stipulation for type Ⅰ treatment solution: the solution contains 20%-25% (volume ratio) of 66% nitric acid and (2.5±0.5)% sodium dichromate (weight ratio), the temperature is 49-54 ℃, and the treatment duration is 20 min. Applicable for: stainless steel parts with high carbon content (carbon content is equal to or more than 0.4%)/high chromium content (chromium content is equal to or more than 17%), parts that contain 12%-14% pure chromium or more (above 0.15%) S or Se.

3.3.3.3 Type Ⅱ

The stipulation for type Ⅱ treatment solution: the solution contains 25%-45% (volume ratio) of 66% nitric acid, the solution temperature is 21-32 ℃, and the treatment duration is 30 min.

Applicable for: austenite nickel-chrome steel (excluding the grades of stainless steel with high carbon/high chromium in

type Ⅰ).

3.3.3.4 Type Ⅲ

The stipulation for type Ⅲ *treatment solution: the solution contains* 20%-25% (*volume ratio*) *of* 66% *nitric acid, the solution temperature is* 49-60 ℃, *and treatment duration is* 30 min.

Applicable for: austenite nickel-chrome steel and chromium stainless steel with chromium content equal to or more than 17% (*excluding the grades of stainless steel with high carbon/high chromium in type* Ⅰ).

3.3.3.5 Type Ⅳ

The stipulation for type Ⅳ *treatment solution: the solution contains* 45%-55% (*volume ratio*) *of* 66% *nitric acid, the solution temperature is* 49-54 ℃, *and treatment duration is* 30 min.

Applicable for: stainless steel parts with high carbon content (*carbon content is equal to or more than* 0.4%)/*high chromium content* (*chromium content is equal to or more than* 17%), *and chromium stainless steel parts with* 12%-14% *chromium* (*except* 1Cr18Ni9, 1Cr18Ni9Se, *etc.*).

3.3.4 Rinse

The parts should be immediately and thoroughly cleaned after being taken out of the passivation solution, a neutralization process by alkali washing can be performed after the first rinse when necessary to remove the residual acid solution in the complex chamber. The last cleaning should use deionized water, which should comply with the quality requirements of deionized water in the GJB 480A.

3.3.5 Chromic acid treatment

All ferrite and martensitic stainless steel parts should be treated with chromic acid within one hour after the last rinse. The solution contains 4%-6% (*weight ratio*) *of sodium dichromate, the temperature is* 60-70 ℃, *and the treatment duration is* 30 min. *The process lasts for* 30 min. *after that, the part must be cleaned with deionized water, and then thoroughly dried.*

3.3.6 Drying

The parts should be dried with compressed or hot air after passivation, oven drying or airing can also be used.

3.3.7 Dehydrogenation treatment

High strength steel structures should undergo a dehydrogenation treatment after passivation to avoid hydrogen embrittlement due to the penetration of hydrogen during the pickling process. The dehydrogenation conditions are usually 190-220 ℃ *for at least* 2 h.

3.3.8 Recording

The operator should record the main process parameters for the pickling and passivation treatments, and keep the recorded data.

c. ASTM A967. The ASTM A967 has detailed descriptions of passivation, mainly including the nitric acid method, the citric acid method and other chemical reagents methods.

6 Nitric acid method

6.1 Method

6.1.1 Stainless steel parts can be treated with the following solution for specific durations of time and at specific temperature intervals.

6.1.1.1 The solution is composed of nitric acid of 20%-25% *volume ratio and sodium dichromate of* (2.5+0.5)% *weight ratio. It reacts for at least* 20 min *at a temperature of* 120-130 °F (49 *to* 54 ℃).

6.1.1.2 The solution is composed of 20%-45% *nitric acid. It reacts for at least* 30 min *at a temperature of* 70-90 °F (21 *to* 32 ℃).

6.1.1.3 The solution is composed of 20%-25% *nitric acid. It reacts for at least* 20 min *at a temperature of* 120-140 °F (49 *to* 60 ℃).

6.1.1.4 The solution is composed of 45%-55% *nitric acid. It reacts for at least* 30 min *at a temperature of* 120-130 °F (49 *to* 54 ℃).

6.1.1.5 If different parameters are adopted for passivation, e.g., different concentration of nitric acid, different temperature and duration of time, other chemicals (catalyst, inhibitor or other special reagent) are added or not added, it should be proved by specific test methods.

6.1.2 Rinse: thorough rinse should be conducted right after the passivation solution is drained by means of static stagnation, convection or one-by-one spraying, or a combination of these methods, including/excluding separate chemical neutralization methods specific to the passivation solution. The final rinse is done using water with total solid contents of at most 200 ppm.

7 Citric acid method

7.1 Method

7.1.1 Stainless steel parts can be treated with the following solution for a specific time duration and at specific temperature intervals.

7.1.1.1 The solution is composed of 4%-10% (*weight percentage*) *citric acid, and reacts for at least* 4min *at the temperature of* 140-160 °F (60 *to* 71 ℃).

7.1.1.2 The solution is composed of 4%-10% (*weight percentage*) *citric acid, and reacts at for least* 10 min *at a temperature of* 120-140 °F (49 *to* 60 ℃).

7.1.1.3 The solution is composed of 4%-10% (*weight percentage*) *citric acid, and reacts for at least* 20 min *at a temperature of* 70-120 °F (21 *to* 49 ℃).

7.1.1.4 If different parameters are used for passivation, e.g., different concentration of nitric acid, different temperature and time duration, other chemicals (catalyst, inhibitor or other special reagent) are added or

not added, it should be proved by a specific test method.

7.1.1.5 If other parameters are adopted for passivation, e.g., different concentration of nitric acid, different temperature and time duration; other chemicals (catalyst, inhibitor or other special reagent) are added or not added, it should be proved by a specific test method. If immersion is used, the pH should be controlled in the 1.8-2.2 *range.*

7.1.2 Rinsing: thorough rinsing should be conducted immediately after the passivation solution is drained by means of static stagnation, convection or one-by-one spraying, or a combination of these methods, including/excluding separate chemical neutralization methods specific to the passivation solution. The final rinse is done using water with total solid contents of at most 200 ppm.

8 Other chemical reagent methods

8.1 It is recognized that the removal of all exogenous materials on the surface of stainless steel, including the removal of free iron, can be performed by a professional team using different solvents, which includes specially developed passivation solutions. These treatment methods include the application of electric potential on the surface of stainless steel, e.g., electropolishing treatment. To meet the specific requirements of passivation, it should be verified whether the treatment method is applicable, and conduct validation according to specific test requirements for the parts to be passivated.

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8.3 Rinsing: thorough rinsing should be conducted right after the passivation solution is drained by means of static stagnation, convection or one-by-one spraying, or a combination of these methods, including/excluding separate chemical neutralization methods specific to the passivation solution. The final rinse is done using water with total solid contents of at most 200 ppm.

d. ASME BPE. The descriptions of passivation in the ASME BPE are the following:

• Procedure description. The passivation provider must obtain welded and non-welded sample component (s) or specimens from each passivation method used (e.g., circulation, spot, bath) for the purpose of demonstrating that the procedure is capable of providing the required surface characteristics, namely, cleanliness, surface chemistry, and corrosion resistance. The passivation process used on the abovementioned welded and non-welded specimens must be reproducible. The procedure description and qualification document must be available for review by the owner/user or his designee. The owner/user will be responsible for verifying that the passivation procedure to be used on their system or components has been qualified.

• Procedure qualification. The passivation provider should develop a passivation procedure for each method used. The procedure should be developed to ensure that each parameter used in the passivation process is reasonable, so as to achieve the effective removal of free iron in the system to be treated and meet the requirements of the norms. Table 11.3 gives a detailed description of the recommended passivation procedures.

In conclusion, the cleaning and passivation methods widely used for 316L stainless steel in the pharmaceutical industry are illustrated in Table 11.4. The detailed passivation standards can refer to ASTM A380 and ASTM A967. It should be noted that the passivation effect is in relation to multiple factors such as the passivation time duration, temperature, chemical concentration, mechanical force, etc. which are integral and interdependent. Therefore, the enterprise should make a reasonable selection according to different conditions.

Table 11.3 Passivation processes

Process type	Process description	Comments	Conditions of process	Chemistry
Pre-cleaning				
Water flushing/filtration processes	High velocity deionized (or owner/user chosen) water flushing for removal of particles and construction debris	Removes debris prior to the passivation process	Ambient temperature for 5 min to 30 min per section; generally includes filtration of fluids	Deionized water
	High velocity water flushing	Removes debris prior to the passivation process. Chlorides in water are detrimental to stainless steel	Ambient temperature for 15 min to 60 min per section	Deionized water (recommended)

cont

Process type	Process description	Comments	Conditions of process	Chemistry
Cleaning				
Cleaning/degreasing processes	Phosphate cleaners	Removes light organic deposits. Can leave phosphate surface contamination	1 to 4 h at heated conditions depending on the solution and contamination level	Blends of sodium phosphates [monosodium phosphate, disodium phosphate, trisodium phosphate] and surfactants
	Alkaline cleaners	Can be selected for specific organic contaminates		Blends of nonphosphate detergents, buffers, and surfactants
	Caustic cleaners	Effective at removal of heavy organic contamination or degreasing		Blends of sodium and potassium hydroxides and surfactants
	Isopropyl alcohol(IPA)	Effective as a degreaser, volatile, highly flammable and sensitive to siatic discharge	Physical wipe	70%-99%
Passivation				
Passivation processes	Nitric acid	Proven method under ASTM A380/A967	30 to 90 min at ambient temperature or higher, depending on concentration used	10% to 40% nitric acid at heated conditions
	Phosphoric acid	Effective at removing iron oxides in addition to free iron.	1 to 4 h at heated conditions	Volume ratio: 5% to 25% phosphoric acid
	Phosphoric acid blends	Can be used at a variety of temperatures and conditions		5% to 25% phosphoric acid plus either citric acid or nitric acid at various concentrations
	Citric acid	Specific for free iron removal. Should be processed at elevated temperatures. Takes longer to process than mineral acid systems. Meets or exceeds ASTM A967		10% citric acid
	Chelant systems	Specific for free iron removal. Should be processed at elevated temperatures. Takes longer to process than mineral acid systems. Meets or exceeds ASTM A967.		3% to 10% citric acid with various chelants, buffers, and surfactants
	Electropolishing	Specific for free iron removal. Should be processed at elevated temperatures. Takes longer to process than mineral acid systems. Meets or exceeds ASTM A967.	Exposure time must be calculated to ensure 5 to 10 μm material removal from all surfaces requiring passivation. Rinsing must include a step to ensure removal of residual film that may adversely affect the passivation quality	Phosphoric acid electrolyte

cont

Process type	Process description	Comments	Conditions of process	Chemistry
Oxidation processes	Hydrogen peroxide	Oxidizes metal surface and sanitizes	30 min to 2 h at ambient to 40 ℃	3% to 10% hydrogen peroxide
	Hydrogen peroxide with peracetic acid blends	Oxidizes metal surface and sanitizes		1% to 2% blend

Notes: the application methods include fluid circulation, gelled applications for welds or surfaces, and spraying methods for vessels and equipment. Special attention should be directed to the removal of metal shavings and construction debris from locations such as spray balls, diaphragm valves, heat exchangers, etc. These passivation processes may produce hazardous wastes based on the metals content, and local and state regulations. The time and correlating temperatures given above are in direct relation to the percent by weight of the base reactants. A change in a formulation may change those corresponding requirements. The rinse must immediately follow each of the above chemical treatments. Chemical percentages are based on weight percent.

Table 11.4 Different passivation methods for 316L stainless steal

Method	Comments	Cleaning condition	Chemical action
Phosphate	Removes light organic contamination, may leave phosphate deposits	1 to 4 h at heated conditions depending on the solution and contamination level	Blends of sodium phosphates [monosodium phosphate, disodium phosphate, trisodium phosphate] and surfactants
Alkaline cleaners	Can be selected for removal of specific organic contamination		Non phosphoric acid/nonphosphate, buffers, surfactants
Caustic cleaners	Effective at removal of heavy organic contamination or degreasing		Blends of sodium and potassium hydroxides and surfactants
Sodium hydroxide	Proven method under *Drug Manufacturing Validation Guide*	Temperature: 70 ℃; Concentration: 1%, Time: not less than 30min	Cleaning by alkaline liquor
Isopropyl alcohol	Can be used as a degreaser, volatile, highly flammable and sensitive to static discharge	Physical wipe by manual	Volume ratio: 70%-99%
Nitric acid	Proven method under ASTM A380/A967	30 to 90 min at ambient temperature or higher, depending on concentration used	Volume ratio: 10% to 40% nitric acid
Nitric acid	Proven method under *Drug Manufacturing Validation Guide* 2003	—	8% nitric acid reacts for 60 min at 49-52℃
Nitric acid	Proven method under national standard SJ 20893—2003	—	20% to 45% nitric acid reacts for 30 min at 21-32 ℃
Nitric acid + hydrofluoric acid	Proven method under *Drug Manufacturing Validation Guide* 2003	—	20% nitric acid + 3% hydrofluoric acid react for 10-20 min at 25-35 ℃
Phosphoric acid	Effective at removing iron oxides in addition to free iron	1 to 4 h at heated conditions	Volume ratio: 5% to 25% phosphoric acid
Phosphoric acid blends	Can be used at a variety of temperatures and conditions		5% to 25% phosphoric acid plus either citric acid or nitric acid at various concentrations
Citric acid	Specific for free iron removal. Should be processed at elevated temperatures. Takes longer to process than mineral acid systems. Meets or exceeds ASTM A967		10% citric acid
Chelant systems	Should be processed at elevated temperatures. Takes longer to process than mineral acid systems. Can remove iron oxides and free ion. Meets or exceeds ASTM A967		3% to 10% citric acid with various chelants, buffers, and surfactants

cont

Method	Comments	Cleaning condition	Chemical action
Electropolishing	This process is generally limited to components rather than systems. Process should be performed according to a qualified procedure. This process removes metal from the surface	Exposure time must be calculated to ensure 5 to 10 μm material removal from all surfaces requiring passivation. Rinsing must include a step to ensure removal of residual film that may adversely affect the passivation quality	Phosphoric acid electrolyte

• Passivation quality control surveillance can ensure the successful implementation of the qualified written passivation procedure and provide a guarantee for controls. A thorough rinse with deionized or owner/user-approved water should follow the chemical treatment. It is generally recommended that the system is rinsed continuously until, as determined by conductivity analysis, the ionic contaminants, process chemicals and byproducts generated from passivation process have been removed.

11.3.3 Passivation effect test

A passive film can inhibit the development of corrosion on the surface of stainless steel effectively. The evaluation methods of passivation effect include passivation depth and optimizing the distribution of surface metallic element, which will determine the corrosion resistance and corrosion rate of the metal after passivation.

The chromium-to-iron (Cr/Fe) ratio is the molar ratio of chromium and iron elements on the surface of the passive film. Passivation is capable of dramatically increasing the Cr/Fe ratio on the surface of 316L stainless steel when properly applied. The degree of enhancement of the Cr/Fe ratio can be measured according to AES, GD-OES, or ESCA/XPS. These procedures are helpful in judging the passivation effect and provide the basis for improvement of the passivation protocol, however, they are not readily adapted to field use. At present, no mature industrial equipment which is portable and able to quantitatively determine the Cr/Fe ratio of the passive film is available.

According to the definition of passivation, the higher the Cr/Fe ratio is the better. The acceptance threshold of the Cr/Fe ratio should be not less than 1 no matter which procedure is used, therefore, it is thought that a Cr/Fe ratio of the passivation layer equal to 1 is the critical point between a good passivation layer and a bad passivation layer from an engineering standpoint. It should be noted that test results may differ with different test methods due to the variability in accuracy.

The thickness of the passive film can also be measured according to AES, GD-OES, or ESCA/XPS. It is usually considered that a thickness of the passive film of 1.5 nm (15 angstrom, i.e., 15 Å) is in compliance with the passivation requirements.

It should be noted that the passivation effect is required to be documented after the completion of passivation. The documenting of the passivation effect is done according to the specific classification in the ASME BPE standard. Table 11.5 is the test matrix for the evaluation of cleaned and/or passivated surfaces, which can be a guidance document for inspecting and accepting the passivation effect by the owner/user. This matrix is a simplified compilation of testing methodologies that an owner/user may want to use in selecting a test or as a means to perform validation through a third-party company. The matrix is divided into groups of four types of testing methods.

• Visual inspection of passivated parts per ASTM A380/A967 (Pass/Fail).

• Precision inspection of passivated parts under ASTM A380/A967 (Pass/Fail).

• Electrochemical field or laboratory tests.

• Surface chemical analysis tests.

Table 11.5 The matrix of testing methods for passivation

Type of test	Test description	Test Criteria	
		Pros	Cons
Visual inspection of passivated parts per ASTM A380/A967			
Visual inspection method	Including visual inspection to the cleanliness of internal wall of treated stainless steel specimen and residual rouge. It can be inspected by naked eyes directly or by means of instrument(e. g. endoscope) for auxiliary observation	Save both time and labor, and not restricted by field environment. It is applicable to detect routine and simple surfaces	No quantitative analysis, and test result is subject to subjective interpretation by the tester
Wipe test(ASTM A380)	Rubbing a test surface with a clean, lint-free, white cotton cloth, commercial paper or filter paper moistened with high-purity solvent(but not saturated). It can be used for evaluating the surface that cannot be readily accessed for direct visual inspection. The wipe test for minor diameter tube can be done by blowing a clean and white felt ball with diameter slightly bigger than the pipe diameter to pass through the pipe using clean, dry and filtered compressed air. The wipe test is evaluated by the cleanliness of cleaning cloth or type of contamination wiped from the felt ball. The stain on the cleaning cloth indicates the existing of contamination	Compared with visual inspection, it is more persuasive. Removable surface contamination can be easily identified and compared	No quantitative analysis. The wipe range is restricted by the size of specimen. There is also a risk of leaving errant fibers behind from the wipe or plug. Can be detrimental to electropolished stainless steel surfaces
Residual pattern test	Clean 20 min at120 °F(49 °C), and then dry the cleaned surface. The presence of stains or water spots indicates the presence of contaminants and incomplete cleaning	A simple test with rapid results	No quantitative analysis. Not very sensitive
Water-break test	Used for test hydrophobic contamination on the clean surface of stainless steel specimen	General cleanliness of surface is easily determined. It is simple and fast	Only applicable to products which are able to be immersed in water, tested with high pure water. Useful in detecting hydrophobic contamination
Water-wetting and drying(A380)/water immersion practice(A967)	It is used to test free ion on stainless steel surface and impurities on other anode surface. The sample of passivation parts should be immersed in a rustless container with distilled water for 1 hr, and then dried in air for 1 hr. The operation should be repeated for 12 times at least. If the specimen has no obvious reaction, it indicates there are no free ion particles or other anode surface impurities	Staining is evidence of free ion, which is detected through visual inspection. Identifies possible pitting corrosion sites or imbedded rouge	No quantitative detection
High humidity test (A967)	The sample of passivation parts should be immersed in acetone or methanol solution, or swabbed with clean gauze dipped in acetone or methanol solution, and then dried in inert gas or water-free container. The cleaned and dried sample should be placed in (97±3)% humidity, (100±5) °F[(38±3) °C] for 24 h or more	Staining is evidence of free ion, which is detected through visual inspection	No quantitative analysis. Not used for installed tubing. Specimen does not prove complete coverage

cont

Type of test	Test description	Test Criteria	
		Pros	Cons
Salt spray test(A967)	It is used to test free ion on stainless steel surface and impurities on other anode surface. This test is conducted inaccordance with ASTM B117 subjecting the test area to a 5% salt solution for a minimum of 2 h	Staining is evidence of free ion, which is detected through visual inspection	No quantitative analysis. Longer term exposure is required to test for passive film quality with interference factor
Precision inspection of passivated parts under ASTM A380/A967			
Solvent ring test(A380)	It is used for surface cleanliness test, place a single drop of high-purity solvent on a clean microscope crystal glass slide and make it evaporate, and then place another drop on the surface to be evaluated, stir temporarily, then transfer to a clean microscope crystal glass slide with clean capillary tube or glass rod, and make it evaporate. Prepare the required number of glass slide for test, and provide reasonable sample of surface to be tested. If foreign matter has been dissolved by the solvent, a distinct ring will be formed on the outer edge of the drop as it evaporates	Good test for organic contamination	No quantitative analysis
Black light inspection (A380)	It is suitable for testing oil film and other transparent film which cannot be detected under white light	Good test for organic contamination	Not practical for cleanliness test of passivation effect
Atomize test(A380)	It is to test the existing of hydrophobic film, the sensitivity is about 100 times of water-break test	The test is very sensitive	No quantitative analysis
Blue point test(380/A967)	Preparation of test solution: in 500 ml of distilled water, add 10 g potassium ferricyanide, and then add 30 ml of 70% nitric acid solution, stir it until all ferricyanide dissolved, and then dilute the solution to 1000 ml with distilled water. Drip the diluent on the surface of specimen, if blue point appears within 30 s, it proves the passivation effect is qualified	Sensitivity is high. It is used fo racceptance inspection of field passivation effect	It is qualitative test, cannot prove the quality of passive film, prepared solution may volatilize cyanide, it should be treated immediately after use
Copper sulfate test (ASTM A380/A967)	Preparation of test solution: pour 1ml of sulfuric acid solution(H_2SO_4, specific gravity: 1.84) into 250 ml of distilled water, and the dissolve 4 g copper sulfate pentahydrate compounds($CuSO_4 \cdot 5H_2O$) in the solution. The copper sulfate solution with preparation time more than two weeks cannot be used. It is acceptable if the surface of specimen has no copper precipitate	Sensitivity is high. It is used for acceptance inspection of field passivation effect	No quantitative analysis. Difficult to detect small discrete iron particles
Electrochemical field or laboratory tests			
Cyclic polarization measurements	It is similar to the ASTM G61 test method to measure the critical pitting potential (CPP). The more noble the CPP, the more passive the stainless steel (performance of passive film). The results obtained from cyclic polarization measurements may be similar to that obtained at the critical pitting temperature(ASTM G510)	The corrosion resistance of passive film on the stainless steel surface is quantified, the measuring data of the passivation effect can be obtained, and the test equipment is relatively inexpensive	The method requires a potentiostat and corrosion software package to make the measurements. Operators should have higher electrochemical test techniques

cont

Type of test	Test description	Test Criteria	
		Pros	Cons
Electrochemical pen test	During the test, a pen-like probe is contacted with the surface of specimen, and makes the instrument and surface keep electrochemical connection. Capillary action causes electrolyte to flow from the reservoir to the surface. There is a stable electrode inside the pen mechanism. Through the electrolytic contact, the electrode expresses electrochemical characterization	Easy to handle, short sample preparation time, real-time results, the tiny pen makes this method applicable to various surface geometries. It is a portable instrument and suitable for field use	This method does not test passive film, but instead provides a fail indication on passivation. The test surface must be cleaned and re-passivated after testing
Surface chemical analysis tests			
Auger electron spectroscopy	Incident beam and substance action can excite the inner electron of atom to form a hole. The energy released by outer electron when it fills in the hole during transition process can emit in the form of X-ray, i. e. generate characteristic X-ray, it may also excite another electron out of the atom to form free electron, which is Auger electron. Use focusing beam to scan the surface area of the specimen to obtain Auger electron spectroscopy, and identify element or its chemical status according to the standard spectrum	Analyze the AES signal collected from the specimen surface scanning to obtain quantitative surface topography and elemental composition, and precisely measure element or composition on the surface to a depth of 2 to 20 angstroms and descript the topography of this area	The specimen chamber must be maintained at ultra-high vacuum. The specimen must be electrically conductive. Instrument is not readily available. Expertise is needed for data interpretation, field test is infeasible
X-ray photoelectron spectroscopy	Using X-ray to radiate specimen, and make the inner electron or valence electron of atom or molecule are ejected. The electron excited by photon is called photoelectron. The energy of photoelectron is measured by taking the kinetic energy of photoelectron as x-coordinate, relative intensity(pulse/s) as y-coordinate to formulate photoelectron spectrum graph, so as to obtain specimen surface element composition	• Accurately measure element-composition of the surface 10-100 angstroms • Accurately measure empirical formula of pure materials • Accurately measure elements that contaminate a surface • Accurately measure valence state of each element in the surface • Determine the structure of components in the specimen to be measured • Accurately measure the thickness of passive film of specimen to be measured.	The specimen chamber must be maintained at ultra-high vacuum. The specimen must be electrically conductive. Instrument is not readily available. Expertise is needed for data interpretation, field test is infeasible

cont

Type of test	Test description	Test Criteria	
		Pros	Cons
Glow-discharge optical emission spectroscopy	Argon ion sent by the electric field in the spectrograph makes the specimen generate uniform sputters, as cathode, the sputtered specimen atom leaves the surface; and collides with argon ion in positive column for excitation to produce characteristic spectrum of specimen component element. The lights with different wavelengths are split by optical splitting system and detect the intensity of each monochromatic light. Obtain the intensity of each element by signal processing of computer system, and calculate the concentration of each element on the specimen surface by standard spectrum curve	The CD-OES method is particularly useful for quantitative and depth profiling of surface films and coatings	The cost of detection is very expensive. Instrument is not widely available

Groups 1 and 2 of the testing methods are the main divisions in the ASTM A380/A967. The most obvious examination method is visual. The examiner should look for a clean surface, free of oxides, scales, weld heat tint, stains, dirt, oil, or any deposits that could prevent the chemical passivation solution from reaching the metal surface.

The test results from the ASTM A380/A967, which are exclusively for passivation, are all based on visual detection of staining or heat tint indicative of the presence of free iron. These test results are subjective and non-quantifiable. However, for some applications this may be all that is required. The visual acceptance criteria in the ASTM A380/A967 apply.

Groups 3 and 4 of the testing methods are distinctly quantitative methods. These tests are not contained in the ASTM standards, but they are designed to provide a more quantifiable research data of a passivated surface. The electrochemical field and bench test, with the exception of cyclic polarization, are suitable for field tests such as those used for post-passivation testing of installed piping systems and passivated welded surfaces.

Passivation is capable of dramatically increasing the chromium-to-iron (Cr/Fe) ratio on the surface of 316L stainless steel when properly applied. One measurement of the degree of enhancement of the layer following a chemical passivation treatment is the Cr/Fe ratio as determined by AES, GD-OES, or ESCA. However, the procedure is not readily adapted to field use, but may be useful in developing the passivation procedure.

At present, the free iron testing method is widely accepted and promoted in the passivation industry due to its advantages i. e. portability and accuracy, and used for determining whether the element or system has been or is in a passive state.

A Cr/Fe acceptance ratio, regardless of the test method, should be not less than 1. Because of the variability in accuracy, identical results obtained with different test methods are not expected. The surface chemical analysis tests in Group 4 include methods for the evaluation of the thickness and chemical state of the passive layer on the stainless steel. Cyclic polarization measurements may also be used to provide a quantitative evaluation of the level of passivation. Cyclic polarization as well as the methodologies in Group 4 might be applied to specimens placed in systems subject to the complete passivation process.

In the Chinese *GB Stainless Steel Pickling and Passivation Practices* (SJ 20893—2003), the inspection of passivation effect is described as follows:

3.4 Appearance

3.4.1 Color and luster

(a) the mechanically processed parts should keep the original color and luster of stainless steel after pickling;

(b) the surface of thermally treated parts should be unglazed light grey to dark grey after pickling due to different components of materials;

(c) the surface of chemically passivated parts after pickling should be yellow grey, while passivated 2Cr13 *parts should be dark grey;*

(d) other materials with special chemical components are accepted to have different colors after passivation.

3.4.2 Allowable defects include

(a) the color and luster of the same part may be slightly different due to different material states;

(b) light water flow traces;

(c) oxidation color exists in welding temperature affected area;

(d) inevitable rack clamp mark.

3.4.3 Unallowable defects include

(a) residual oxides, mechanical impurities, dirt, etc. on the surface of the pickled or passivated parts;

(b) the location having passivation requirement is not passivated locally;

(c) the parts have been corroded;

(d) parts are not dried thoroughly of residual water;

(e) the main surface of the same part has serious shade deviation.

3.5 Adhesive force of the passive film

The passive film should have good adhesive force, and the film shows no shedding during inspection.

3.6 Integrity of the passive film

The passive film should be continuous and uniform, the surface of the passivated part should have no occluded foreign substances such as free iron.

3.7 Residual water, acid and alkali in the pipe

There should be no residual acid, alkali and ponding in the pipe.

4 Test method

4.1 The appearance test method

Visual inspection should be conducted under white transmission light with natural scattered light or no reflected light, the illumination intensity should be lower than 300 lx, and the spare parts (components) should meet requirements.

4.2 Test method for adhesive force of passive film

Rub the specimen surface with non-sand eraser by hand back and forth at normal pressure for 10 times, the film should show no shedding.

4.3 Test method forthe integrity of the passive film

The integrity of the passive film test checks whether the surface of the passivated part has non-passivated areas or whether the film has black metal particles such as iron embedded. The test method can be selected from the following methods:

(a) Neutral salt spray test, it is performed as per neutral salt spray test method stipulated in GJB 150.11—1986, the time duration is 2 h. Check whether signs of iron corrosion exist by visual inspection after the test, no corrosion is considered as acceptable;

(b) High humidity test: put the specimen into a moist heat cabinet for at least 24 h, maintain the relative humidity at (97±3)%, and temperature at (38±1)℃, take it out for visual inspection after test, the specimen should have no corrosion.

When there is divergence between contracting parties on test methods, method (a) should prevail for arbitration.

4.4 Test method for water, acid and alkali used in the pipe

The pH of water at the pipe orifice should be tested with pH test paper after the final rinse of the pipe (if the pipe has been dried, appropriate water can be filled in), it is acceptable if the pH is neutral, otherwise, it should be rinsed until it is neutral. After drying, blow with compressed air at one end of the pipe, and test whether there is water drained at the other end with filter paper, no water is regarded as acceptable, otherwise it should be dried until no water is present.

11.3.4 Re-passivation Technique

The spontaneous passive film of austenitic stainless steel is very thin, corrosion is easily initiated and results in damage in specific anionic environments, and the stainless steel color is too dull. The re-passivation experimental process can make the metal surface form a chemical conversion coating, which not only improves the corrosion resistance performance of stainless steel, but also makes the metal surface appear different colors due to the light interference effect.

As shown in Fig 11.20, passivation is divided into Spontaneous Passivation, Chemical Passivation and Electrochemical Passivation, Derouging Passivation, the specific passivation mechanisms and methods have been described above.

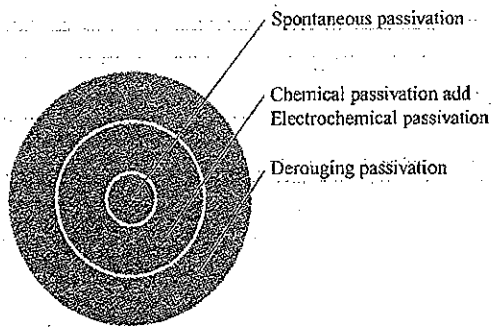


Fig 11.20 Classification of passivation

The dual function of chemical passivation and electrochemical passivation is also called re-passivation, for this passivation is performed after spontaneous passivation. Re-passivation has an important characteristic, the passivation treatment is performed after derouging. Derouging is to remove the iron oxidation layer and free irons on the surface. However, if the stainless steel surface is not repaired (i.e. re-passivation) after derouging, the stainless steel surface is not protected by a passive layer, the outside corrosive environment will contact the stainless steel body (i.e. iron-rich layer) and generate various corrosion rapidly, so as to result in fast growth of rouge. Therefore, it is necessary to perform re-passivation after derouging.

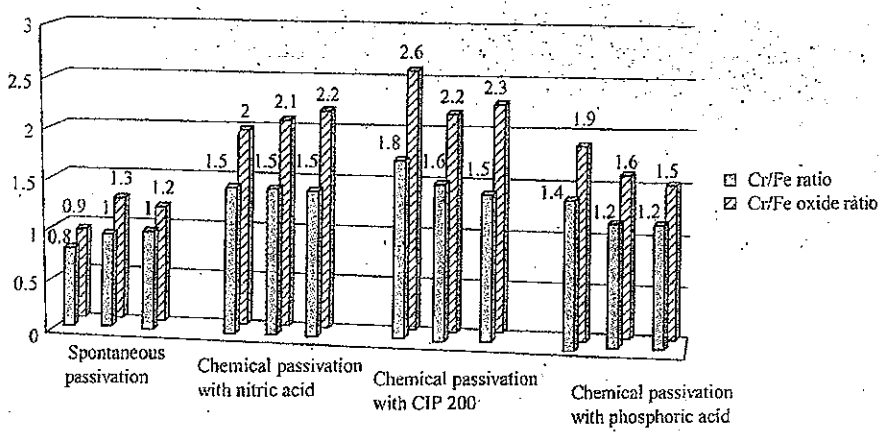


Fig 11.21 Comparison of passivation effect

The passivation quality is in close relation with the corrosion resistance of stainless steel, therefore, the enterprise should perform re-passivation according to relevant standards before new equipment, new components or new systems are put into use, and after equipment, components or systems are derouged; ensuring a good passivation effect and reducing corrosion to stainless steel is the standard for whether the passivation technique is advanced or not.

Passivation is also a type of cleaning procedure, which should be in strict accordance with four cleaning elements (i.e. temperature, mechanical action, chemical action and time), the four elements are strictly controlled to achieve the passivation of the stainless steel system. It is shown by Fig 11.21 that the Cr/Fe ratio of the passive layer after the stainless steel surface is treated with four methods respectively. The first alternative is only to clean, that is the passive layer is formed only by the spontaneous passivation of stainless steel. The Cr/Fe ratio is near 1, Cr/Fe oxide ratio is close to 1.2; The second alternative is to conduct chemical passivation with nitric acid, Cr/Fe ratio is 1.5, Cr/Fe oxide ratio is close to 2.1; The third alternative is to passivate using CIP200 reagent with citric acid as main component, the Cr/Fe ratio is near to 1.6, the Cr/Fe oxide ratio is close to 2.3; The fourth alternative is to passivate with phosphoric acid, the Cr/Fe ratio is near to 1.2, the Cr/Fe oxide ratio is close to 1.6.

It is obvious from comparison that the obtained Cr/Fe ratios and Cr/Fe oxide ratios of the passive layer are the highest, when the system is passivated using CIP 200 reagent with citric acid as main component. It is indicated by experience, if one parameter such as temperature, chemical concentration, mechanical force and time duration is not properly controlled, the passivation effect will be greatly diminished.

11.4 Documentation System

The documentation system is important for recording and attestation of the quality control of a pharmaceutical water system, it is an integral part of the pharmaceutical water system. Documentation inspection is a critical inspection step during the GMP inspection. The pharmaceutical water systems mainly include purified water systems, water for injection systems, pure steam systems and clean gas systems, etc. Each system has its corresponding document requirements, Table 11.6 gives the list of regular documents for a pharmaceutical water system, the list can be used as a reference standard of equipment documentation system acceptance by the company (including but not limited to the following documents).

Table 11.6 Document list of the pharmaceutical water system

Document No.	Designation	Remarks	Due Date
	Design General		
01	Document list		
02	Drawing list		
	Mechanical & Process Design		
03	Symbol, legend & general notes		
04	PW system P&ID		
05	PW system layout drawing		
06	WFI system P&ID		
07	WFI system layout drawing		
08	PS system P&ID		
09	PS system layout drawing		
10	PA system P&ID		
11	PA system layout drawing		
12	GN system P&ID		

cont

Document No. :	Designation	Remarks	Due Date
13	GN system layout drawing		
14	Main component list and pipeline specification list		
15	Technical and functional specification		
	Construction Drawing		
16	Piping isometric drawing of PW		
17	Piping isometric drawing of WFI		
18	Piping isometric drawing of PS		
19	Piping isometric drawing of PA		
20	Piping isometric drawing of GN		
21	Piping layout drawing of public section		
22	Piping isometric drawing of public section		
	Automation Design		
23	HDS		
24	SDS		
25	Wiring diagram		
26	Functional logic		
	Equipment Documentation		
27	Manuals or technical data sheets from sub-suppliers		
28	Operation, sanitization and installation manual		
29	Maintenance manual		
	Project Management		
30	Quality & Project plan		
31	Project schedule plan		
32	Welding procedure SOP		
33	Welding certificates & machine certificates		
	Hydrostatic test protocol and report		
	Pickling and passivation protocol and report		
34	Cleaning protocol and report		
	Slope checking test protocol and report		
	Dead legs test protocol and report		

cont

Document No. :	Designation	Remarks	Due Date
35	Endoscope inspection protocol and report		
	Quality Management		
36	Material and roughness certificate from sub-suppliers		
37	Calibration certificates from sub-suppliers		
	Other Documentation		
38	Welding record document		
39	Print-outs from the orbital machine		
40	20% of automatic orbital welding or orbital welded sample will be done endoscopy test		
41	Piping isometric drawing of PW with weld numbers		
42	Piping isometric drawing of WFI with weld numbers		
43	Piping isometric drawing of PS & cleaning gas with weld numbers		
	Qualification Documentation		
44	DQ		
45	IQ		
46	OQ		
47	PQ		
48	Risk analysis report		
49	Requirements traceability matrix (RTM)		
	FAT/SAT Procedures and Results		
50	FAT procedures and results		
51	SAT procedures and results		

Fig 11.22 is a set of documents complying with the GMP requirements for pharmaceutical water systems. The documents cover the whole set of design documents, construction documents and validation documents for purified water systems, water for injection systems, pure steam systems and clean gas systems.

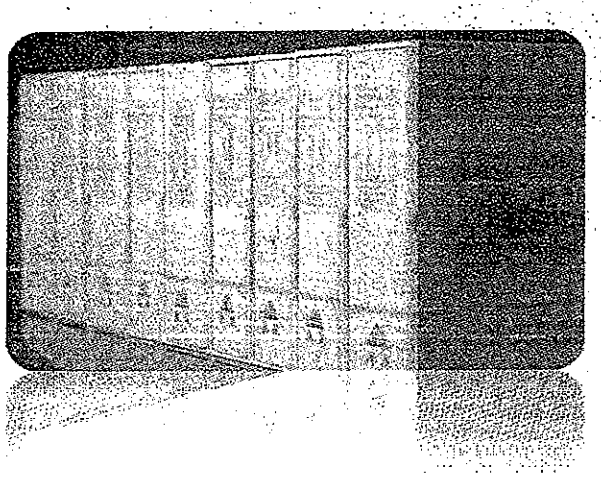


Fig 11. 22 Documentation system examples

Chapter 12

Automatic Control Technology

The pharmaceutical water system is a key element of the drug production process, and the automatic control of the pharmaceutical water system is an important part of it. How to better apply the automatic control technology in the pharmaceutical water systems has attracted more and more attention. This book will discuss the design of control systems for turnkey projects of pharmaceutical water systems.

12.1 Introduction of Automatic Control Technology

The operations in industrial production processes can be divided into manual control and automatic control. Manual control is to manually complete a series of operations and controls, e.g., the information is obtained through visual or auditory observations or perceptions of the body, judged by the brain, and then actions on valves or buttons are completed by controlling the hands or feet. Automatic control is a simulation of the manual control. The measuring instruments used in the automatic system are equivalent to the eyes, ears or other sensory organs of humans, controllers such as the PLC are equivalent to the brain of a human, and various actuators are equivalent to hands and feet of humans.

In the process industry, intermittent production processes and continuous production processes are two types of widely applied production methods. An intermittent production process is also called a batch production process; it is a production process that uses a given recipe to produce a certain amount of products. For example, an aseptic dispensing process system is a typical intermittent production process. A continuous production process is a production process conducted continuously. For example, a pharmaceutical water storage and distribution system is a continuous production process. The intermittent production process control can be divided into the real-time control level and production management level. The real-time control level includes real-time production management, sequence control, switching value/analog value control, production process interlocking, safety interlocking, alarm, process I/O, etc. The production management layer includes the production plan, production schedule, recipe management, etc.

The automatic control system of pharmaceutical water should accomplish remote computer control and monitoring of the production process, and onsite production process control; it should ensure the operation and control are flexible, rapid, accurate and uniform, that important parameters comply with regulatory requirements, and reduce the increased cost resulted from untimely control of important parameters; it must optimize the control, improve the energy and equipment utilization rate; realize computer control parameters management, prompt the maintenance and repairing of each equipment component through the computer system to realize simultaneous operation of the standby system; also it must carry out the storage, inquiry and report printing of important parameters historical data, realize production process interlocking, safety interlocking, alarm and troubleshooting. The pharmaceutical water automated system is a GMP critical system, so it should follow the GAMP (the latest version is GAMP5) and comply with the electronic signatures and electronic records, and other relevant GMP regulations.

An automatic control system is a closed loop negative feedback control system composed of sensors, controllers, actuators and controlled objects. Its basic function is maintaining the controlled variables within set values. Controlled object refers to the process equipment, mechanical or production processes required to be realized. A controlled variable is a physical quantity

indicating whether the operation of the production equipment (process) is normal and is required to be controlled. A control action is a physical quantity and energy generated by the automated device to keep the controlled variable maintained at the set value. A disturbance refers to all factors that act on the object and cause the change of the controlled variable. The set value is the predetermined or expected value of the controlled variable. The measured value is the output value of the sensor corresponding to the controlled variable. It is usually direct current within the range of 4-20 mA or other digital communication protocol, e.g., HART communication protocol, PROFIBUS communication protocol, Fieldbus communication protocol, 485 communication protocol, etc.

The difference between the measured value and set value is a deviation, it has three basic elements: size, direction and change rate. The automatic control system can be divided into fixed set point control system, following control system and program control system based on the difference between set values. A fixed set point control system is a control system with a constant set value. The controlled variable of the control system is required to be maintained at a production index invariably during the production process, this technical index is the set value. A following control system is also called an automatic tracking system, the features of this type of system are constantly changing set values and this requires the output of the system to be changed accordingly. A program control system is also called a sequence control system, the set value of this system is also in changing, but it is a known time function, i.e. the generated technical index is changed according to a certain time program. The set value is constantly changed, which requires the output of the system to also be changed accordingly.

12.1.1 Type of Controls

The hardware of an automatic control system has generally four types of controls: the distributed control system (DCS), programmable logic controller (PLC), single loop digital controller (SLC) and industrial personal computer (IPC). DCS is usually used in large-scale applications, PLC+IPC is used for medium and small-scale systems, and other types of controls are generally used in small-scale systems or applications with special requirements.

The typical batch production process control includes sequence control, regulation control and discrete control. The design of DCS in the early phase has an emphasis on the application of continuous production processes; it generally consists of programmable process control functions. To meet the requirements of the intermittent process control, it is required to combine the system with PLC. At present, for meeting more requirements, a new type DCS system has emerged as an integrated control system with multiple control functions to meet the requirements of continuous process control, intermittent process control and various integrated automated controls. Continuous process control systems configured as the new type DCS are the ideal choice for large-scale applications, but the price is usually higher than that of other systems.

The design of the PLC at an early phase is generally used to meet the requirements of logic control; its programming language is ladder diagram and instruction list. It has deficiencies in programming when it is used for meeting the requirements of logic control. With the development of the PLC technology, a new type of PLC has been developed as an integrated control system with multiple control functions to meet the requirements of intermittent process control, continuous process control, discrete process control and various integrated automated controls. The process control system configured by new type PLC+IPC is the ideal choice of large, medium and small-scale applications. It is the first choice of pharmaceutical liquid process systems at present due to its price being usually lower than that of DCS systems; the performance price ratio is also high.

An intermittent process control system has generally two structural forms: centralized control system and distributed control system. All control functions of the centralized control system are controlled by one computer, due to the centralized functions, a failure may cause overall shutdown, and therefore, it is usually used in small-scale systems, while large and medium-scale systems usually adopt a distributed structure. A distributed control system has a centralized management and distributed control to divide the control functions into relatively independent function modules and execute different control functions using several controllers. At present, distributed control systems have become a widely used structural approach.

12.1.2 Software Design

The programming software of a control system usually adopts the programming configuration language provided by the control equipment supplier. It generally includes: ladder diagram (LD), function block diagram (FBD), sequential function chart (SFC), structure test (ST) language and programming language dedicated to the continuous process. Usually, if several programming languages are used in the same project, it can improve the programming efficiency and simplify the program. The programming software should be selected according to different actual conditions. Considering the requirement of the GMP certification, the programming software should be developed by a mature established company, besides its matching with the selected controller. It should realize the amendment record among the programs of different versions; meet the requirements of source code review, software module test, trail audit, electronic signature, electronic record, etc.

It is recommended to select the software platform provided by hardware supplier for the configuration software of the upper computer (operator station, engineer station) when using PLC+IPC to configure the control system. For example, a control system can use the SIEMENS S7-300 series PLC, a upper computer can use the SIEMENS WinCC software; in this case, it should not only be confirmed whether the common configuration function is complete, but also known whether it can provide a software package such as batch control and management information system interface to facilitate future extension. It is very important that the selected software should meet the relevant stipulations on electronic signatures and electronic records of the GMP, the further information can be referred to the relevant stipulations in the FDA 21 CFR Part11, the new appendix of the *Chinese GMP* 2015 *Computerized System*, and *General Principles* in the *Chinese GMP* 2010. Table 12.1 illustrates some commonly used control system software alternatives for pharmaceutical water systems.

The design of real-time continuous control usually includes real-time production management, operation sequence control, motor logic control, continuous regulation control of analog quantities such as temperature and pressure, process interlocking, safety interlocking, process I/O, etc. In which, the functions such as real-time production management, parameter alarm, data archiving, backup, electronic signatures and electronic records can be realized in the upper computer, and other functions can be carried out by the controller.

The design of the software should follow the principle of structured design; the control software of a pharmaceutical water system can be divided into three levels. The first level is the combined coordination module of the operation unit, which relates to the whole water generation system; the second level relates to the equipment unit, which is used to combine and coordinate the basic process operations of the equipment unit, which relates to the equipment units such as the purified water machine and the water distiller; the third level relates to the basic unit on site. Fig 12.1 shows the typical structure of the first and second level.

In order to better monitor the water quality, the control system will classify the monitoring index of critical parameters as per "design scope", "normal operating range" and "allowable operating range" (Fig 12.2).

Table 12.1 Commonly used automatic control software

No.	Name	Development environment	Remarks
1	PLC application software	SIMATIC Step7 SIMATIC TIA Portal	Edit, upload and download logic control program; Logic action among valve, pump and monitoring point
2	HMI application software	SIMATIC WinCC Flexible 2008 SIMATIC TIA Portal	Monitor site valves, pumps and instruments; monitor and save data; generate and record alarm
3	Upper computer software	WinCC and its components	System monitoring, data storage, date report, data printing

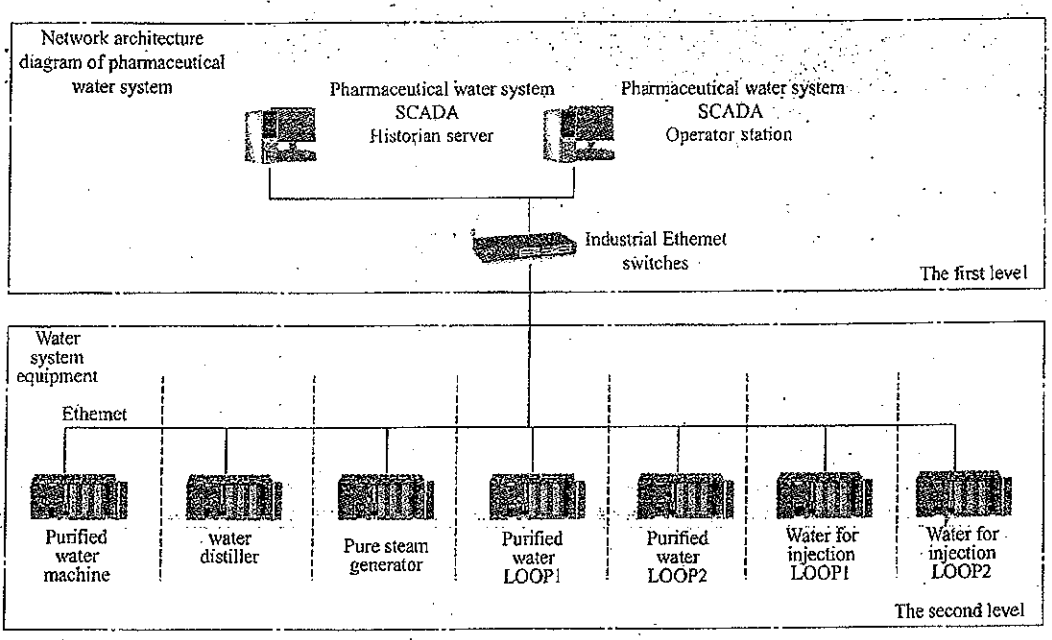


Fig 12.1 Network architecture diagram of a pharmaceutical water system

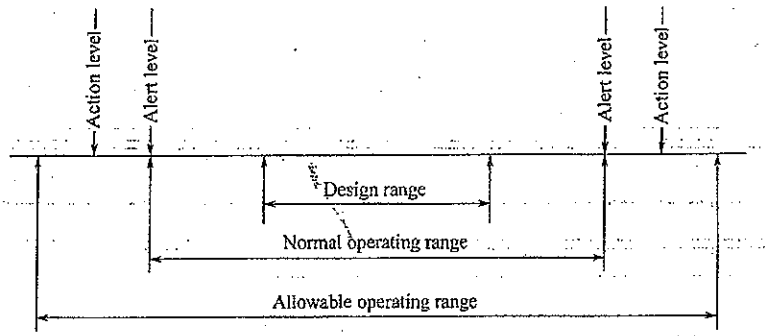


Fig 12.2 Setting principles of the critical parameters of the water system

The design scope is the precision of the stipulated scope or control variable used by the designer as the basis of determining the characteristic requirements of the water system. The water quality being within the design scope represents that the system is very safe, and does not exceed the set alert limits. For example, the enterprise can stipulate the design scope of the TOC of water for injection as 0-50 ppb. The normal operating range is the range selected as per the expected acceptable value of the parameter during normal operation recommended by the manufacturer. The range must be within the allowable operating range; when the water specification is out of the normal operating range, the system will alarm automatically. For example, the enterprise can stipulate the normal operating range of the TOC of water for injection as 0-100 ppb. The allowable operating range is the validated critical parameter range of the qualified pharmaceutical water; the operating range is usually consistent with the specifications in the pharmacopoeia. For example, the pharmacopoeia stipulates the allowable operating range of the TOC of water for injection is 0-500 ppb.

The alert limit is a limit seton the basis of the normal operating range, used for initiating corrective actions such as sanitation. The alert limit will not initiate formal corrective action protocols, for example, the alert limit of the TOC of water for injection is usually set as 100 ppb. The action limit is a limit set on the basis of operation experience and taking into consideration the annual fluctuation or worst case scenario. Usually, the action limit is also called enterprise in-house specification, the action limit is usually set within the allowable operating range, for example, the action limit of TOC of water for injection is usually set as 250 ppb.

12.1.3 Hardware Design

The automatic control hardware system is the core

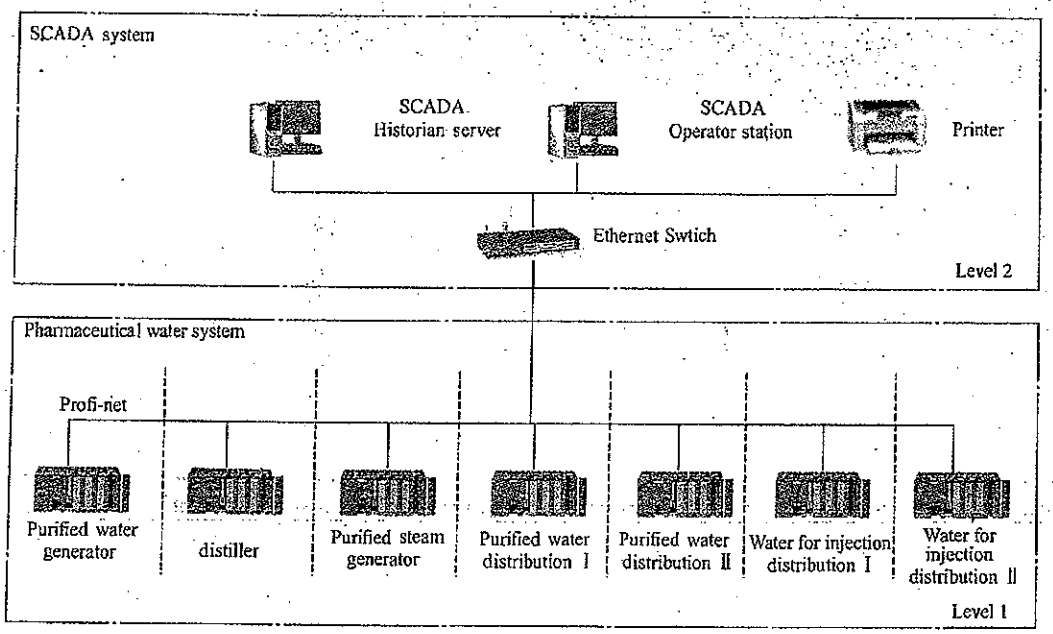


Fig 12.3 Schematic diagram of the hardware structure

framework of the whole system. It is generally composed of electrical elements, power supply, frequency converter, PLC, wiring module, touch screen HMI, site instruments, valve terminals, etc. This book discusses the selection of controllers in automatic control systems of pharmaceutical liquid processes on the basis of products manufactured by SIEMENS. Fig 12.3 and Table 12.2 show typical pharmaceutical water systems automatic control applications designed with the SIEMENS control system in pharmaceutical enterprises.

Table 12.2 List of commonly used hardware

Description	Type
SIEMENS S7 315 PLC	PLC CPU SIEMENS/6ES7 315-2EH14-0AB0, it is composed of: • Memorizer: standard 96 bytes storage • Flash card: standard 2048 bytes(micro storage card, maximum, 8M bytes) Power supply: SIEMENS/6ES7 307-1KA01-0AA0, AC120/220V Digital input module: SIEMENS/6ES7 321-1BH02-0AA0 16DI Digital output module: SIEMENS/6ES7 322-1BH01-0AA0 16 DO Analog input module: SIEMENS/6ES7 331-7KF02-0AB0 AI8 Analog output module: SIEMENS/6ES7 332-5HD01-0AB0 AO4 Digital front connector module (20 cores): 6ES7 921-3AB00-0AA0 Analog front connector module (20 cores): 6ES7 921-3AG00-0AA0 Digital input wiring module: 6ES7 924-0CA10-0BA0 Digital output wiring module: 6ES7 924-0BD10-0BA0 Analog wiring module: 6ES7 924-0CC10-0AA0

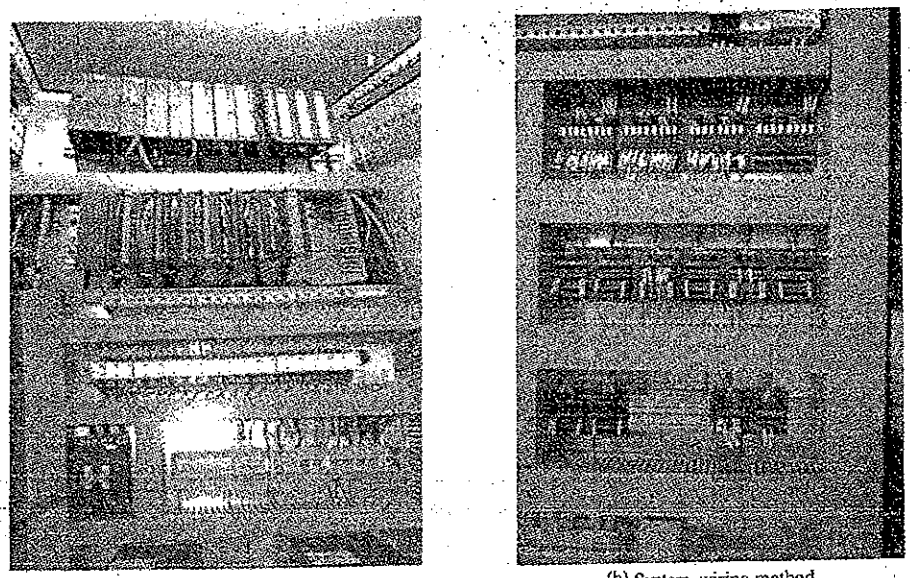
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Description	Type
SIEMENS MP277 HMI 面板 HMI panel	SIEMENS/TP1200- 12″ Comfort touch screen Power supply: DC+18...30V, 500 mA Communication: serial port/MPI/PROFIBUS-DP/PROFINET (Ethernet)/USB interface/SD card slot Programming language: WinCC flexible 2008, SP3 Screen resolution: TFT-LCD/1280 x800/1600 ten thousand colors Storage card: 2G

12.1.3.1 Whole Control System

The control cabinet is the integration site for the hardware of the whole control system. Each point of use in the control cabinet has a miniature circuit breaker installed, and the door of the control cabinet is equipped with an emergency stop button, human machine interface (HMI) and audible and visual alarm devices. In the event of the system operating under abnormal conditions, the operator will press the emergency stop button to end the program in the controller and power off the output device. The control cabinet is equipped with an automatic attemperator to prevent the temperature in the control cabinet from being too high and affect the service life of the control module.

The wiring work inside the control cabinet will require a lot of traditional cabling at PLC module and the control system; the larger the control system, the larger the probability of error; traditional wiring uses many intermediate relays, the more terminals, the



(a) Traditional wiring method (b) System wiring method

Fig 12.4 Wiring methods for the control cabinet

more the work of manual wiring. The wiring of the system combines the plug-in type wiring with wiring modules to solve the problems of traditional wiring, and improve the assembly efficiency and appearance of the control cabinet (Fig.12.4).

12.1.3.2 Normal PLC Module

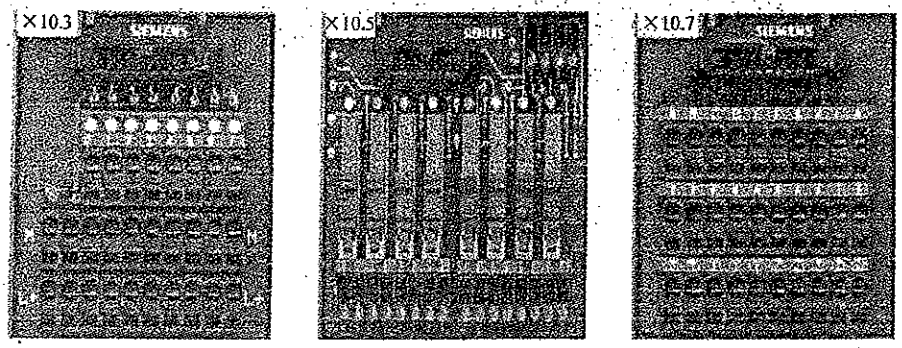
The digital input module (DI module), digital output module (DO module), analog input module (AI module) and analog output module (AO module) are four hardware modules commonly used in the automatic control system.

a. The DI module is generally used for the connection between the PLC and the digital signal, e.g. frequency converter, valve on-off, etc. The SIEMENS digital input module is SM 321, and the conventional model selection is 6ES7 321-1BH02-0AA0 DI16, the number of digital input channels is 16.

b. The DO module is generally used to output digital signal from the controller to the process variable. The digital output module converts the S7-300 internal signal level to the external signal level required by the process, which is used for the starting and stopping control of the pumps and valves, transmitting status signals between equipment, etc. The SIEMENS digital output module is SM 322, and the conventional model selection is 6ES7 322-1BH01-0AA0 DO16, the number of digital output channels is 16.

c. The AI module is generally used for the connection between the PLC and the analog process signal. For example, the AI module can be used to connect analog signals from the pressure sensor, temperature sensor, flow meter and conductivity meter. An analog input module converts the analog signal sent from the process to a digital signal used for the PLC internal processing. The resolution is 13 bits+sign bit (used for different conversion times). It can set different measuring ranges; the basic measuring ranges of the current and voltage can be mechanically regulated through a measuring range module, and fine adjusted by the TIA Portal hardware configuration tool on the PG. The AI module has the function of sending the diagnosis and over range interruption to the central processing unit (CPU), and sending detailed diagnosis information to the CPU when the module fails. The SIEMENS analog input module is SM 331, and the conventional model selection is 6ES7 331-7KF02-0AB0 AI8, the number of analog input channels is 8.

d. The AO module is generally used to output the analog signal from the PLC to the process variable. For example, the AO module can be used to connect an analog actuator, control frequency convertor, etc. The analog output module converts the PLC digital signal to the analog signal required by the process. The module resolution is 15 bits, the measuring range of various voltages and currents can be set by the parameter assignment software separately for each channel, a diagnosis alarm report can be sent to the CPU when an error occurs in the module to facilitate the troubleshooting during maintenance. The SIEMENS analog output module is SM 332, and the conventional model selection is 6ES7 332-5HF00-0AB0 AO8, the number of



(a) DI wiring module (b) DO wiring module (c) AI/AO wiring module

Fig 12.5 PLC wiring module

Table 12.3 List of fieldbus types

Type	Technical name	Type	Technical name
Type 1	TS61158 fieldbus	Type 11	TC net real-time Ethernet
Type 2	CIP fieldbus	Type 12	Ether CAT real-time Ethernet
Type 3	PROFIBUS fieldbus	Type 13	Ethernet Powerlink real-time Ethernet
Type 4	P-Net fieldbus	Type 14	EPA real-time Ethernet
Type 5	FF HSE high speed Ethernet	Type 15	Modbus RTPS real-time Ethernet
Type 6	SwiftNet(cancelled)	Type 16	SERCOSI, IIfieldbus
Type 7	World FIP fieldbus	Type 17	VNET/IP real-time Ethernet
Type 8	Interbus fieldbus	Type 18	CC-Link fieldbus
Type 9	FF H1 fieldbus	Type 19	SERCOS Ⅲ real-time Ethernet
Type 10	PROFINET real-time Ethernet	Type 20	HART fieldbus

analog output channels is 8.

12.1.3.3 Wiring module

The wiring module (Fig 12.5) is a special component for system wiring. It is generally used for the connection between the PLC module and site instruments, opening of the regulating valve, control of frequency convertor, control signal of valves, etc.; the wiring module is the interface between the site equipment and PLC controller. The commonly used digital input wiring module is 6ES7 924-0CA10-0BA0, and the digital output wiring module is 6ES7 924-0CC10-0AA0.

12.1.4 Bus Valve Terminal Technology

Fieldbus is the digital, serial, and multipoint communication data bus installed between the field device in the manufacturing or process area and the automatic device in the control room. Fieldbus is a type of industrial data bus; it is the underlying data communication network in the automated field. Briefly, the fieldbus is using data communication to substitute the transmission of traditional 4-20 mA analog signal and common digital signal; it is a full-digital, bi-directional, and multi-station communication system for connecting intelligent field equipment and automated systems. Fieldbus communication is used generally to provide the digital communication between field equipment such as intelligent instruments, controllers and actuators, and information transmission between these field control equipment and the top layer control system. Specific types of fieldbus are illustrated in Table 12.3.

As shown in Fig 12.6, the automated communication network of a large-scale factory usually adopts a three-level network structure: field equipment level, workshop monitoring level and workshop management network. The main function of the field equipment level is to connect field equipment, e.g., distributed I/O, sensor, driver, actuator, switchgear in order to realize the field equipment control and the equipment interlocking control. The workshop monitoring level is also known as unit level, which is used to connect the production equipment in the workshop and monitor the equipment of the workshop level. The workshop management network, as a subnet of the major network of the

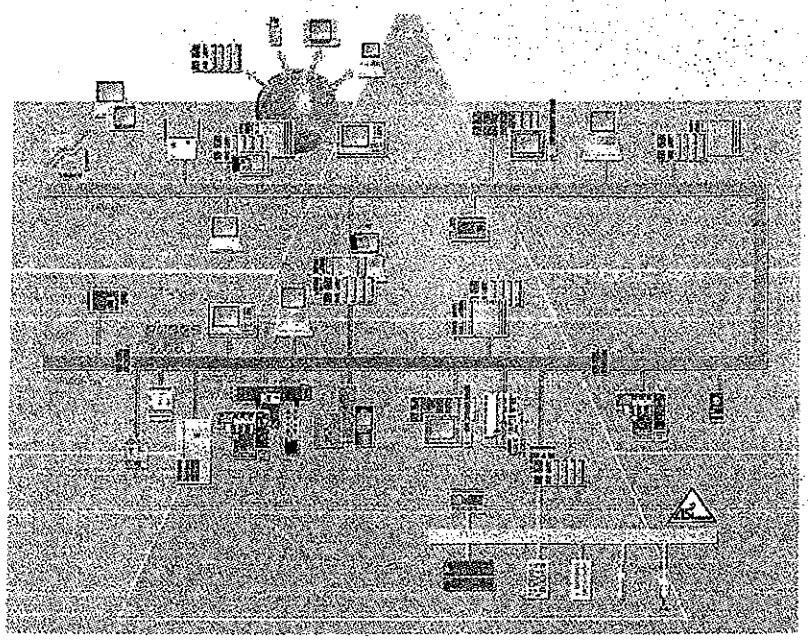


Fig 12.6 Automated communication network architecture diagram of large-scale factory

factory, is connected to the backbone network of the factory by a switch, network bridge or router, so as to integrate the workshop data into the factory management level.

PROFIBUS is an open style international standard (EN50170) bus system, which is used for process and field communication of the field equipment as well as data communication within automated units. The applied range of PROFIBUS is from production and process automation to building automation. The main features of PROFIBUS are as follows:

- Data transmission is conducted by economical and efficient communication medium (e.g. twisted pair).
- The application range is wide (profits from programmable controller and operator control); the equipment communication is monitored by uniform bus.
- Standardized data communication, which complies with EN 50170, EC 61158 (service and protocol) and IEC 61784.
- Commissioning, configuration and troubleshooting can be executed at any point in the bus.
- Investment is safe (benefit of the existing PROFIBUS system); it can be expanded with no adverse effects.

The PROFIBUS specifications are very flexible, which allow implementing various optimized protocols specific to designated tasks in different application fields. The FDL data link layer (the second layer of the ISO/OSI reference model) ensures the visits to the bus using token passing are uniformly controlled. The token passing control of the visit to the bus means only the bus node currently having the token is allowed to send data. After a fixed time (token holding time), the token will be transferred to the next station. With the completion of the cycle, the station will receive the token again.

If the communication is based on a master station/slave station system, the master station can actively trigger the communication with the slave station, and then, the slave station will respond to the master station. The slave station can transmit data during the response period. The difference from the master station is that the slave station cannot activate itself (Fig 12.7).

There are two basic types of nodes in the PROFIBUS network, active nodes and passive nodes. The active node (master station) controls the bus communication; each active node receives the token once in each cycle, and then it communicates with active nodes and passive nodes. After the token holding time, the node will immediately transfer the token to the next master station. For example, the DP master station and the S7 server are active stations, passive nodes (slave stations) cannot initiate communication by themselves, they do not receive the token and only respond to the polling from passive stations, a typical

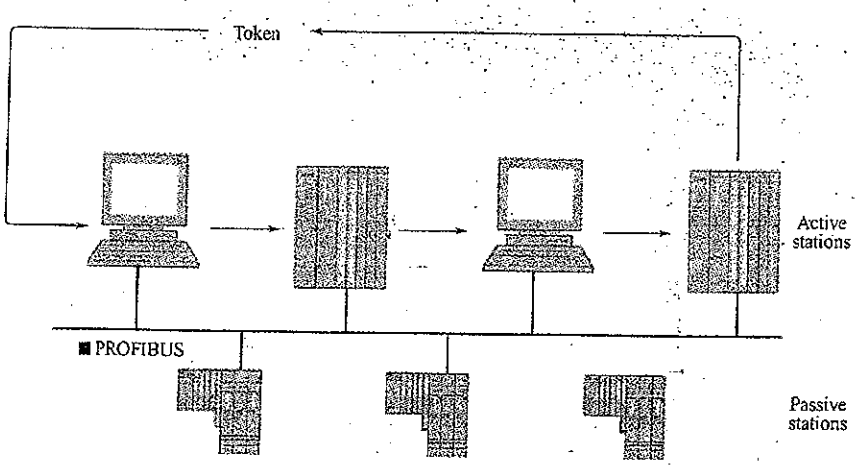


Fig 12.7 PROFIBUS schematic diagram

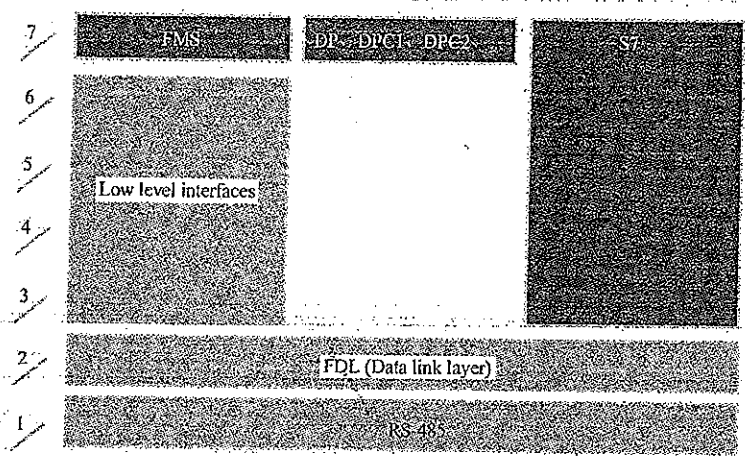


Fig 12.8 Relationship between PROFIBUS and ISO/OSI reference model

example of passive station is the DP slave station.

PROFIBUS is following the ISO/OSI reference model, but that is not implemented on all layers. Fig 12.8 illustrates which layers of the ISO/OSI reference model are included in various protocols defined by PROFIBUS. Each protocol provides an interface for the last implemented layer, and the data communication service can be used through the interface.

PROFINET stands for Process Field NET, it is an industrial automation open innovation standard based on industrial Ethernet. The solution can be implemented in production automation and motion control applications using PROFINET. In a totally integrated automation (TIA) framework, PROFINET continuously extends the established PROFIBUS fieldbus system and communication bus of the industrial Ethernet unit level. With PROFINET, it can adopt the same method as the module based distributed automaton system (module based automation) to apply the simply distributed field equipment and time-critical applications (PROFINET IO) (TIA) in the framework. PROFINET continuously extends the established PROFIBUS fieldbus system and communication bus of the industrial Ethernet unit level. With PROFINET, it can use the same approach as the module based simply distributed automaton system (module based automation) to integrate the simply distributed field equipment and time-critical applications (PROFINET IO) into the Ethernet communication.

PROFINET can satisfy all requirements of automated engineering. At present, the experience obtained from PROFIBUS and industrial Ethernet has been integrated into PROFINET. From the very beginning, the definition of PROFINET is determined by the use of open standards and integration of simple processing and existing system modules (Fig 12.9).

Nowadays, PROFINET is defined as a cross-supplier communication, automation and engineering

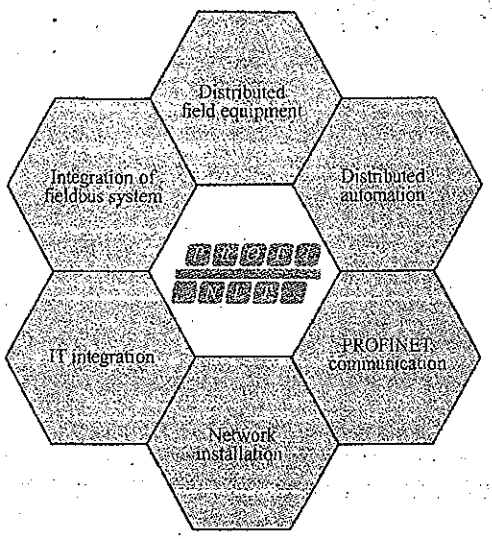


Fig 12.9 PROFINET definition complying with PNO

model of the PROFIBUS public network operator, and integrated into Ethernet communication as per IEC 61158.

The objectives of PROFINET are to conduct fully integrated and real-time communication through fieldbus and Ethenet, and realize open and distributed automation using open standards. During automated engineering, some applications require faster refresh and response time. Therefore, the PROFINET standard defines the real-time communication mechanism (Fig 12.10). Real-time communication is standardized as real-time channel (RT channel) and isochronous real-time channel (IRT channel).

Thereal-time channel (RT channel) is a real-time communication channel directly based on the second layer of the Ethernet, it uses an RT protocol. This solution bypasses some communication levels, therefore, the time required for communication is reduced to the minimum. The refresh rate of the process data is increased to some extent, because the preparation of data helps to transmit faster, and the user program for receiving data can process data faster. The refresh and response time is only 5-10 ms.

The isochronous real-time channel (IRT channel) is specially developed for motion control. It requires a refresh and response time of less than 1 ms. To achieve this objective, the IRT channel is based on the second layer of fast Ethernet (100 Mbps), and uses the IRT protocol. Besides, the data transmission is controlled by time slot. Due to the time synchronization of the communication partner in Ethernet, the time slot can be designated, and thereby the communication is divided into the fixed and open channels. Time-critical real-time data is transmitted through the fixed channel and non-time-critical data is transmitted through the open channel.

The bus valve terminal is a solenoid valve combination with public air inlet and outlet and with centralized control (Fig 12.11). The bus valve terminal technology solves the problem of a lot of manual wiring, and greatly reduces the wiring failure rate; the valve terminal totally adopts structured assembly. In which, the design of the solenoid valve adopts the internationally advanced friction-free Fipper technology and supports hot plug technology; the solenoid valve can be replaced in place with no necessity to turn off the main air supply, avoiding production loss caused by the replacement of the solenoid valve.

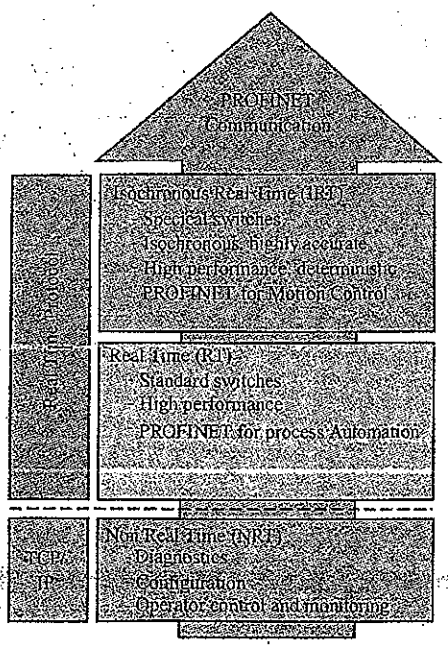


Fig 12.10 PROFINET real-time communication diagram

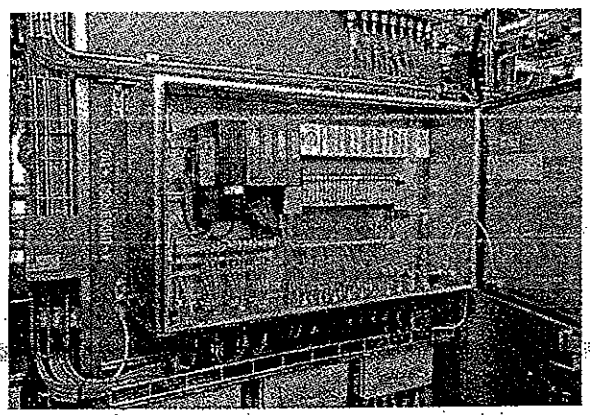


Fig 12.11 Bus valve terminal technology

12.2 Sensor Technology

The sensor in an automatic control system is usually called a transmitter, its basic function is similar to a human's sensory organs such as eyes and ears. Various sensors have different functions, but they have the same function, that is to collect various pieces of information in the system, and then transmit the information to system control center by means of current or digital communication and help the automatic control system complete various actions.

A pharmaceutical water system in the pharmaceutical industry is a critical system having direct contact with drugs; therefore, sanitary components must be used when selecting instruments and sensors to ensure the sterility requirements of the system. Most instruments and sensors are used in purified water/water for injection and pure steam systems, therefore, the temperature resistance performance of sensors should be taken into consideration. The sensors involved in the pharmaceutical water system are generally pressure sensors, temperature sensors, flow sensors, liquid level sensors, conductivity sensors, pH analyzers, OPR analyzers, weighing module sensors, residual chlorine analyzers, TOC analyzers, ozone sensors, online microorganism detectors and online rouge detectors, etc. Table 12.4 lists the types of commonly used sensors in pharmaceutical water systems.

Table 12.4 Main sensor selection list

No.	Instruments	Remarks
1	Liquid level sensor	4-20 mA signal output, 316L stainless steel, high temperature resistance
2	Temperature sensor	4-20 mA signal output, 316L stainless steel, high temperature resistance
3	Pressure sensor	4-20 mA signal output, 316L stainless steel, high temperature resistance
4	Flow sensor	4-20 mA signal output, 316L stainless steel, high temperature resistance
5	Conductivity sensor	4-20 mA signal output, 316L stainless steel, high temperature resistance
6	Weighing module sensor	4-20 mA signal output, 304 stainless steel, precision 0.1%
7	pH analyzer	4-20 mA signal output, 316L stainless steel, high temperature resistance
8	TPC analyzer	4-20 mA signal output, sanitary design, high temperature resistance
9	ORP analyzer	4-20 mA signal output, sanitary design
10	Residual chlorine analyzer	4-20 mA signal output, sanitary design
11	Online microorganism detector	4-20 mA signal output, sanitary design, high temperature resistance
12	Online rouge detector	4-20 mA signal output, sanitary design, high temperature resistance

12.2.1 Pressure Sensor

A pressure sensor is a field instrument which receives pressure variable input, and converts the pressure variable input to standard output signal in a certain proportion after converting it. The design is divided into plug-in type and flow-through type. The output signal of the sensor is transmitted to an in-process control room for pressure indication, record or control.

The pressure sensors can be divided into capacitive pressure sensors, inductive pressure sensors and resistive pressure sensors according to the working principle. Capacitive pressure sensors are usually divided into metal capacitive pressure sensors, ceramic capacitive pressure sensor and silicon capacitive pressure sensors. Inductive pressure sensors are usually divided into coil inductive pressure sensors and silicon resonant pressure sensors. A resistive pressure sensor usually refers to a silicon resistive pressure sensor. Pressure sensors can be divided into low accuracy pressure sensors, common accuracy pressure sensors and high accuracy pressure sensors according to the measuring accuracy class. Usually, low accuracy pressure sensors have the accuracy class of $\leqslant 0.5\%$, common accuracy pressure sensors have the accuracy classes of 0.1%, 0.2% and 0.25%, and high accuracy pressure sensors have the accuracy classes of 0.075% and 0.05%. The pressure sensors can be divided into gauge pressure sensors, absolute pressure sensors and differential pressure sensors according to the measuring conditions. They can be divided into digital communication pressure sensors and analog signal pressure sensors according to the communication method.

The anti-interference performance of the pressure transmitter has been paid more and more attention by users. A pressure transmitter with excellent electromagnetic compatibility is usually suitable for applications in

Table 12.5 List of electromagnetic compatibility

No.	Test item	Basic standard	Test condition	Performance level
1	Radiated interference(shell)	Table 5 of GB/T 9254—2008	30-1000 MHz	Qualified
2	Conducted interference(direct-current power port)	Table 1 of GB/T 9254—2008	0.15-30 MHz	Qualified
3	Anti-interference degree of electrostatic discharge(ESD)	GB/T 17626.2—2006	4 kV(contactor) 8 kV(air)	B
4	Anti-interference degree of radiofrequency electromagnetic field	GB/T 17626.3—2006	10 V/m(80 MHz-1 GHz)	A
5	Anti-interference degree of power frequency magnetic field	GB/T 17626.8—2006	30 A/m	A
6	Anti-interference degree of electrical fast transient burst	GB/T 17626.4—2008	2 kV(5/50 ns,5 kHz)	B
7	Anti-interference degree of surge	GB/T 17626.5—2008	1 kV(between wires) 2 kV(between wire and ground) (1.2 μs/50 μs)	B
8	Anti-interference degree of radio-frequency field inductive conducted interference	GB/T 17626.6—2008	3 V(150 kHz-80 MHz)	A

Note: 1. A performance level: the performance is normal within the limit of technical specifications during the test.

2. B performance level: the function or performance is temporarily reduced or lost, but it can recover by itself, with no change of actual operation conditions, storage and data.

various working conditions; it can ensure long-term reliability and accuracy. Table 12.5 shows the commonly used electromagnetic compatibility standard requirements for pressure transmitters.

a. Gauge pressure sensor. It usually takes the atmospheric pressure as reference; the measured pressure value is obtained by subtracting the atmospheric pressure value. A gauge pressure sensor is usually used to measure the pressure of a pipe, the height of the liquid level of an open tank, etc. Fig 12.12 shows the schematic diagram of a gauge pressure sensor, the negative chamber of the pressure sensor is connected to the atmosphere, the diaphragm (positive chamber) of the pressure sensor is filled with silicone oil, the pressure of the measured medium is obtained by the isolation diaphragm and process connection, and then the signal is output by the signal terminal after being processed by the electronic components of microprocessor.

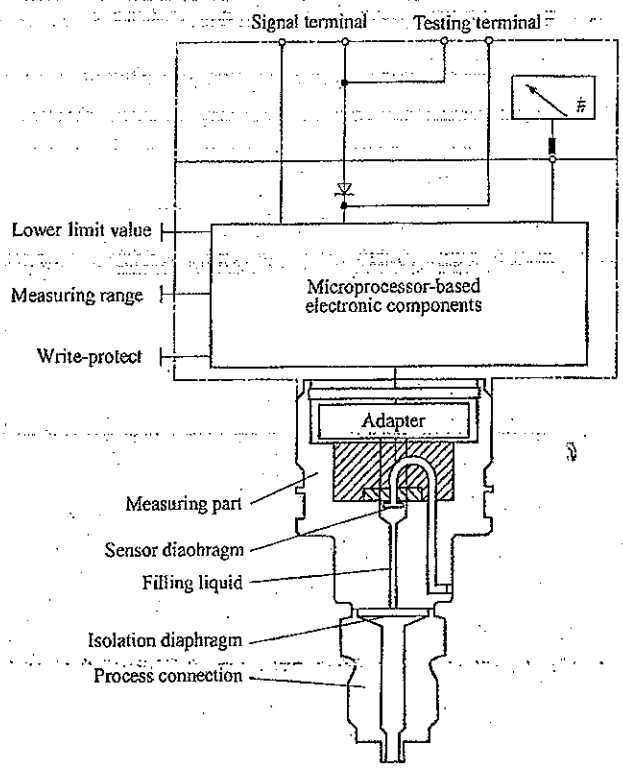
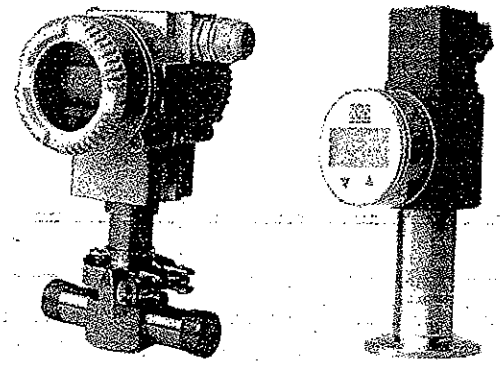


Fig 12.12 Schematic diagram of a gauge pressure sensor

Gauge pressure sensors can be divided into digital communication gauge pressure sensors and analog signal gauge pressure sensors according to the communication method. Digital communication gauge pressure sensors are usually divided into micropressure digital communication gauge pressure sensors, medium pressure digital communication gauge pressure sensors and high pressure digital communication gauge pressure sensors according to the measuring range. Usually the accuracy of a digital communication gauge pressure sensor is higher, usually better than 0.2%. The sensor can be equipped with a liquid crystal display, its

measuring range and scope are relatively limited, the lowest measuring range is 0-0.6 kPa or 0-6 kPa. The accuracy class of an analog signal pressure sensor is usually low, usually lower than 0.2%. The sensor usually has no liquid crystal display, its measuring range and scope are usually wider, the lowest measuring range is usually 0-25 kPa. Compared with that of an analog signal pressure sensor, the measuring range of a digital communication pressure sensor can be adjusted and revised at any time, therefore, it is appropriate for applications with higher measuring requirements, while the measuring range of an analog signal pressure sensor usually cannot be revised on site, it is set and calibrated by the manufacturer before leaving the factory, therefore, it is appropriate for applications with lower measuring requirements (Fig 12.13).



(a) Digital communication type (b) Analog signal type

Fig 12.13 Pressure sensor

For a gauge pressure sensor with tri-clamp connection, capillary remote transmission installation can be adopted, besides the body-mounted installation. This type of sensor with a capillary chuck can be itself installed in an appropriate location for convenient operation and observation (Fig 12.14).

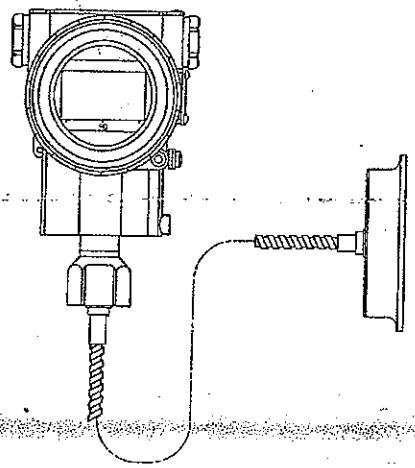


Fig 12.14 Drawing of a sanitary remote transmission gauge pressure sensor with capillary

Because the inside of the capillary is filled with silicone oil, its volume will vary with the change of temperature, therefore, the size of the capillary will be limited by the size of the chuck. Generally, a chuck with a large diameter can be configured with a long capillary, while the chuck with a small diameter can be configured with a short capillary. Table 12.6 shows a commonly used capillary length comparison table, in which, X represents "not recommend to be used".

Table 12.6 Capillary length selection table

Capillary length	0 m	1 m	2 m	3 m	4 m	5 m	6 m
DN25	√	×	×	×	×	×	×
DN38/DN40	√	√	√	×	×	×	×
DN50/DN51	√	√	√	√	√	×	×
DN76.1	√	√	√	√	√	√	√

b. Absolute pressure sensor. It usually takes the internal vacuum chamber as reference; the measured pressure value is obtained by subtracting by the vacuum pressure. An absolute pressure sensor usually measures the pressure of a vacuum pipe, liquid level of a vacuum tank, atmospheric pressure, etc. Fig 12.15 shows the schematic diagram of an absolute pressure sensor, its negative chamber is isolated from the outside, the diaphragm (positive chamber) of the absolute pressure sensor is filled with silicone oil, the pressure of the measured medium is obtained by the isolation diaphragm and process connection, and then the signal is output by the signal terminal after being processed by the electronic components of the microprocessor.

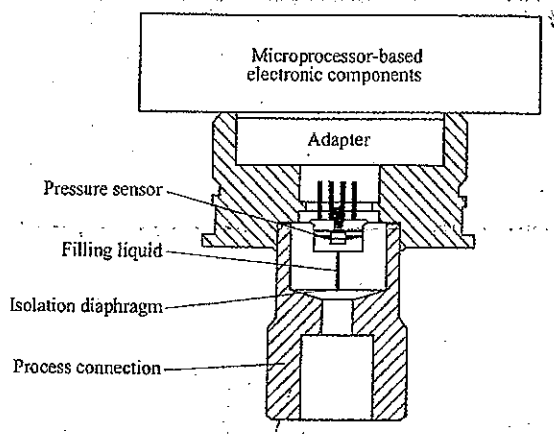


Fig 12.15 Schematic diagram of an absolute pressure sensor

Absolute pressure sensors can be divided into

digital communication absolute pressure sensors and analog signal absolute pressure sensors according to the communication method. Digital communication absolute pressure sensors are usually divided into low absolute pressure digital communication pressure sensors and medium absolute pressure digital communication pressure sensors according to the measuring range. The appearance of digital communication and analog signal absolute pressure sensors is identical. Usually the accuracy of digital communication absolute pressure sensors is higher, usually better than 0.2%. The sensor can be equipped with a liquid crystal display, its measuring range and scope are relatively low, the lowest absolute pressure measuring range is 0-0.6 kPa or 0-6 kPa. The accuracy class of analog signal absolute pressure sensors is usually low, typically less than 0.2%. The sensor has usually no liquid crystal display, its measuring range and scope are usually wider; the lowest measuring range is typically 0-1 bar. Compared with that of an analog signal absolute pressure sensor, the measuring range of a digital communication pressure sensor can be adjusted and revised at any time, therefore, it is applicable to the instances with higher measuring requirements, while the measuring range of an analog signal absolute pressure sensor usually cannot be revised on site, it is set and calibrated by the manufacturer before leaving the factory, therefore, it can be used for applications with lower measuring requirements only.

c. Differential pressure sensor. It has two pressure measuring ports, usually, the high pressure side is the measuring pressure end, while the low pressure side is the reference pressure end, the pressure value at the high pressure side is subtracted by that at the low pressure side to get the differential pressure signal. Differential pressure sensors can be divided into micro differential pressure sensors and medium differential pressure sensors according to the measuring range. A differential pressure sensor is usually used to measure the differential pressure of a pipe, liquid level of closed tank, the differential pressure at the two sides of a throttling device, etc. Fig 12.16 shows the schematic diagram of a differential pressure sensor, the positive side of the differential pressure sensor is connected with the positive process flange of the sensor by the filling liquid and isolation diaphragm, the negative side of the differential pressure sensor is connected with the negative process flange of the sensor by the filling liquid and

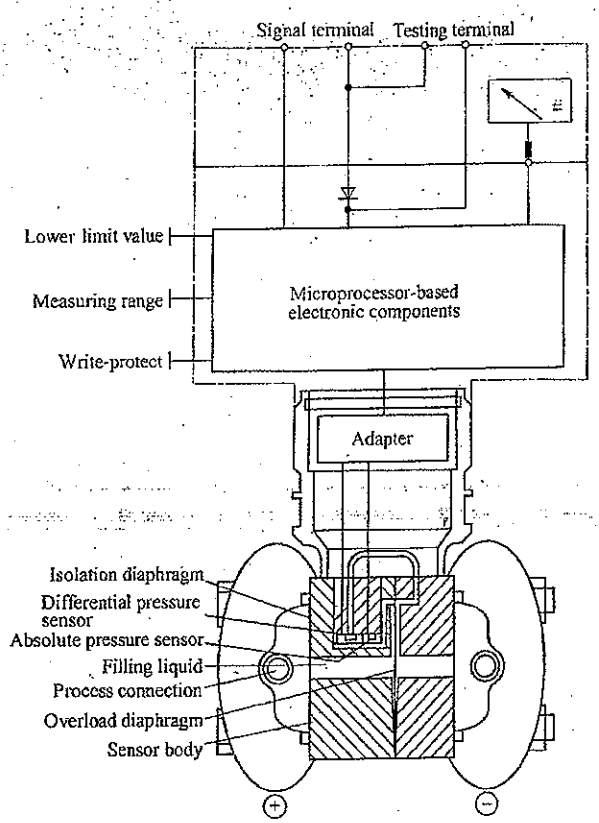


Fig.12.16 Schematic diagram of a differential pressure sensor

isolation diaphragm. The internal differential pressure sensor can acquire the pressure difference of the positive and negative process flanges directly to realize the measurement of the differential pressure. The information is transmitted to the outside using a general standard signal processed by the microprocessing electronic components within the sensor.

The sanitary differential pressure sensor is a derivative product of the differential pressure sensor (Fig 12.17). It has a wide range of application in the pharmaceutical industry, especially for the measurement of the liquid level in sealed or semi-sealed tanks. The sensor is connected by tri-clamp, which can ensure the sterility of the sensor.

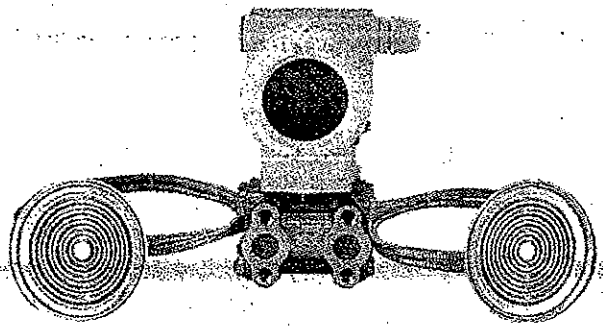


Fig 12.17 Sanitary differential pressure sensor

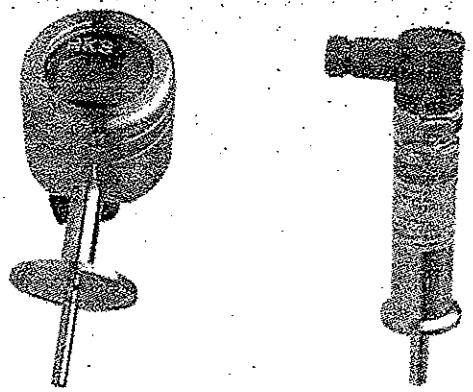
12.2.2 Temperature Sensor

A temperature sensor usually uses a thermocouple and thermal resistance as temperature measurer, the signal is transmitted from the temperature measurer to the sensor module, and converted to 4～20 mA current which has a linear relationship with the temperature; the current is used as output after circuit processing such as voltage stabilization smoothing, operational amplifying, non-linear rectification, V/I conversion, constant current and reverse protection.

A temperature sensor is an instrument which converts the temperature variable to a transmissible standard output signal. Its design is divided into plug-in type and flow-through type. It is generally used to measure and control the temperature parameter in industrial processes. A temperature sensor is usually composed of a sensor and a signal converter. The sensor is generally a thermocouple and thermal resistance, and the signal converter is generally composed of the measuring unit, signal processing and converting unit (The phasing meter of the thermal resistance and thermocouple for industrial use is standardized, therefore, when the signal convertor is an independent product, it is also called a transmitter). Some sensors have a display unit, and some have a fieldbus function. The sensor output signal has a given continuous function relationship with the temperature variable (it is usually a linear function). The output signal of the earlier manufactured sensors has a linear function relationship with the resistance value (or voltage value) of the temperature sensor.

The commonly used standard output signals are generally direct current signals of 0-10 mA and 4-20 mA (or 1-5 V). The temperature sensors can be divided into two-wire systems and four-wire systems according to the power supply wiring method. It can be divided into screw thread, clamp and flange methods according to the connection type. It can be further divided into analog type and digital intelligent type according to the communication mode.

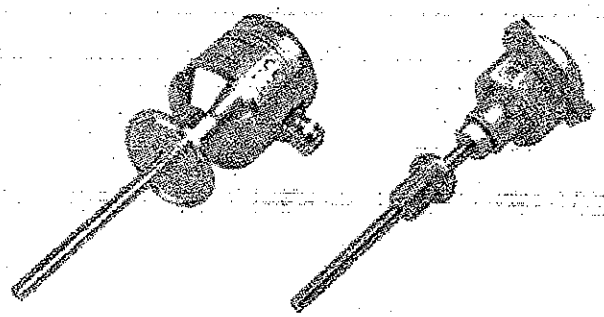
a. Resistance-type temperature sensor. In the pharmaceutical industry, its temperature measuring range is usually −50-+250 ℃, it has a stainless steel protective tube, and uses a HART communication output, and the core sensor has a Pt100 grade A high accuracy temperature sensor. The configuration of the resistance-type temperature sensors is divided into sensors with display and sensors without display (Fig 12.18).



(a) Sensor with display (b) Sensor without display

Fig 12.18 Resistance-type temperature sensor

b. Thermocouple temperature sensor. Its temperature measuring range is relatively wider, usually −50-+1800 ℃, it has a stainless steel protective tube, and uses a HART communication output, and the core sensor is a thermocouple temperature sensor. The configuration of a thermocouple temperature sensor is divided into aluminium alloy shell and stainless steel shell (Fig 12.19).



(a) Stainless steel shell (b) Aluminum alloy shell

Fig 12.19 Thermocouple temperature sensor

12.2.3 Flow Sensor

Flow sensors have a great variety. They can be divided into oval gear flowmeters, roots flowmeters, sliding vane (cam/concave line) flowmeters, rotary-piston flowmeters, nutating disc flowmeters, wet-type flowmeters and bellows flowmeters according to the volume integral principle of the flow sensor. They can be further divided into differential pressure flowmeters, orifice plate flowmeters, nozzle flowmeters, 1/4 circular nozzle flowmeters, venturi tube flowmeters, V plug tube flowmeters, laminar flowmeters and weir flowmeters according to the dynamic pressure energy

and static pressure energy conversion principle. They can also be divided into target flowmeters, baffle flowmeters, dynamic pressure tube flowmeter and pitot tube (Annubar/flute) flowmeter according to fluid dynamic pressure principle. The float flowmeter is based on the flow area change principle. The elbow flowmeter and the circle pipe flowmeter use the fluid centrifugal force principle. The Karman vortex (vortex-street) flowmeter and vortex flowmeter use the fluid oscillation principle. The electromagnetic flowmeter is based on the electromagnetic induction principle. The thermal flowmeter and thermal-conduction flowmeter use the fluid and solid thermal energy exchange principle. The ultrasonic flowmeter is based on ultrasonic measurement. The mass flowmeter is based on the mass principle.

For a pharmaceutical water system, sanitary design requirements need to be considered, therefore, applicable flow sensors include the float flowmeter, vortex street flowmeter, electromagnetic flowmeter, mass flowmeter, differential pressure flowmeter and surface acoustic wave flowmeter, etc.

a. Float flowmeter. It is also called rotor flowmeter (Fig 12.20), its flow detection element is composed of one vertical cone-shaped tube which is expanded from bottom to top and a float fluctuating along the axle of the cone-shaped tube. The working principle of a float flowmeter is to form a rising floating force due to the differential pressure generated from the top and bottom ends of the float when the fluid to be measured flows through the annular gap formed by the cone-shaped tube and the float from bottom to top. When the rising force applied to the float is greater than the weight of the float immersed in the liquid, the float will rise, and the area of annular gap is increased accordingly, the flow rate of the fluid in the annular gap is decreased immediately, the differential pressure between the top and bottom ends of the float is reduced, the rising force applied to the float will be reduced accordingly, the float will stabilize at a certain level until the rising force equals the weight of the float immersed in the fluid. The height of the float in the cone-shaped tube has a corresponding relationship with the flow rate, which is the basic equation of volume flow. The transparent cone-shaped tube of float flowmeter is usually made of borosilicate glass; it is usually called a glass tube float flowmeter for short. The scale division of the flow rate is engraved in the outer wall of the cone-shaped tube directly, or the scale division ruler is installed beside the cone-shaped tube. The inner chamber of the cone-shaped tube has an even surface and ridge ribs with orientation (or a flat surface). The float moves in the cone-shaped tube freely or moves along the cone-shaped tube guiding ribs, the instrument on the inner wall of the larger mouth even surface is guided by a guide rod.

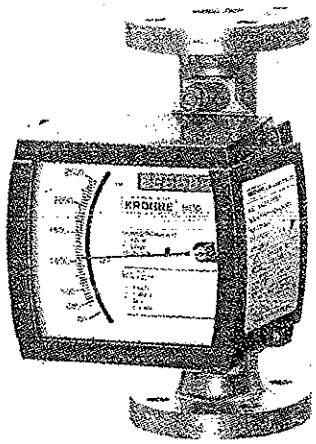


Fig 12.20 Float flowmeter

Based on the material of the cone-shaped tube, float flowmeters are divided into transparent cone-shaped tube float flowmeters and metal cone-shaped tube float flowmeters. The most widely used material for the transparent cone-shaped tube is glass, the careless operation of a meter for measuring gas without a guiding structure will break the glass tube. It can be made of transparent engineering plastic such as polystyrene, polycarbonate and organic glass, with the advantage being break resistant. Compared with a transparent cone-shaped tube float flowmeter, a metal cone-shaped tube float flowmeter can be used in a medium with higher temperature and pressure, with no potential risk of breaking the glass. The typical structure is to integrate the cone-shaped tube and the shell or the isolated structure by inserting the cone-shaped tube into the shell. Changing the flow rate only requires changing the cone-shaped tube with one with a different cone angle, this is relatively convenient. The sanitary metal cone-shaped tube float flowmeter is widely used in equipment such as purified water machines and CIP workstations in the pharmaceutical industry.

The float flowmeters are divided into in-place indication float flowmeters and remote signal output float flowmeters according to the availability of remote signal output. Some transparent tube float flowmeters are mainly used for in-place indication, they are equipped with a

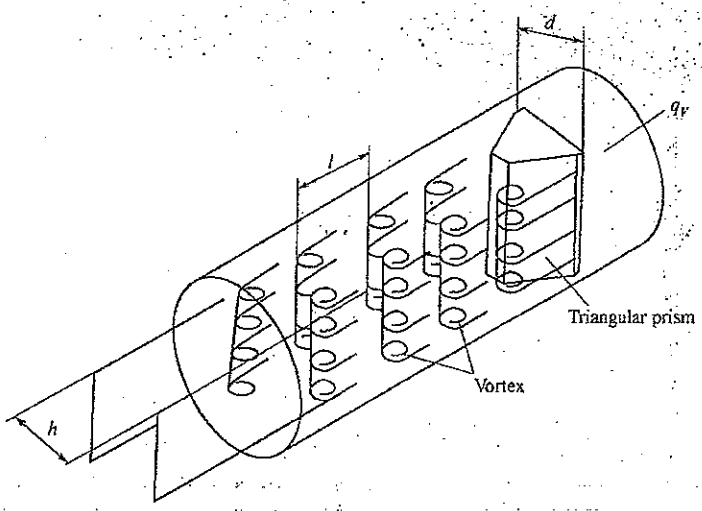


Fig 12. 21 Schematic diagram of a vortex street flowmeter

proximity switch to output an alarm signal for the flow rate upper and lower limits. Some in-place indication metal tube float flowmeters have the same appearance with remote signal output float flowmeter, but the float displacement is transferred out by magnetic coupling, and indicated in place after being processed by a linearizing mechanism such as a linking rod and cam. In some cases the conversion part of the remote signal output instrument converts the float displacement to current or air pressure analog signal for output; these instruments are called electrical remote float flowmeter and air remote float flowmeter.

Float flowmeters can be divided into float flowmeters used for liquid, gas and steam respectively according to the type of liquid to be measured. The float flowmeters can further be divided into full flow type (it refers to the instrument with the fluid to be measured flowing through the float flowmeter completely) and divided flow type (relative to the full flow type, only part of the fluid to be measured flows through the flow detection part such as float) according to the amount of fluid to be measured passing through the float flowmeter.

b. Vortex street flowmeter. It is generally used to measure the flow rate of fluid media in industrial pipelines, such as gas, liquid, steam and other media. It is characterized by small pressure loss, wide measuring range, high accuracy, and is almost not affected by parameters such as liquid density, pressure, temperature and viscosity when measuring the volume flow. A vortex street flowmeter has no movable mechanical parts, therefore, its reliability is high, maintenance activities are few, and instrument parameters are stable for a long term. The vortex street flowmeter uses a piezoelectric stress sensor, it has high reliability, and can work within a temperature range of −20-+250 ℃. The vortex street flowmeter has analog standard signal and digital pulse signal outputs. It is easy to be used by matching with a digital system such as a computer, and is an advanced measuring instrument.

A triangular prism vortex generating body is set in the fluid, then both sides of the vortex generating body will generate a regular vortex alternately, this type of vortex is called a Karman vortex. As illustrated in Fig 12. 21, the vortex series are arranged asymmetrically downstream of the vortex generating body.

The vortex street flowmeter (Fig 12. 22) is used to measure the volume flow of gas, steam or liquid according to the Karman vortex street principle; it can be used as the flow sensor in an automatic control system. The vortex street flowmeter measures the flow using the liquid vibration principle. The liquid will produce alternately two columns of vortexes in direct proportion to the flow rate behind the triangular prism vortex generating body, when it flows through the vortex street sensor in the pipe. The release frequency of vortexes is related to the average flow rate of the fluid flowing through the vortex generating body and the characteristic width of the vortex generating body.

c. An electromagnetic flowmeter is a flowmeter used to measure the fluid media flow rate using the electromagnetic induction principle. It is a flow measuring instrument with high precision, high reliability and long service life; it is composed of a sensor with direct contact with the pipe media and an upper signal converter. An electromagnetic flowmeter works based

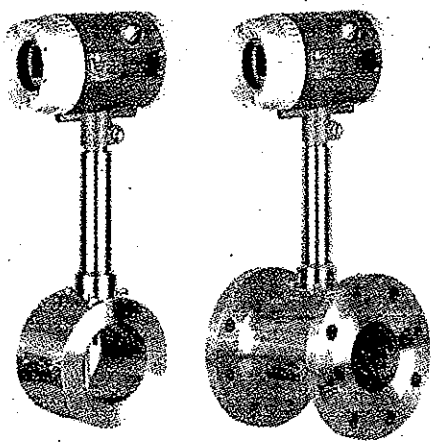


Fig 12.22 Vortex street flowmeter

on Faraday's law of electromagnetic induction; it measures the flow rate of a conducting liquid with conductivity >5 μS/cm; it is an instrument used to measure the flow rate of conducting media. It can be used to measure the flow rate of highly corrosive liquids such as strong acids and strong alkali and liquids containing uniformly suspended solids such as slurry, ore pulp and paper pulp, in addition to measuring the flow rate of common conducting liquids. The electromagnetic flowmeter is widely used in pharmaceutical water systems to measure the flow rate of raw water and concentrated water.

An electromagnetic flowmeter (Fig 12.23) has a magnetic field installed at both sides of the pipeline, the medium to be measured will disrupt the magnetic lines when flowing through the pipeline, and generate an induced electromotive force at the two detection electrodes, its value is in direct proportion to the speed of the fluid movement. When a conductor is in movement and cuts the magnetic lines in the magnetic field, an induced electromotive force will be generated in the conductor. The value of the induced electromotive force is in direct proportion to the medium-efficiency length of the conductor in the magnetic field and the speed of the movement of the conductor perpendicular to the field direction in the magnetic field. In the same way, when a conducting fluid moves in a perpendicular direction in the magnetic field and cuts the magnetic lines, it will generate an induced electromotive force at the electrodes at both sides of the pipe.

d. Coriolis force mass flowmeter. The fluid will generate a force when the fluid flows in a rotating tube, it is called Coriolis force, it was discovered by Coriolis when studying a marine turbine engine in 1832. The first practical mass flowmeter was researched and developed on the basis of this principle by the founder of the US Micro Motion Company in 1977. A mass flowmeter is based on the Coriolis force, two parallel flow tubes are in the sensor, and a drive coil is installed in the central part, and detecting coils are installed at the two ends. The vibrating tube will do a periodic back and forth vibration when the excitation voltage provided by the sensor is impressed on the drive coil. When the fluid media in an industrial process flows through the vibrating tube of the sensor, it will generate a Coriolis force effect in the vibrating tube, making the two vibrating tubes have a torsional vibration, the detecting coil installed at both ends of the vibrating tube will generate two groups of signals with different phases. The phase difference between these two signals is proportional to the mass flow of fluid passing through the sensor. The computer calculates the mass flow passing through the vibrating tube, the master frequency of the vibrating tube is different when different media flow through the sensor, thereby, the media density is calculated. The platinum resistor installed on the vibrating tube of the sensor can measure the temperature of the media indirectly.

A mass flowmeter (Fig 12.24) can directly meas-

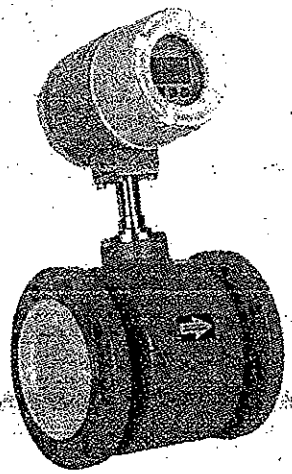


Fig 12.23 Electromagnetic flowmeter

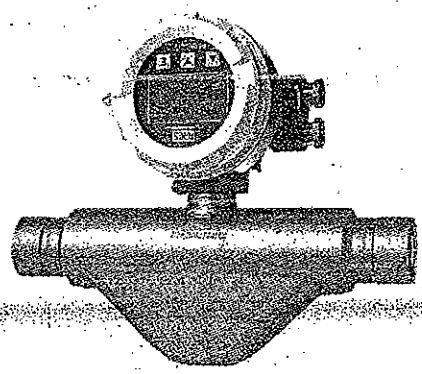


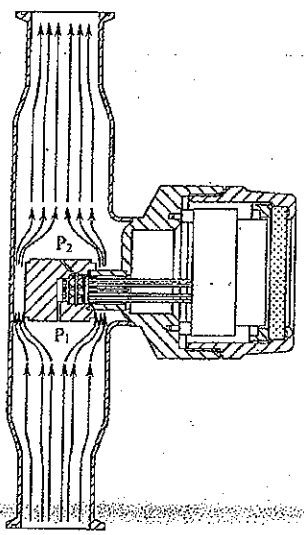
Fig 12.24 Outside view of a mass flowmeter

ure the mass flow and density of the medium passing through the flowmeter, and it can measure the temperature of the medium indirectly. Because the sensor is an intelligent instrument having a single chip as the core, more than ten types of parameters can be output for user according to the above three fundamental quantities. The configuration of a mass flowmeter is flexible with multiple functions and high cost performance ratio. It is a new generation of flow instrument. If only volume flow is measured by the flow measuring meter when measuring the mass flow in the pipe, it will have a large measuring error due to the change of fluid density due to large changes in parameters such as the pressure and temperature of the liquid. For volumetric flowmeters and differential pressure flowmeters, the density of fluid may change by 30%, this will cause an error of 30%-40%. With the improvement of the automation level, many production processes have new requirements for flow measurement. Chemical reaction processes are controlled by the quality of raw materials, the heating and cooling effects of steam and air flow are also in proportion to the mass flow. Therefore, the mass flowmeter is an important flow measuring instrument. The mass flowmeter is widely used in pharmaceutical water systems, it can be used to keep the water for injection at a constant volume in the liquid preparation tank, or control the consumption of cleaning water in the CIP workstation.

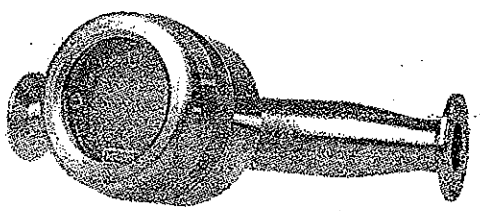
e. Differential pressure flow sensor. The working principle of differential pressure flow sensor (Fig 12.25) is to generate a pressure difference ($P_1 - P_2$) before and after the throttling device when a fluid is flowing through the throttling device; the pressure difference has a given function relationship with the flow rate, the larger the flow rate, the larger the pressure difference. The differential pressure signal is transmitted to the differential pressure sensor, and converted to 4-20 mA DC signal for outputting and transmitting to the flow totalizer, realizing the measurement of the fluid flow. A sanitary differential pressure flow sensor has a no dead leg design inside the throttling device, which is made of 316L stainless steel, with polishing treatment. A sanitary differential pressure flow sensor can substitute the mass flowmeter for applications in the pharmaceutical water system after it undergoes sanitary design treatment.

The sanitary differential pressure flow sensor can output pipeline pressure and liquid temperature signal in addition to the output of instantaneous flow and cumulative flow due to the fact that the differential pressure sensor integrates a pressure sensor and a temperature sensor. Such a sanitary flow sensor with temperature and pressure signal output is designed to display and output three parameters, flow, pressure and temperature, simultaneously. Its simple structure and convenient installation can not only save the application costs for the user, but also lower the requirements of installation space on site.

f. Surface acoustic wave flow sensor. Surface acoustic waves (SAW) are generated during natural phenomena such as seismic activity. A surface acoustic wave flow sensor uses the principle for online measurement of liquid flow (Fig 12.26), and activates an interdigital transducer by an electrical signal and generates



(a)



(b)

Fig 12.25 Differential pressure flow sensor

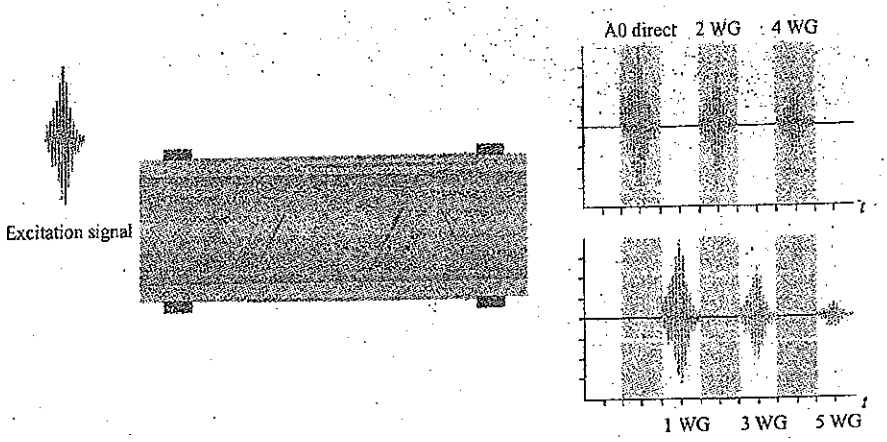


Fig 12.26 Schematic diagram of surface acoustic wave

surface acoustic waves. The surface acoustic wave is spread on the pipeline surface and refracted by the liquid at a certain angle, and then generates one or more received signals through the liquid. The process can be conducted in two directions, downstream and upstream. The operational time difference of this type of wave is in direct proportion to the flow rate. It has excellent measuring performance and evaluation capability for the liquid type and other physical properties by comparing a single wave and multiple waves passing through the liquid medium.

There is no measuring element coming in contact with the medium in the measuring tube of a surface acoustic wave flow sensor. It is a typical sanitary flow-through sensor (Fig 12.27), and has the obvious advantage of "no dead leg". The measurement is not affected and restricted by the conductivity of the liquid medium, and it is insensitive to strong electromagnetic fields in the external environment. Similarly to the differential pressure flowmeter, the surface acoustic wave flowmeter has obvious installation advantages such as small volume and light weight, and provides convenience for the equipment module assembly in the sanitary aseptic industry.

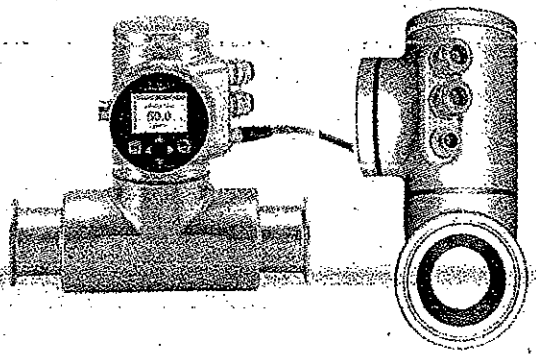


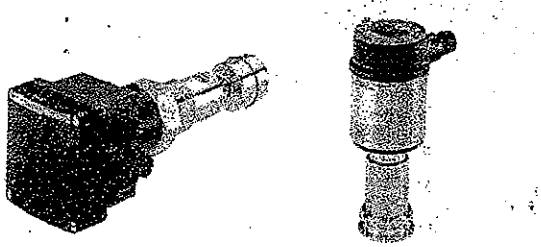
Fig 12.27 Surface acoustic wave flowmeter

12.2.4 Liquid Level Sensor

Liquid level sensors can be of many types, including simple float switch, tuning fork switch, ultrasonic level gauge, radar liquid level meter, capacitance liquid level meter, guiding microwave liquid level meter and differential pressure transmitter. The generation unit, storage unit and distribution pipeline in a pharmaceutical water system requires the use of many different liquid level meters. The liquid level meter of a pharmaceutical water storage tank usually has a capacitance liquid level meter, guiding microwave liquid level meter or differential pressure liquid level meter, or uses a static pressure transmitter to measure the liquid level when no impact of pressure.

The capacitance liquid level meter and guiding microwave liquid level meter usually have rod-shaped or soft rope-shaped parts in contact with the water, while the probe side of a differential pressure liquid level meter and static pressure liquid level meter also is in contact with water. From the perspective of no contacting parts, the ultrasonic level gauge and radar liquid level meter are the best choice, but the liquid level sensor used in pharmaceutical water is required to have sanitary design and resist high temperature sanitation or sterilization, the selection of ultrasonic level gauge and radar liquid level meter tends to be limited.

The liquid level measurement is a part of the process control. It includes the liquid level switch/alarm and continuous liquid level measurement/control (Fig 12.28). The liquid level switch is used to indicate that the liquid level has reached a preset level and outputs a switching signal, which can be used to control the switch valve to fill the storage tank from the lower limit level to the upper limit level of the liquid level.



(a) Liquid level switch (b) Continuous liquid level sensor

Fig 12.28 Liquid level sensor

The common liquid level switch uses the following float and tuning fork principles. A continuous liquid level sensor can provide a systematic and complete liquid level measurement and measure the liquid level at all points within the whole measuring range, provide an analog output signal which is proportional to the liquid level, distance and volume. It includes medium-contact and non-medium-contact measurements. The common continuous liquid level meter adopts the following principles: a guiding microwave and static pressure transmitter is used for medium-contact measurement, while ultrasonic and radar meters are used for non-medium-contact measurement.

The working principles are different for different liquid level switches or continuous liquid level sensors. The basic principles of measurement for the float liquid level switch, tuning fork liquid level switch, guiding microwave liquid level meter, static pressure liquid level meter, ultrasonic level gauge, radar liquid level meter, capacitance liquid level meter and differential pressure liquid level meter will be introduced below.

a. The principle of measurement for a float liquid level switch. The float floating on the liquid changes its vertical position according to the liquid level, the permanent magnet integrated in the float generates a constant magnetic field to make the reed contact in the magnetic field act, the float with magnet is mechanically connected to the reed contact to form a liquid level switch contact. The mechanical stop dog in the float switch prevents the rising of the float when the liquid level rises continuously, maintaining the loop state. Only when the liquid level falls back to below the stop dog, the float will reset. The float liquid level switch is not applicable for use with media with lower density (lower than 0.7 g/cm^3) and the coating generating media.

b. The principle of measurement for the tuning fork liquid level switch. The tuning fork is powered by piezoelectricity, and vibrates with a mechanical resonant frequency of about 1200 Hz. When the tuning fork is immersed in liquid, the vibration frequency is changed, the built-in oscillator detects the change and converts it to switching signal. Because the measuring element is simple and solid, it is not affected by the chemical and physical properties of the liquid to be measured (Fig 12.29).



Fig 12.29 Tuning fork liquid level switch

c. The principle of measurement for the guiding microwave liquid level meter. A high frequency microwave pulse is transferred along the steel cable or steel bar in the steel tube and reflected back when reaching the medium surface; it is then received by the electronic components. The transmitter calculates the travelling time of the microwave pulse and converts it to corresponding liquid level for output. The transmitter can have the length of probe preset when purchased, rather than undergoing time-consuming adjustments. The steel cable and steel bar can be adjusted to the length suitable for actual requirements.

d. The principle of measurement for the static pressure liquid level meter. The static pressure generated by a liquid column is function of the liquid density and liquid level. The pressure sensor installed at the bottom of the storage tank measures the gauge pressure relative to the atmospheric pressure, and the measured value is converted to the liquid level value according to the known density of the medium. The principle is $p=\rho gh$, in which, p is pressure, ρ is liquid density, g is the acceleration of gravity constant, h is the height of the liquid level. In the conditions of a certain gas phase pressure (atmospheric pressure), liquid density and acceleration of gravity, the liquid pressure in the tank is in direct proportion to the height of the liquid level in the tank. The principle of the static pressure liquid level meter is simple; it is usually installed at the

side wall or bottom of the tank. The static pressure liquid level measurement is applicable to almost all media. The storage tank can adopt a static pressure liquid level meter to monitor the liquid level in the conditions of no pressure or temperature fluctuations, for example, the raw water tank or softened water tank. When the tank volume in a pharmaceutical water storage system is relatively small, water temperature fluctuation is frequent or the tank is used under pressure; the static pressure liquid level sensor may have liquid level value deviations, therefore, it is rarely used in the storage systems of pharmaceutical water systems such as water for injection and purified water.

e. The principle of measurement forthe ultrasonic level gauge. The transmitter of the ultrasonic liquid level sensor transmits an ultrasonic short pulse to the medium to be measured at the frequency of 70 kHz. The pulse is reflected back by the medium surface and received by the transmitter as a return wave. The time required from transmitting to receiving the ultrasonic pulse is in direct proportion to the distance; therefore, it is also in direct proportion to the liquid level. The integrated temperature sensor detects the temperature of the storage tank, and compensates for the impact of temperature on the signal operating time, the measured liquid level is converted to output signal and transmitted as measured value, the shape of storage tank is known, then the liquid volume in the storage tank can be calculated and displayed.

f. The principle of measurement of the radar liquid level meter. the radar liquid level transmitter includes an electronic shell, process connector, probe and sensor. The sensor transmits a radar pulse to the medium to be measured at intervals of 1ns. These pulses are reflected back by the medium surface, and received as a return wave by the probe, radar waves travel at the speed of light. The time elapsed from transmitting to receiving the radar pulse is in direct proportion to the distance, therefore, it is also in direct proportion to the liquid level. The measured liquid level is converted to output signal, and transmitted as measured value.

g. The principle of measurement for the capacitance liquid level meter. It is designed using the principle the interelectrode capacitance being in direct proportion to the liquid level when the liquid dielectric constant is does not change. Because the deviation of the liquid dielectric constant is relatively small in purified water systems and water for injection systems, it has no effect on the normal liquid level detection; this type of meter has been widely used in pharmaceutical water storage and distribution systems. For the storage tanks of dosing systems and CIP systems, the conductivity value will have frequent changes; a capacitance liquid level meter cannot meet the requirements of liquid level monitoring. The capacitance liquid level sensor should be inserted from the top of tank for installation; it has certain requirements on the height of the tank and water treatment room, which should be paid attention to during the system design.

h. The principle of measurement for the differential pressure liquid level meter. The principle is $\Delta p = \Delta\rho g h$, in which, Δp is the pressure difference of the liquid and gas phases, $\Delta\rho$ is the density difference between the liquid phase and the gas phase, g is acceleration of gravity constant, h is the height of the liquid level. The monitoring of the liquid level is realized using the pressure difference between the liquid phase and the gas phase in the tank. Similar to the capacitance liquid level sensor, the differential pressure liquid level sensor has been widely used in pharmaceutical water storage and distribution systems. Compared with the static pressure liquid level sensor and capacitance liquid level sensor, the changes in the pressure of the gas phase, fluctuations of the water temperature and conductivity value in the water will not affect the detection accuracy of a differential pressure liquid level sensor, also, it will not be affected by the tank installation height. Therefore, differential pressure liquid level sensor is the most ideal liquid level sensor for pharmaceutical water storage tank. A differential pressure liquid level sensor has two sensor probes, which are used to measure the gas phase pressure and liquid phase pressure respectively, and are installed at the upper head and bottom head (or side wall) of the tank (Fig 12.30).

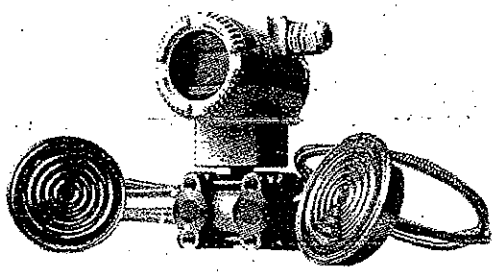


Fig 12.30 Differential pressure liquid level sensor

12.2.5 Conductivity Sensor

Pharmaceutical waters for the pharmaceutical in-

dustry generally include purified water and water for injection. In addition to the water molecules in the purified water and water for injection there is also a slight ionization that generates a very low concentration of hydrogen and hydroxide ions. Although the conduction capacity is very weak, it has a well-defined low conductivity value.

Conductivity can reflect a contamination index of all ionic contaminants in the pharmaceutical water, but it cannot identify which ions are present. In most applications, the conductivity is used to reflect the purity of water. The commonly used instrumentation for measurement of the conductivity of pharmaceutical water reads out with units of $\mu S/cm$ (reciprocal of electrical resistivity), with the cell constant of 0.01-1.0 cm^{-1}. The cell constant depends on the geometrical shape of the sensor; it is determined by the ratio of the effective sectional area of sample between two plate electrodes and the distance between the two plate electrodes. The cell constant is the main calibration parameter for conductivity measurement. When using conductivity internationally, the unit of $\mu S/m$ is used as the unit of conductivity. 1 $\mu S/m$ is equivalent to 0.01 $\mu S/cm$. The conductivity of ultrapure water is 0.055 $\mu S/cm$ at 25 ℃, the typical high limit value of the pharmaceutical water conductivity is 0.3-5 $\mu S/cm$ at 25 ℃.

The generation, storage and distribution units of pharmaceutical water systems require monitoring the conductivity of the water and taking actions based on those measurements. The sanitary online conductivity meter and sensor complying with the pharmaceutical industry (Fig 12.31) should meet the following requirements:

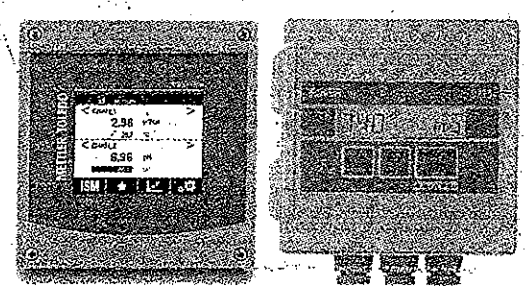


Fig 12.31 Sanitary conductivity sensor

- Applicable to the measurement range of low conductivity, 0.05-20 $\mu S/cm$;
- High stability, and ease of calibration;
- High measuring accuracy: at least 2 digits are displayed after the decimal point;
- Good temperature and pressure resistance: the operating temperature range can go higher than 130 ℃, and pressure can go higher than 2 bar;
- Electrode surface roughness $< 0.4\mu m$;
- Quick connection, for ease of installation and disassembly;
- Material compliant with FDA related certification;

Conductivity is usually measured by direct electrode measurements as previously described, or by electromagnetic or ultrasonic measurements. The former two methods are more widely used. The electromagnetic induction conductivity method uses induction coils, which have no contact with the medium. It is applicable to corrosive media such as strong acids and alkali. The electromagnetic conductivity measurement has limited ability to measure in low conductivity ranges. The conductivity of purified water or water for injection is very low which prevents the use of the electromagnetic method for those samples. Traditional electrode conductivity is the principal method of measurement of these waters.

The cell constant can be obtained by theoretical calculation, but the electrode distance and area of each sensor has manufacturing and measuring tolerances, which can yield significant differences between the calculated and actual value. With some electrode arrangements the cell constant cannot be expressed and calculated by the formula due to the complex structure. Normal industry practice is to use a standard solution calibration method or reference conductance cell method. Fig 12.32 is an example of measuring ranges and application scenarios for different cell configurations.

The electrode conductivity probe has direct contact with the solution, with high requirements on the material. Electrodes can be divided into two electrodes, three electrodes, four electrodes and seven electrodes based on the number of electrodes. In the pharmaceutical industry, the two-electrode conductivity sensor is used to measure pharmaceutical waters with low conductivity values (unit: $\mu S/cm$). Four-electrode conductivity sensor is used to measure CIP acid-alkaline concentrations with higher conductivity values (unit: mS/cm).

a. Two-electrode type. Two-electrode conductivity sensors are generally used in purified water and water for injection systems with low conductivity values. This measurement impresses alternating current voltage across the two electrodes and measures the current between them. Two-electrode conductivity instrumentation is generally composed of two electrodes, a temperature sensor and an amplifier, as illustrated in

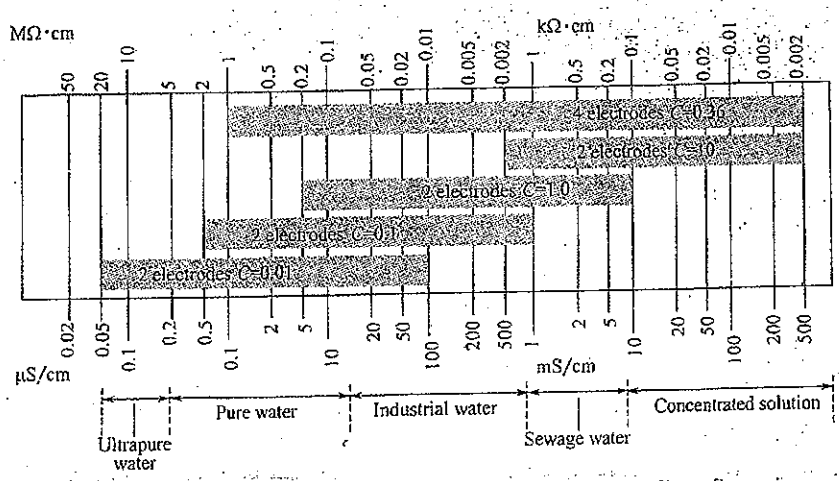


Fig 12.32 Application scenarios of electrodes with different cell configurations

Fig 12.33. Because conductive ions existed in the solution, which is equivalent to a resistance, alternating voltage is impressed alternating voltage between two electrodes contacting solution to generate current between electrodes. The generated current magnitude is in direct proportion to the resistance of the medium (ion concentration of the solution). The built-in Pt1000 or Pt100 is used for temperature compensation.

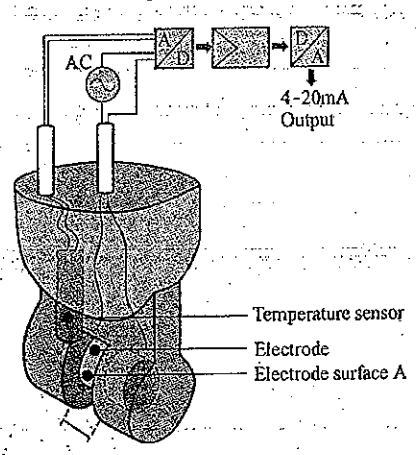


Fig 12.33 Schematic diagram of a two-electrode conductivity sensor

The traditional legacy sensor design uses two parallel electrodes with identical geometrical shape and size. This type of sensor has a simple structure, and is often used for measurements in the laboratory. For CIP and SIP are required in pharmaceutical industry, a coaxial electrode design is commonly used; it is composed of a cylindrical inner electrode and a tubular outer electrode (Fig 12.34).

The measuring range of a two-electrode conductivity sensor can be 0-20,000 μS/cm. Sensors also have different measuring ranges due to different cell constants: for a cell constant of 0.01 cm^{-1}, the measuring range

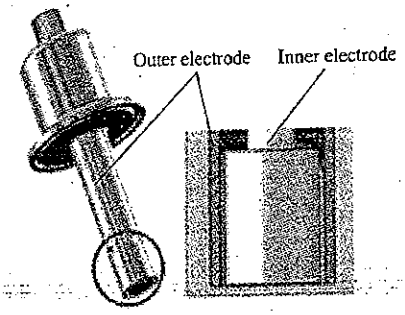


Fig 12.34 Structure of coaxial electrode sensor

can be 0-20 μS/cm; for a cell constant of 0.1 cm^{-1}, the measuring range can be 0.1-200 μS/cm; for a cell constant is 1.0 cm^{-1}, the measuring range is 10-20,000 μS/cm. Therefore, the smaller the cell constant C, the higher the measuring accuracy, the smaller the measuring range; the larger the cell constant C, the lower the measuring accuracy, the wider the measuring range.

b. Four-electrode type. The conductivity value of acid and alkaline solutions is much higher than that of purified water and water for injection. The conductivity sensor used for determining the concentrations of CIP detergents for alkaline washing and acid washing should have four electrodes. Four-electrode conductance cells are composed of two current electrodes and two voltage electrodes. Their working principle is shown in Fig 12.35.

Current is impressed to two opposite electrodes (current electrodes) and meanwhile the point location difference between voltage electrodes is remained unchanged. The current can be ignored when measuring the voltage; therefore, the voltage electrodes are not polarized. Four-electrode conductivity sensors have the following characteristics: the current electrodes are separate from the voltage electrodes and the current electrodes

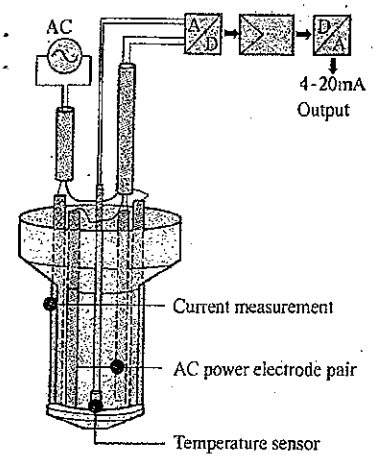


Fig 12.35 Schematic diagram of a four-electrode conductivity sensor

are powered by a constant current source to avoid the impact of polarization resistance. Four-electrode sensors provide high sensitivity, strong anti-fouling capacity and wide measuring range. The structure of common four-electrode conductivity sensors is shown in Fig 12.36.

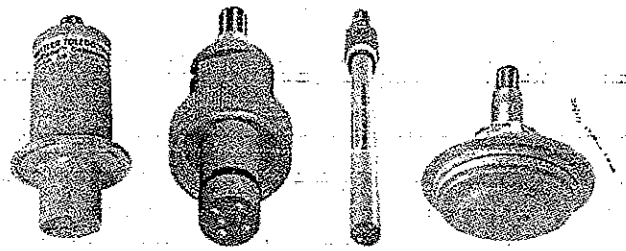


Fig 12.36 Common four-electrode conductivity sensors

Conductivity sensors can be divided into plate type and cylindrical type according to structure. The pharmaceutical industry generally uses the cylindrical type. Online conductivity sensors are usually designed as coaxial, where the inner electrode is a cylinder with small diameter and containing a built-in temperature sensor for temperature compensation (Fig 12.37). The outer electrode is designed with a tubular shape to encircle the inner electrode. The distance and area between them determines the conductance cell constant of the sensor. The inner electrode is separated from the outer electrode with an insulating spacer.

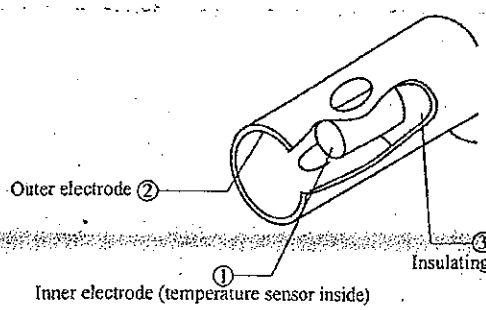


Fig 12.37 Structure chart of conductivity sensor

The process connection of a sanitary conductivity sensor is commonly designed with a quick-disconnect connector. The resistance to pressure, temperature and chemical corrosion must be in full compliance with the process requirements of clean in place (CIP), steam in place (SIP) or other sanitization methods used in the water system. When the conductivity sensor is installed in the pipeline, it must be ensured that the electrodes are completely immersed in the medium to be measured and air bubbles or solid particles are completely prevented from accumulating on the electrode surfaces and insulator. The ideal installation method is to install the sensor in a right-angle position relative to the pipeline (Fig 12.38), and install the electrode towards the fluid flow, so that the water sample can flow in from the end of the electrode and flow out from the side circulation holes.

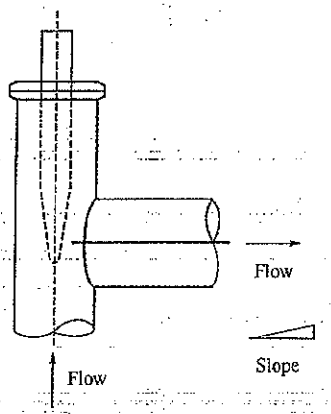


Fig 12.38 Recommended installation method of a conductivity sensor

In order to prevent measuring errors caused by polarization effects, the sensor should use alternating voltage during measurement. However, alternating current will generate capacitance effects through long cables and could result in measuring errors, this phenomenon is called capacitance difference. Some conductivity measuring systems integrate the measuring circuit into the head of sensor, and transmit the measured value to the transmitter by digital signal to avoid cables generating capacitance effects, so as to eliminate capacitance difference.

Conductivity is directly proportional to the concentration of ions, and the migration of ions is affected by temperature. The viscosity of water will be reduced at higher temperature and the mobility of all ions will be enhanced. Temperature has a direct impact on the degree of ionization, solute solubility, ion migration rate

and expansion of the solvent, affecting the conductivity of the solution. The conductivity of ions varies with temperature. For most ions, the conductivity will increase by 2% if the temperature rises by 1 ℃. However, the temperature coefficients of various ions are slightly different, the compositions of various solutions are different, and so the temperature coefficients of various solutions are also different. Even if the conductivity is the same, the species of ions contained in the solution may be different and the temperature coefficients of the conductivity would also be different. Moreover, the temperature coefficients of the conductivity can also be different in different ranges of temperature. Thus it can be seen that the temperature coefficients of the solution conductivity vary with the species of ions, solution temperature range and ion concentration.

According to the standard analytical method, the identification of conductivity is commonly referenced to a 25 ℃ sample temperature, although the sample may actually be at lower or more than 25 ℃. The measured conductivity should be corrected with a stipulated temperature correlation formula. Almost all conductivity measuring systems have the function of temperature compensation, and compensate the measured value of conductivity to the corresponding value at 25 ℃ through the compensation factor 2%/℃, ensuring conductivity values measured at any temperature have comparability.

For routine measurements the temperature should be adjusted to 25 ℃ for each determination. However, the process is tedious and many control sites cannot stabilize the solution temperature at the conductance cell to 25 ℃. Additionally, if the temperature deviates much from 25 ℃, the calculation result could exceed the allowable error when using a formula to conduct temperature correction. Moreover, different instrument manufacturers use different automatic temperature compensation algorithms. As a result, comparison deviations can be significant. Therefore, the USP does not allow temperature compensation so that the measured results of each instrument manufacturer are similar. For whether temperature compensation is required, it shall be conducted as per specific process and requirement. If conductivity comparison is required under different temperature, the temperature compensation is required.

Instead of compensating conductivity measurements to 25 ℃, which could lead to errors and differences among compensation algorithms and formulas, the USP requires measurement of uncompensated conductivity. USP also defines limits on uncompensated conductivity based on temperature. The limit value of water conductivity at different temperatures in USP is listed in Fig 12. 39.

The difficulty in determining the pharmaceutical water conductivity lies in the fact that at a higher water temperature, more ions are dissociated. The hydrogen ion (H^+) and hydroxide ion (OH^-) concentration in water will be increased with the raising of temperature. This dissociation effect combined with the viscosity effect caused by the water temperature rise can increase the compensation factor of the pharmaceutical water to (3-7)%/℃. As illustrated in Fig 12. 40, the curves gradually become steeper at low conductivity and low temperature. The impact of ions generated by the dissociation of water itself is very small when the ionizable

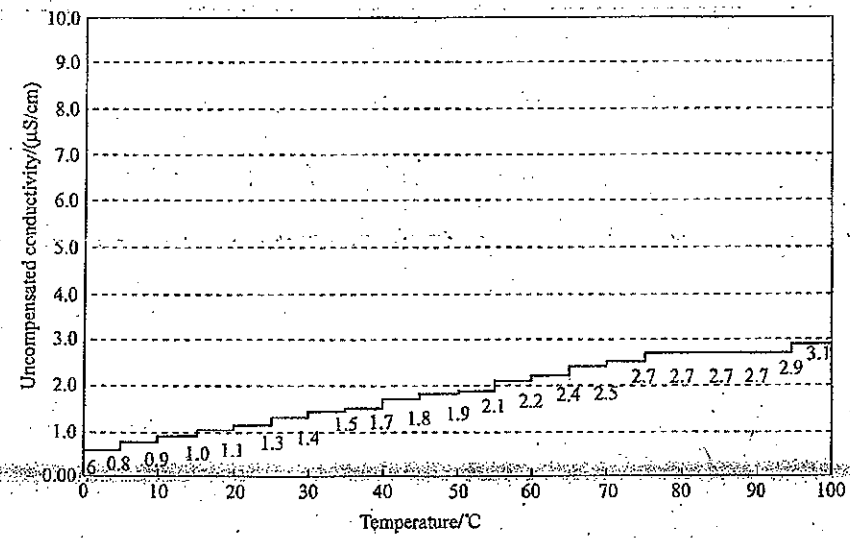


Fig 12. 39 Limitation graph of water conductivity at different temperature in USP

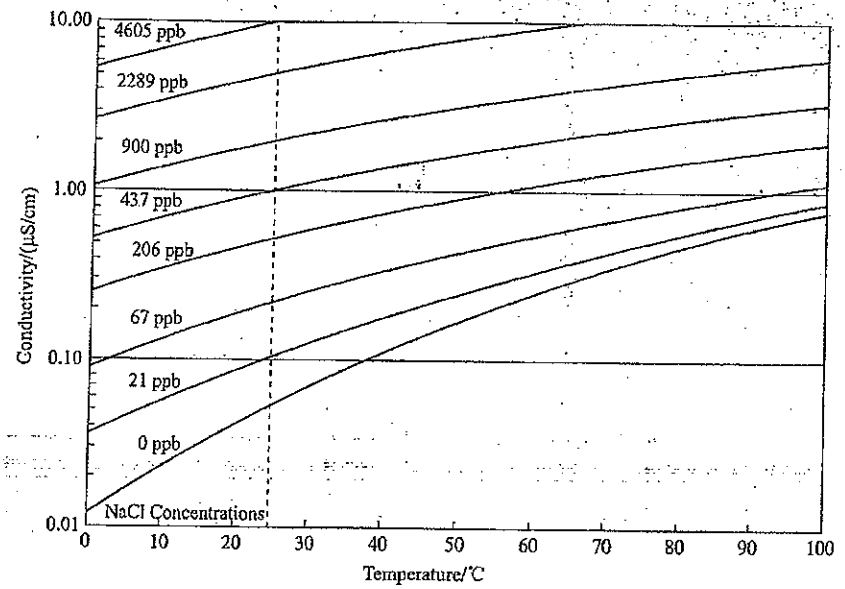


Fig 12.40 Temperature vs. conductivity of water with different purities

impurities in the water produce a conductivity above 5 μS/cm (i.e. compared with other ions, the concentration of H^+ and OH^- generated by water dissociation can be ignored). But the conductivity limits of pharmaceutical waters are right within the critical range.

Some conductivity sensors on the market provide advanced temperature compensation algorithms to conduct accurate temperature compensation for the conductivity of the pharmaceutical water within the critical range. This type of compensation method is usually used in upstream stages of the pharmaceutical water generation process, but not in the final quality control measuring points. This is because the temperature compensation algorithms of conductivity measuring systems in different instrument manufacturers are specific to different ion compositions, and affected by the change of temperature. Pharmacopoeia regulations require that the final water quality verification must be judged by the measured value without temperature compensation. Instead, the control limit value is determined by temperature. In order to comply with the requirements of major pharmacopoeia regulations internationally (e.g., *United States Pharmacopoeia*, *European Pharmacopoeia*, *Chinese Pharmacopoeia*, etc.), the temperature compensation function must be turned off when measuring the conductivity of final quality control points. Then the measured value must comply with regulatory requirements in the comparison table of conductivity and temperature limit values.

For measurement without temperature compensation, some online conductivity instruments store the comparison table of conductivity and temperature limit values from international major pharmacopoeia regulations in the system program. These instruments will alarm automatically when the measured value reaches the pharmacopoeia limit value based on the measured temperature, and the functions of conductivity sensors are compared as required by pharmacopoeia regulations to ensure its suitability and convenient operation. The same type of conductivity measuring system can conduct temperature compensated measurements at the measuring points before the final quality control points by program setting. This function is very effective to detect the water quality without temperature influence.

The online conductivity meter used for measurements of pharmaceutical water must be precise and subjected to periodic calibration. The pharmacopoeias of each country have specific stipulations on the calibration/validation of measuring instruments. The complete calibration of a conductivity measuring system includes temperature calibration, conductivity measuring circuit calibration and sensor conductance cell constant calibration. The temperature sensor can be calibrated by another calibrated temperature sensor existing in the water system. Validation and calibration of the conductivity measuring circuit can be conducted using precision resistances. Sensor conductance cell constant validation can be conducted by comparing with conductivity standard solutions or a calibrated measuring system.

According to the instrument design function and

use extent, the conductivity meter should be calibrated periodically, and conductance cell constant can be calibrated directly using conductivity standard solution, or conducted instrument comparison indirectly. The conductance cell constant must be known within ±2% of the stipulated value of the instrument. Each measuring range of the conductivity meter should be calibrated separately during instrument calibration. The minimum resolution of the instrument should be 0.1 μS/cm, the instrument accuracy should be within ±0.1 μS/cm, and the accuracy of the temperature measurement should be within ±2 ℃.

The conductivity standard solution calibration method should be used carefully. It should be verified that the conductivity of the standard solution is high enough, and it will not be affected by potential contamination such as absorption of carbon dioxide from the air or such impact can be ignored completely. Generally, it can be regarded as high enough when the conductivity standard solution exceeds 100 μS/cm, and it can be not contaminated or the contamination can be ignored completely. The linearity of the conductivity measuring system must include the full range from pharmaceutical water to the standard solution value.

12.2.6 TOC analyzer

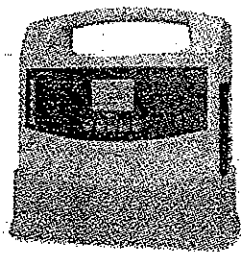
TOC measurement is a sensitive test used for detecting the contamination level of organic carbon in pharmaceutical waters. It is compulsory to use a correctly calibrated and validated analyzer and to control the TOC to less than 500 ppb. Organic compounds have the common characteristic of carbon existing in the molecule. Most methods of TOC analysis oxidize the organic matter in water to carbon dioxide and then measure the carbon dioxide concentration.

The differences in design principle of various TOC analyzers are generally reflected in two aspects: the organic matter oxidization method and the carbon dioxide detection method. There are now commercial TOC analyzers using at least 7 oxidation methods, including high temperature combustion oxidation, supercritical water oxidation, ultraviolet oxidation, ultraviolet and titanium dioxide oxidation, persulfate heating oxidation, ultraviolet and persulfate oxidation, ultraviolet and persulfate heating oxidation.

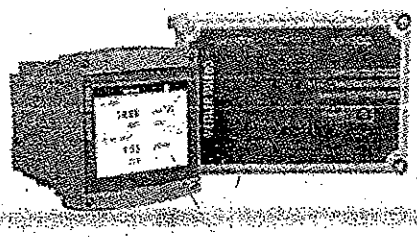
Ultraviolet oxidation is a common principle of online TOC analyzers used in the pharmaceutical industry. The organic matter in water is oxidized to carbon dioxide under the irradiation of an ultraviolet lamp. The advantages of this method are that no reagent is used, it offers a fast, truly continuous measurement, there is no catalyst poisoning and it requires only simple maintenance. The disadvantage is the inability to detect TOC at higher concentrations. Usually it is only applicable to water samples with TOC less than 2.5 mg/L, it gives incomplete oxidization of particulate organics, and requires periodic replacement of the UV lamp. Most online TOC measurement methods for pharmaceutical water are completed with the following procedures.

- Measure or remove inorganic carbon: measure the background conductivity value or remove it by means of acidification and degassing;
- Oxidize by use of ultraviolet irradiation, chemical substance and/or heating;
- Measure carbon dioxide by means of direct conductivity detection, non-dispersive infrared (NDIR) detection or selective membrane conductivity detection.

TOC analyzers are divided into offline portable types and online fixed types (Fig 12.41). Offline portable type TOC analyzers are generally used for rapid sampling in the laboratory, water system rapid certification and troubleshooting. They are easy to carry, detect rapidly, eliminate sampling error, etc. Online TOC analyzers are installed and connected permanently to the pipeline of a pharmaceutical water system. The major advantages are requiring no manual procedure, conducting continuous determinations, and providing continuous trend monitoring of the water system with



(a) Portable type



(b) Online fixed type

Fig 12.41 Online TOC analyzers

the capacity to respond to contamination immediately. Online measurements exclude any contamination errors from sample collection, handling and transportation. The online TOC method applied in many pharmaceutical water systems uses ultraviolet oxidation and conductivity detection. It is designed for waters with low conductivity. When the TOC sample line is directly connected to the sample pipe, the sample will not contact air, and will therefore not increase the total inorganic carbon (TIC) level. Although the background is usually required to be calibrated to some extent, the water sample with low conductivity is not required to remove TIC.

Online TOC analyzers use either batch processing or continuous measuring technology. With the continuous measuring technology, the TOC analyzer measures the conductivity (including inorganic carbon) of the sample water continuously. The sample then flows through the UV oxidization chamber continuously where the organic matter in the sample is decomposed to inorganic matter and then its conductivity is measured. The TOC concentration is calculated according to the increase of conductivity (Fig 12.42). The measuring technology uses continuous sample flow to give rapid continuous response with the measuring value refreshed every second.

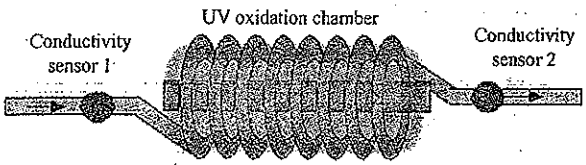


Fig 12.42 Continuous TOC measuring technology

Another method is by selective membrane conductivity detection. It is suitable for measuring samples that contain more ionic contaminations with higher conductivity levels (Fig 12.43). The technology of this method takes the carbon dioxide generated by oxidized organic matter and passes it through the carbon dioxide selective membrane from the sample water to a deionized water stream on the other side. The resulting bicarbonate and hydrogen ions raise the conductivity of the deionized water stream. The conductivity increase represents the concentration of carbon dioxide.

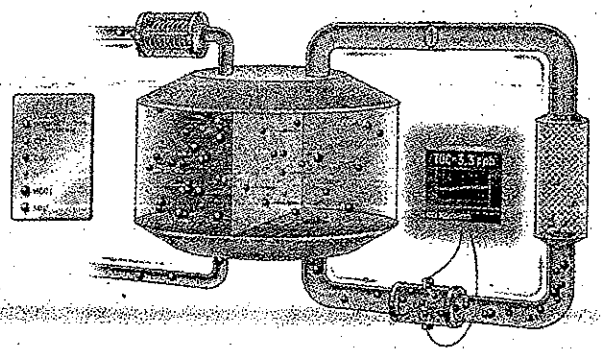


Fig 12.43 Selective membrane conductivity detection method

The selective membrane conductivity detection method is applicable to fixed online detection and offline portable detection. The selective membrane conductivity detection method separates the carbon dioxide and retains the high sensitivity of the conductivity method due to effective exclusion of other background ions. It is also an applicable detection method for purified water and water for injection.

The detection limits of different TOC measurement technologies and online analytical methods are different, but they must comply with the requirements of system suitability and TOC detection precision in the pharmacopoeias. For example, the ChP and USP require the minimum detection limit of 50 ppb. The analysis time of each technology can be 3-30 min, with different calibration requirements from every day to every year. The calibration can be completed by the user on site, by sending the analyzer back to the manufacturer, or by trained contract personnel on site. For example, during a TOC analyzer calibration, first calibrate the conductivity sensor by use of a separate calibrated conductivity system, and then perform a system calibration with standard TOC solutions. 250 ppb and 500 ppb sucrose solutions are usually used.

In order to ensure TOC analysis can oxidize different types of organic compounds sufficiently, all pharmacopoeias worldwide require performing a system suitability test (SST) for TOC analyzers. The test is to measure two organic material solutions, one easy to be oxidized and a second, more difficult to be oxidized, by the TOC analyzer. One is a sucrose solution, the other is a 1,4-benzoquinone solution, with both at 500 ppb concentration. If the measured values of the two solutions (subtracting out the measured value of blank water used to make them) are between 85% and 115% of each other, the system suitability test is passed.

It is very important to verify the TOC calibration and system suitability test with fresh solutions within their expiry dates. These solutions are unstable and easily decomposed in storage especially in exposed conditions and can even breed microorganisms. Usually,

the expiry date of test solutions is only several weeks.

12.2.7 pH Analyzer

The pH is used to measure the activity of acidic or alkaline substances in the solution, and can reflect the corrosive nature of a water solution indirectly. During the water treatment process, pH adjustment can prevent scaling or optimize the rejection rate of ions of reverse osmosis membranes. The pH affects the acid-base equilibrium in solutions, for example, at low pH values, carbon dioxide exists in the form of non-ionic gas or carbonic acid and penetrates reverse osmosis membranes. At high pH values, carbon dioxide exists in the form of carbonate or bicarbonate, which will be rejected by the membrane.

The pH measurement usually uses a glass combination electrode, including a thin pH sensitive glass film (measuring electrode), reference system and temperature sensor. The pH sensitive glass film generates a millivolt (mV) signal, proportional to the pH. The electrical contact of the reference electrode with the sample is through a porous junction or salt bridge, and completes the electrical circuit with the measuring electrode to conduct the mV signal representing the pH. The mV signal produced by the measuring electrode is affected by temperature in addition to pH, according to the Nernst equation. The pH analyzer can eliminate this effect by temperature compensation. Fig 12.44 shows a typical online pH sensor.

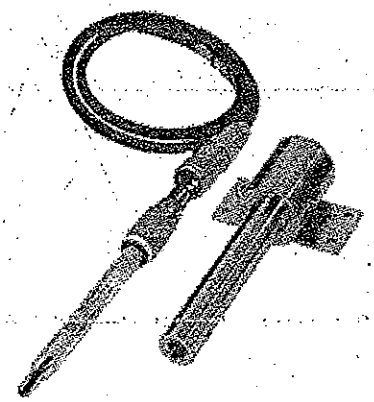


Fig 12.44 Online pH sensor

The electrode glass pH-sensitive film has high impedance so its measuring circuit, cable and insulation must be specially designed to prevent signal loss. Some pH sensors have the measuring circuit built into the electrode head to reduce pH signal loss to a minimum and avoid external disturbance. With this design, the sensor can transmit a stable pH signal to the transmitter over much further distances. This same sensor design includes built in memory that enables the sensor to store calibration data, so that the electrode can be calibrated in the laboratory if desired. Calibration data is stored in the chip inside the electrode, and then the electrode can be installed at the process site, simplifying maintenance. Moreover, this electrode can conduct self-diagnosis and help the user make preventive maintenance plans.

Although pH electrodes have good linear response to most acid-alkaline solutions, extremely alkaline solutions, e.g., pH>12, may cause a negative error, which is commonly known as alkaline error. Moreover, the aging of the glass film will be accelerated if it is in contact with strong alkaline solutions over a long term, especially at high temperature, and the response efficiency will be reduced rapidly. Therefore, conductivity is often more suitable for measuring alkaline solutions and monitoring the concentration of alkaline chemical substances.

A pH buffer solution should be a standard reference solution which can be traced to a national standard, for pH electrode calibration. The pH range of standard solutions used for calibration should include the pH measuring range. A one-point calibration is used to correct for a reference drift of the pH measuring system, and can be regarded as a zero point calibration. A two-point calibration is used to calibrate the reference drift/zero point and the slope response drift of the Nernst equation. The internal memory of online pH analyzers often stores the properties of various buffer solution groups to enable automatic identification of the buffer solution, as well as the effects of temperature on each buffer solution.

12.2.8 Ozone Analyzer

In pharmaceutical water systems designed with ozone sanitization, the ozone concentration should be measured downstream of the ozone generator to ensure the ozone concentration complies with sanitization requirements. In order to meet the requirement of "no added substances" in pharmaceutical water, an ultraviolet ozone destruction unit should be installed downstream of the contact tank and before the point of use distribution pipeline. Meanwhile, the ozone concentration must also be monitored at the outlet of the ultravi-

olet ozone destruction unit to verify that ozone is decomposed completely. The third ozone measuring point is at the end of the distribution water return pipe to confirm this pipe has reached the ozone concentration meeting sanitization requirements during the ozone sanitization period. The specific design principles can be found in 8. 4. 3.

The measuring unit of ozone concentration is parts per billion (ppb), which is equivalent to micrograms per liter (μg/L). The ozone concentration for sanitizing purified water is required to be 20-200 ppb, and higher concentrations must be used in long pipe loops to ensure the end of the water return pipe will reach sufficient ozone concentration during sanitization.

Ozone sensors belong to the membrane electrochemical polarography family of sensors. The measuring principle involves the ozone gas permeating the membrane selectively to isolate the sample from the chemical reaction chamber of its internal electrodes. Ozone enters into the reaction chamber by penetrating the membrane and generates a chemical reaction at the cathode. The size of the current signal is in direct proportion to the ozone concentration. The complete measuring system is composed of the internal electrolyte, the anode and the measuring circuit (Fig 12. 45). All ozone sensors have a built in temperature sensor to eliminate the effect of temperature change on ozone solubility and membrane diffusion efficiency by temperature compensation. It is recommended to install the polarographic ozone sensor in a flow cell with small volume for measurement and to control adequate flow to ensure the samples flow through the membrane rapidly.

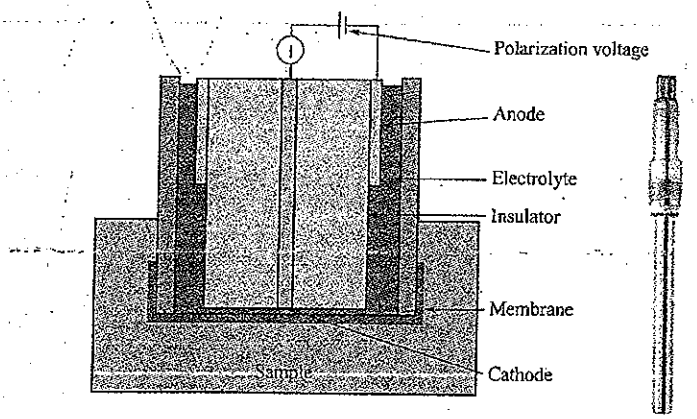


Fig 12. 45 The principle and outline drawing of an ozone sensor

An ultraviolet spectrometry method can also be used for determining ozone concentration. The measuring method uses ultraviolet light of 254 nm wavelength to measure ozone of high concentrations according to the law of Lambert-Beer. It should be noted that some substances in the solution may also absorb ultraviolet and cause interference with the measurement.

Ozone is very unstable; therefore, there are no ozone standard solutions. Generally, reference standard values can be provided for online polarographic ozone measurements using a colorimetric method. The water system should be kept at a stable ozone concentration during calibration and then samples should be rapidly taken to be measured with an offline colorimetric instrument; results are used to calibrate or validate the online ozone measurement. The zero point of ozone analyzers can be calibrated in air.

12. 2. 9 Online microorganism detector

The measuring unit of bacteria is the total bacteria count per unit volume. Pharmacopoeias stipulate that the microbial limit of purified water is100 CFU/ml; the microbial limit of water for injection is 10 CFU/100ml. Microbial contamination or bioburden estimates the concentration of colony forming microorganisms in water. At present, the routine measuring method is to take samples and then incubate them in a plate medium and count the resulting bacteria colonies (Fig 12. 46). This measuring method can estimate the number of growing microorganisms.

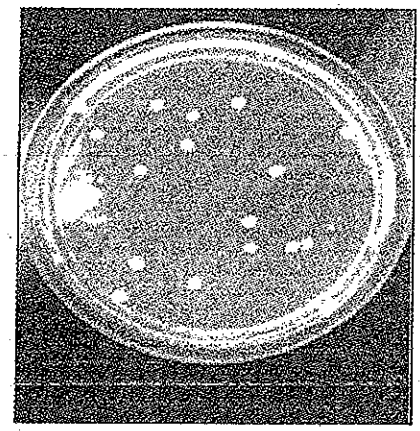


Fig 12. 46 Plate count method for bacteria detection

The traditional laboratory plate count method requires taking samples, incubating them in a culture dish and waiting for several days. The whole process has many variables, including sample preparation, type of medium, incubation time and temperature. For special samples, conditions can be adjusted to the optimal

state to accelerate detection speed. The estimate is made by manually counting and converting to total bacterial count in unit volume. This method requires a lot of manual work, the samples are easily contaminated during preparation and a very long time is needed for incubation and growth. Some instruments or equipment have the functions of automatic sampling and counting, but they still require a very long incubation time.

The purpose of the USP <1231> *Standard on Pharmaceutical Waters* is to ensure pharmaceutical water systems are monitored periodically to ensure they can produce qualified water continuously. The general information section requires monitoring continuously to record data in the process for inspection. The continuous production measurements and trend analysis data can also be the basis of system maintenance.

The FDA published the document "*Advancing Regulatory Science at FDA*" in 2011. It indicated that FDA supported the development of sensitive, rapid and high capacity methods to detect, identify and calculate microbial contamination and to validate the effectiveness of these methods in product sterility assessment. To accept the challenge of the above documents and the requirements of online microorganism measuring instruments in the pharmaceutical industry, seven leading pharmaceutical companies established a working team for online water bacteria analyzer (OWBA) development in 2013. The team aimed at providing development guidance for a new microorganism measuring system for instrument manufacturers so that the instruments meet the requirements of the industry and regulatory authorities.

The online microorganism detector uses the laser-induced fluorescence (LIF) spectrometry principle to measure the number of microorganisms and inert particles in the sample (Fig 12.47). LIF spectrometry is a measuring technology for microbial content which can meet the industry requirements. Microorganisms regulate their growth and proliferation speed by metabolites such as riboflavin and NADH. These metabolites will release a special fluorescence when exposed to light of specific wave length. LIF is a highly sensitive technology used to detect microorganisms based on this principle. An analyzer using LIF technology for measurements in the air has been in the market for many years. With further development of the technology, LIF technology can be used to measure the microbial content in water.

In practical work, the sample from the water system enters the measuring chamber of the analyzer through the connecting tube. A laser with wave length of 405 nm excites the microbial metabolites to produce fluorescence and a photomultiplier detects any emitted fluorescence. The number of particles in the water is determined by another sensor by means of Mie scattering and data from the two detectors are processed by advanced algorithms. Most inert materials (e.g. 304 or 316L stainless steel) will not emit fluorescence, but some particulate materials including some polymers will be taken for organisms in the system. By analyzing the emitted fluorescence and the scattered light, the rapid microbial detection system (RMS) algorithm built into the online microorganism detector can distinguish microbial and non-microbial particles accurately.

The touch screen of the detector can display the microbial concentration in microorganism counts [one microorganism count is equivalent to the number of colony forming units (CFU)] and inert particles. It can be set for alarming, linking and stipulating limit. The 7000 RMS microorganism detector can measure particles between 0.52 μm and 50 μm, and withstand

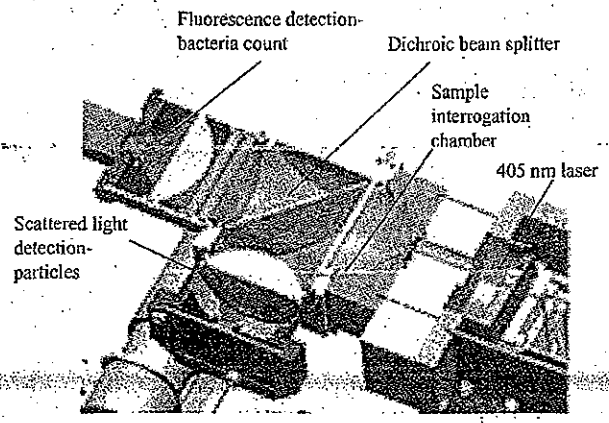


Fig 12.47 Laser-induced fluorescence (LIF) spectrometry principle

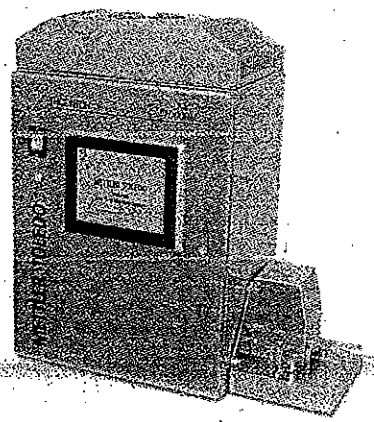


Fig 12.48 Online microorganism detector

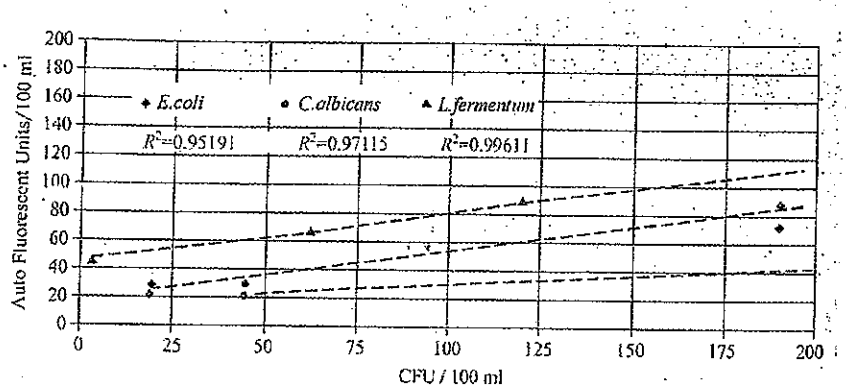


Fig 12.49 Comparison graph of plate count method and online detection

sample temperatures up to 90 ℃, which facilitates the online determination of microbial indicators of normal temperature purified water and high temperature water for injection. See (Fig 12.48).

For a continuous measurement analyzer, it is very important to calibrate periodically. To obtain accurate results, calibration can be accomplished using fluorescent and inert particle standard materials. The storage method and expiry date of standard substances must be strictly followed during operation. A continuous microorganism detector for microbial content has been researched and developed successfully and applied in the industrial field. The online unit can detect microbial concentration continuously and instantaneously, with no waiting. It reduces sampling labor, routine tests and materials effectively, lowering the cost for testing. In addition, the online microorganism detector can help the validation department of the pharmaceutical water system to ensure accurate and safe sterilization cycles, greatly reducing unnecessary "excessive" sanitization and sterilization and helping the enterprise with normal production, energy conservation and emissions reduction.

Process analytical technology (PAT) and quality by design (QbD) promote pharmaceutical enterprise acceptance of real-time monitoring of purified water and water for injection. This trend is supported by the use of instruments that enable biotechnology companies to reduce their dependence on microbial test by the laboratory plate method. The real-time microbial test method can find potential microorganisms rapidly and improve the quality of pharmaceutical waters. The advanced test method and rapid response allow pharmaceutical enterprises to monitor the status of water systems much better and make the manufacture of products more efficient to reach the market sooner. Rapid microbial test can detect any existing microorganism timely and effectively, and take corrective measures rapidly. Fig 12.49 is a comparison graph of the plate count method and online automatic fluorescence detection method test results (The data is from the 7000 RMS online microorganism detector of Mettler Toledo).

The use of the online microorganism detectors helps to improve the operation of pharmaceutical water systems, reduce cost and guarantee water quality. Online microorganism detectors can realize better process control and product safety by real-time monitoring, while achieving "process analytical technology" promoted by the automated control field. It is projected that online microorganism detection will gain higher visibility and will be applied by more and more pharmaceutical enterprises, similar to the history of online conductivity and online TOC detectors. Meanwhile, the availability of this technology will enable further improvement and development of relevant laws and regulations.

12.3 Automatic Control of Unit Operation

A typical pharmaceutical water process flow is illustrated in Fig 12.50. The equipment selected by different pharmaceutical enterprises is different due to different pharmaceutical production processes. The equipment installation area, purified water machine, water distiller and pure steam generator are usually installed in a non-clean area, except for some water points of use which may be installed in the clean area.

12.3.1 Raw Water Device

A raw water device is usually composed of a raw water tank, raw water inlet valve and raw water pump (Fig 12.51). It is generally used to guarantee the raw water supply for ultrafiltration, pretreatment or purified water machine. The basic operations of the automatic

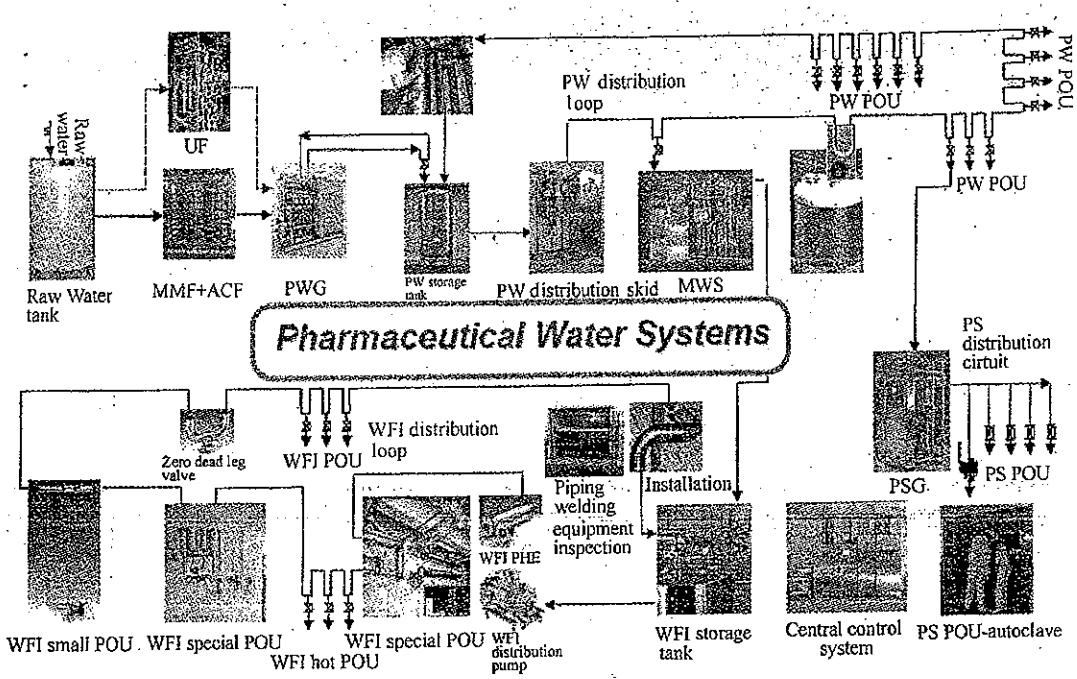


Fig 12.50 Pharmaceutical water process flow diagram

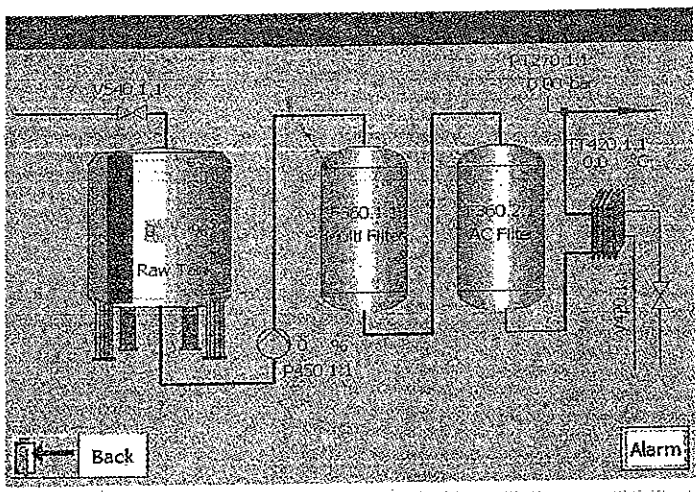


Fig 12.51 Operation interface of the raw water device

control system include the interlocking of the raw water tank liquid level and raw water inlet valve to ensure the liquid level of the raw water tank meets operation requirements (Table 12.7).

Table 12.7 List of main control parameter points of raw water device

No.	Description	DI	DO	AI	AO	Remarks
1	Raw water pump frequency converter	2	1	1	1	Provide stable pressure for water supply
2	Liquid level of raw water tank	1		1		Water replenishing control and low liquid level protection pump. Raw water tank is usually not contained, static pressure transmitter can be adopted
3	Replenishing valve of raw water tank		1			Replenish water according to the liquid level of raw water tank, because the pressure of raw water is higher, usually, throttle valve + pneumatic valve can be selected to reduce the impact on pipeline

12.3.2 Pretreatment Device

A pretreatment device is usually composed of a multi-media filter, active carbon filter (hot water sanitation), softener (some manufacturers adopt antisludging agents) (Fig 12.52). The pretreatment of raw water is done before it enters into the membrane purification system using certain physical or chemical methods on the basis of analysis of the water quality of the municipal water supply or underground water supply used by the pharmaceutical enterprise, to reduce the turbidity, hardness and silt density index (SDI) of raw water, as well as the content of chemical compounds such as chlorides in raw water, regulate the pH range and other basic indexes of water quality in raw water, so as to meet the requirements of quality of water supplied to the membrane system, reduce the pressure of the RO membrane purification system, improve the work efficiency of the membrane system and prolong the service life of the membrane system (Table 12.8).

12.3.3 Purified Water Machine

A purified water machine is usually composed of a security filter, heat exchanger, RO membrane, EDI, TOC detector, etc. It is generally used to generate purified water complying with requirements (Fig 12.53). The basic operations of the automatic control system include inlet water/outlet water/return water conductivity, temperature control, reverse osmosis, EDI, liquid level, flow rate, CIP/SIP state, etc. (Table 12.9).

Table 12.8 List of main control parameter points of pretreatment device

No.	Description	DI	DO	AI	AO	Remarks
1	Multi-media filter valve		5			It is mostly pneumatic valve(the number is determined as per actual condition).
2	Active carbon filter valve		5			It is mostly pneumatic valve(the number is determined as per actual condition).
3	Softener valve		10			It is mostly pneumatic valve(the number is determined as per actual condition).
4	Sodium hypochlorite dosing pump	1	1			
5	Softener salt tank liquid level	2				Used for water replenishing for salt tank
6	Softener inlet water pressure			1		
7	Softener outlet water flow			1		Control the regeneration backflushing frequency of softener
8	NaCl dosing pump		1			Used for resin regeneration

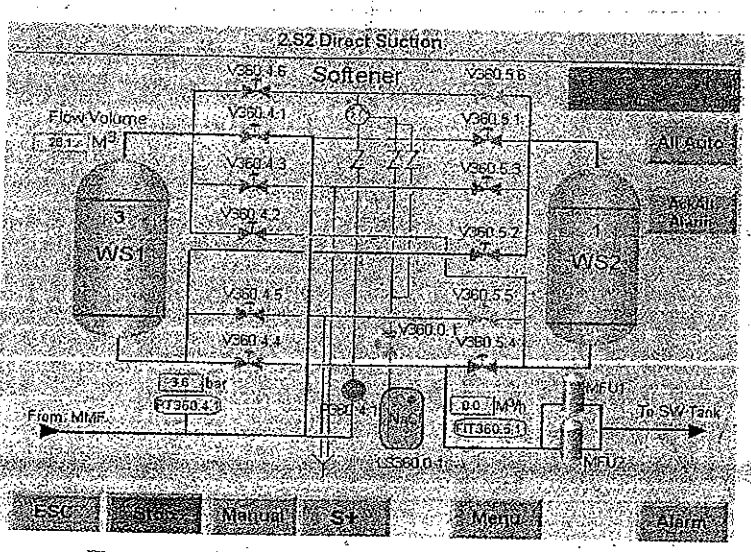


Fig 12.52 Operation interface of a pretreatment device

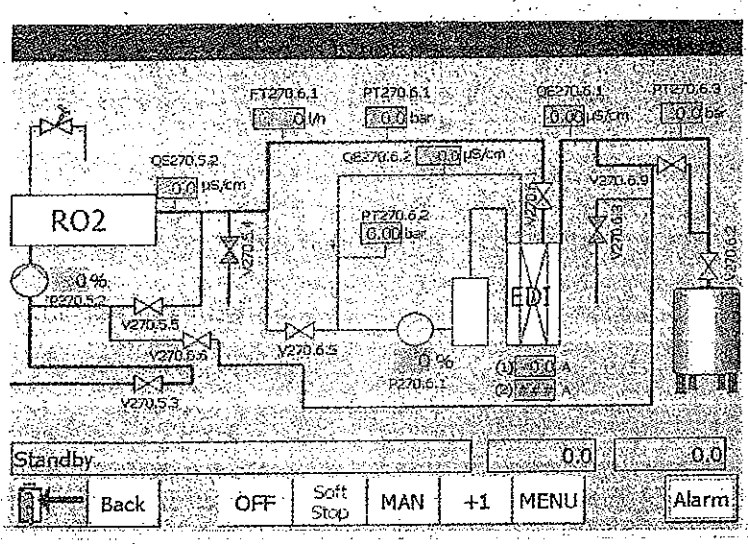


Fig 12.53 Operation interface of a purified water machine

Table 12.9 List of main control parameter points of a purified water machine

No.	Description	DI	DO	AI	AO	Remarks
1	Pressure before RO high pressure pump			1		It cannot be negative pressure during equipment operation to protect RO high pressure pump
2	ORP oxidation reduction potential			1		It cannot be higher than 400 mV
3	pH sensor			1		Control the adding amount of alkali
4	RO high pressure pump frequency converter	2	1	1	1	Reduce water hammer effect and prolong the service life of RO
5	Pressure before RO membrane			1		Used for protecting RO membrane
6	Flowmeter before high pressure pump			1		Monitor inlet water flow rate
7	Outlet water conductivity behind RO membrane			1		Monitor outlet water conductivity
8	SIP steam heating valve				1	Control SIP circulating temperature
9	RO outlet water temperature			1		Used for equipment SIP monitoring
10	EDI inlet water pressure			1		Used for protecting EDI
11	EDI power supply	1	1	2		Monitor EDI voltage and current
12	EDI outlet water pressure			1		Monitor EDI outlet water pressure
13	EDI outlet water conductivity			1		Monitor the conductivity of outlet water
14	EDI outlet water temperature					Used for monitoring equipment SIP
15	EDI produced water flow					
16	NaOH dosing pump	1	1	1	1	
17	Sanitation circulating pump frequency conversion	2	1	1	1	
18	Pneumatic diaphragm		10			

12.3.4 Purified Water Storage and Distribution System

A purified water storage tank is generally composed of a tank and relevant temperature sensor, liquid level sensor, inlet valve, vent filter and outlet valve (Fig 12.54). It is generally used for storing purified water complying with pharmacopoeia requirements. The basic operations of the automatic control system include circulation between the purified water machine and storage tank, circulation between the storage tank and each point of use, control of various

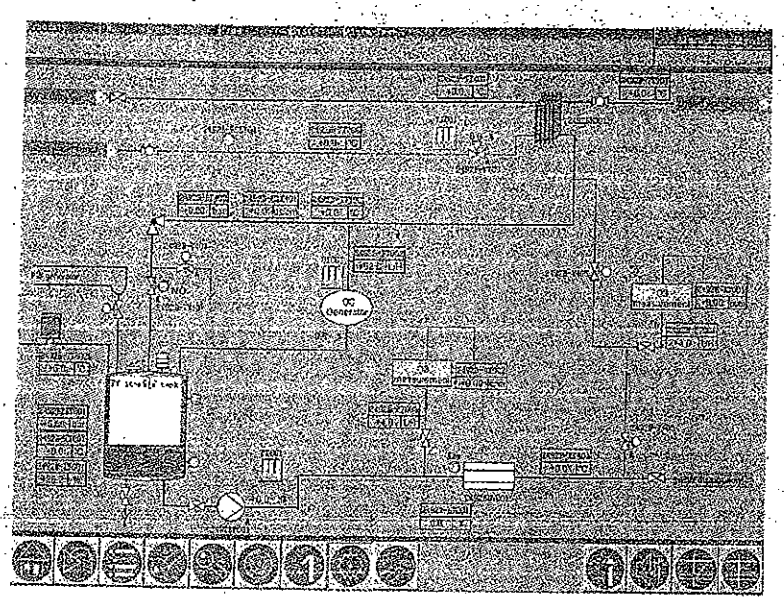


Fig 12.54 Operation interface of a purified water storage and distribution system

instruments and valves in the storage tank, etc. (Table 12.10).

Purified water is transferred from the purified water storage tank to each point of use through sanitary pumps. The basic operations of the automatic control system include the control of the frequency converter of the pump, flow rate of purified water in the pipeline, start stop of each valve in the circulating state. Sanitation is usually conducted by hot water or ozone with little difference in control methods.

Table 12.10 List of main control parameter points of purified water storage and distribution system

No.	Description	DI	DO	AI	AO	Remarks
1	Liquid level of purified water storage tank	1		1		Dual protection of differential pressure liquid level meter and liquid level switch
2	Temperature of purified water storage tank			1		Used for normal operation and SIP
3	Inlet valve of purified water storage tank		1			Used for water replenishing of purified water storage tank
4	Return water conductivity of purified water			1		
5	Return water flow of purified water			1		
6	Return water TOC of purified water			1		
7	Return water pressure of purified water			1		
8	Purified water pump frequency converting control	2	1	1	1	Control return water flow of purified water and pressure of pump outlet
9	Steam regulating valve of heat exchanger				1	Control SIP temperature
10	Return water temperature of purified water circulation			1		Used for operation monitoring and SIP
11	UV lamp signal	2	1	1		Alarm, state and start
12	Ozone content monitoring			1		Used during sanitation
13	Ozone generator control	3	1	1	1	Used during sanitation

12.3.5 Water Distiller

At present, the distillation method is the main method for generating water for injection. The steps required for automatic control in the water distiller (Fig 12.55) are as follows: water filling, preheating, heating, sanitation, distillation, discharging, precooling, cooling, etc. The main control parameters

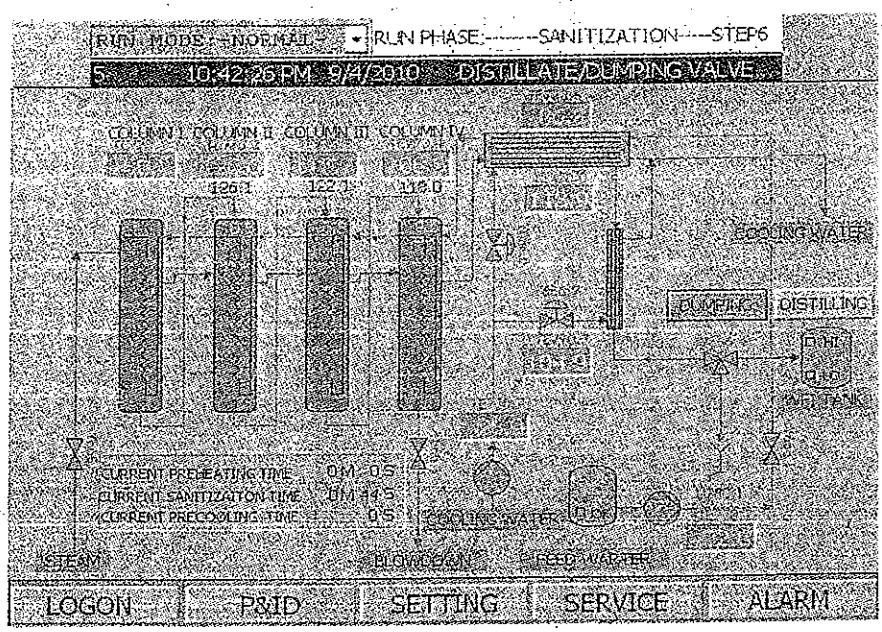


Fig 12.55 Operation interface of a water distiller

are the equipment operation state and phase, inlet and outlet water temperature, inlet and outlet water pressure, inlet and outlet water conductivity, each water pump and valve state, etc. (Table 12.11).

12.3.6 Water for Injection Storage and Distribution System

A water for injection storage tank is generally composed of a tank and relevant temperature sensor, liquid level sensor, inlet valve, vent filter and outlet valve (Fig 12.56). It is generally used for storing water for injection complying with pharmacopoeia requirements. The basic operations of automatic control system include circulation between water the distiller and storage tank, circulation between the storage tank and each point of use, control of various instruments and valves in the storage tank, etc. (Table 12.12).

Water for injection is transferred from the water for injection storage tank to each point of use through sanitary pumps. The basic operations of the automatic control system include the control of the frequency converter of the pump, flow rate of water for injection in the pipeline, start stop of each valve in the circulating state. Sanitation is usually conducted by superheated water or pure steam with little difference in control methods.

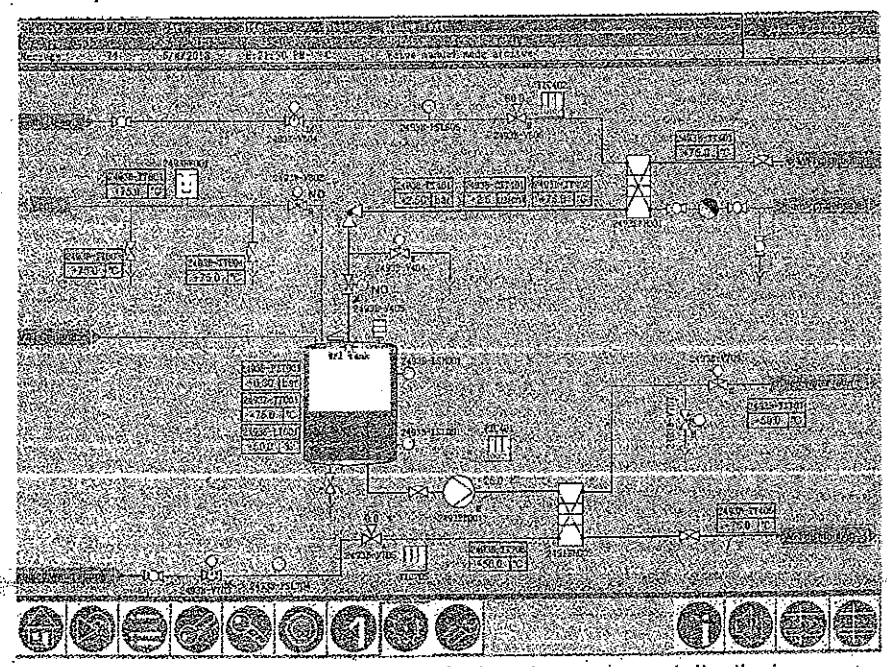


Fig 12.56 Operation interface of a water for injection storage and distribution system

Table 12.11 List of main control parameter points of a water distiller

No.	Description	DI	DO	AI	AO	Remarks
1	Inlet water conductivity of purified water			1		
2	Outlet water temperature of distilled water			1		
3	Outlet water conductivity of distilled water			1		
4	Outlet temperature of first efficiency			1		
5	Outlet temperature of secondary efficiency			1		
6	Outlet temperature of third efficiency			1		
7	Outlet temperature of fourth efficiency			1		
8	Pneumatic diaphragm valve		X			
9	Frequency conversion of water-supply pump	2	1			
10	Cold water regulating valve of heat exchanger				1	Control WFI outlet water temperature
11	Steam regulating valve				1	Control WFI output

Table 12.12 List of main control parameter points of a water for injection storage and distribution system

No.	Description	DI	DO	AI	AO	Remarks
1	Liquid level of water for injection storage tank	1		1		Dual protection of differential pressure liquid level meter and liquid level switch
2	Temperature of water for injection storage tank			1		Used for normal operation and SIP
3	Inlet valve of water for injection storage tank		1			Used for water replenishing of water for injection storage tank
4	Return water conductivity of water for injection			1		
5	Return water flow of water for injection			1		
6	Return water TOC of water for injection			1		
7	Return water pressure of water for injection			1		
8	Water for injection pump frequency converting control	2	1	1	1	Control return water flow of water for injection and pressure of pump outlet
9	Steam regulating valve of heat exchanger				1	Control SIP temperature
10	Return water temperature of water for injection circulation			1		Used for operation monitoring and SIP

12.3.7 Water for Injection Cold Point of Use

The main control parameters of a water for injection cold point of use include temperature control, valve state monitoring, etc. Its main control points are chilled water at the end of the heat exchanger or linkage of the steam regulating valve and temperature sensor (Fig 12.57, Table 12.13).

Table 12.13 List of main control parameter points of a water for injection cold point of use

No.	Description	DI	DO	AI	AO	Remarks
1	Steam valve of heat exchanger				1	Control temperature
2	Pneumatic diaphragm valve		X			Control the connection of water point of use, the number is determined by actual conditions

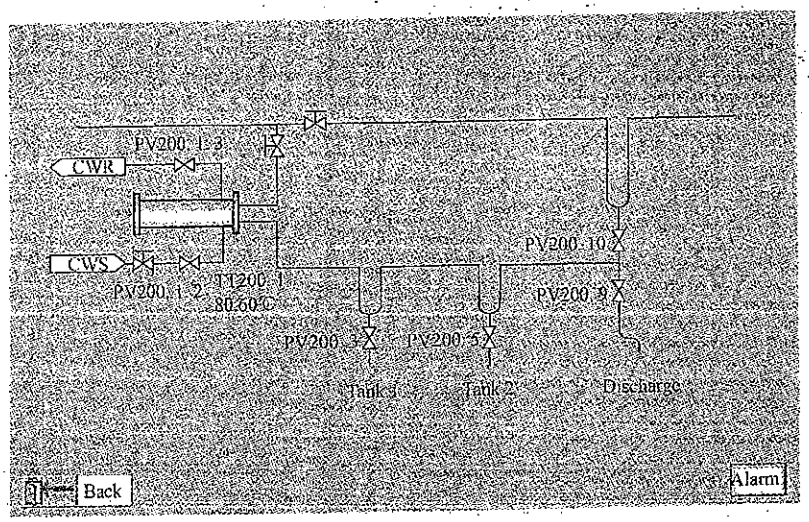


Fig 12.57 Operation interface of a water for injection cold point of use

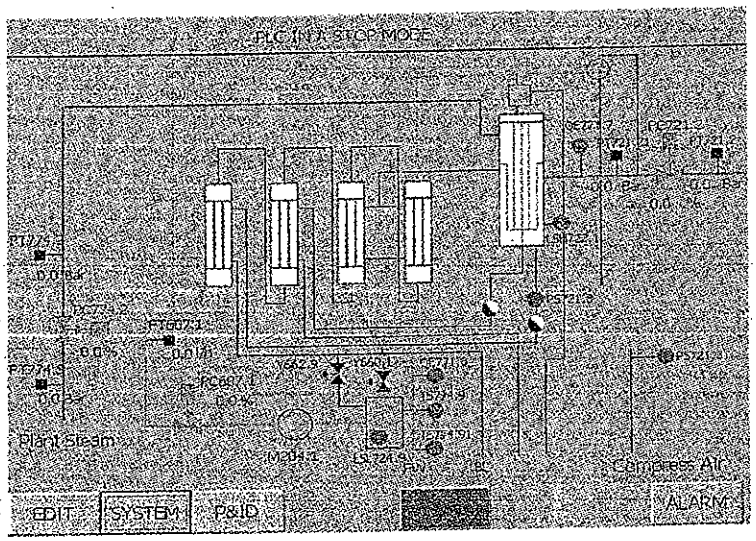


Fig 12.58 Operation interface of a pure steam generator

12.3.8 Pure Steam Generator

The main control parameters of a pure steam generator (Fig 12.58) include the equipment operation state and phase, inlet water temperature, inlet water conductivity, pure steam temperature, pure steam pressure, pure steam conductivity, circulating water pump state and alarm information, etc. (Table 12.14).

Table 12.14 List of main control parameter points of a pure steam generator

No.	Description	DI	DO	AI	AO	Remarks
1	Inlet water conductivity of purified water			1		
2	Pressure of pure steam			1		
3	Conductivity of pure steam			1		
4	Important alarm information	X				
5	Steam regulating valve				1	Control the output of pure steam
6	Recorder					With paper or paperless
7	Pneumatic diaphragm valve		X			
8	Water supply pump	2	1			
9	Pressure of compressed air			1		

12.4 Good Automated Manufacturing Practice

The Good Automated Manufacturing Practice

(GAMP) is computerized system theory and practice guide generally edited by ISPE. The first edition of the GAMP was proposed by ISPE in 1995, and the fifth edition was published in 2008, that is a risk-based approach to compliant GxP computerized systems. The GAMP is the main reference for computerized system validation methods in the international pharmaceutical industry at present, at the same time, it is the most important compliance guide for pharmaceutical automation.

At present, the latest version of the Good Automated Manufacturing Practice is GAMP5; its purpose is to provide a set of effective methods based on current industry practice to make computerized systems achieve their intended purpose and meet the requirements of current regulations. The GAMP5 is not an official method or standard, but provides a set of practical knowledge, methods and tools for practitioners. The life cycle and risk management methods of computerized systems provided by the GAMP5 can achieve the aim of making the control systems of pharmaceutical water systems comply with regulatory requirements and achieve their intended performance goals.

The life cycle method requires defining and implementing activities in a systematic way. It includes four main phases: concept, project, operation and retirement. Fig 12.59 shows the schematic diagram of a project life cycle.

a. Concept. Activities in this phase will depend on company approaches to initiate and justify project commencement. Gaining management commitment to provide appropriate resources is an important pre-project activity.

b. Project. Project implementation phases and supporting processes make up the life cycle of a computerized system (Fig 12.60). These project stages are also applicable to the phase change activities during product implementation and subsequent operation phases. The planning phase of a computerized system should include all necessary validation activities, responsibilities, procedures and practices.

Three documents should be compiled in the specification stage of a computerized system. They are the functional specification (FS), hardware design specification (HDS) and software design specification (SDS) respectively. The FS is an important document, which defines how to meet the function requirements of the customer stipulated in the user requirements specification (URS). This document is compiled according to the URS, it is the responsibility of supplier, while the URS is the responsibility of the customer who should maintain and control the URS. The FS provides the basis for main function tests for the system FAT and SAT, it should be approved by the user, and usually revised during the project life cycle. The HDS stipulates the hardware design conditions of the control system, it provides the main basis for the FAT hardware test, which should be approved and implemented by the user, and usually revised during the project life cycle. The SDS stipulates how to design and configure software to meet the function requirements of the water system. This document is the responsibility of the supplier, the items in the SDS will be tested during the FAT.

Computerized system configuration should be conducted as per controlled and repeatable process. Software programming should be conducted as per stipulated standards, code review is handled as part of risk management, and configuration management is the

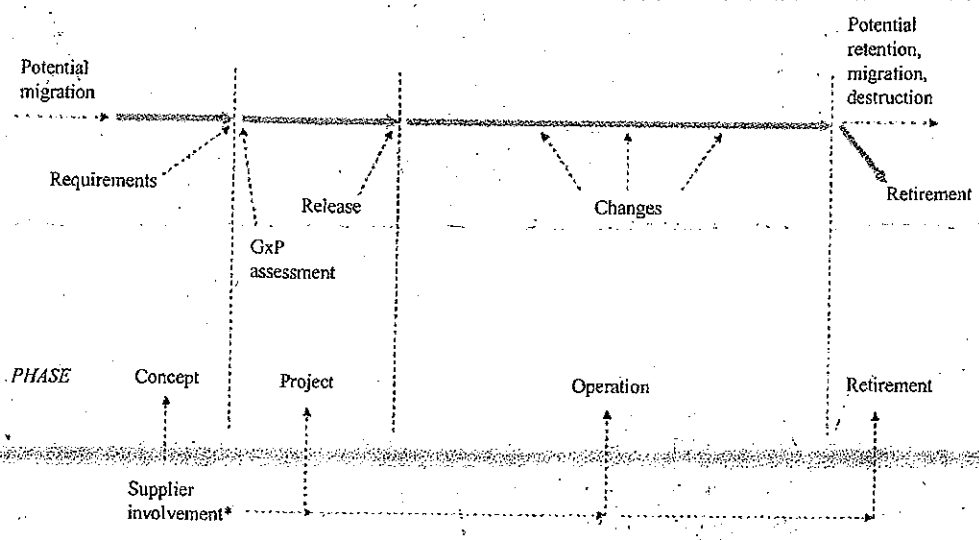


Fig 12.59 Schematic diagram of project life cycle

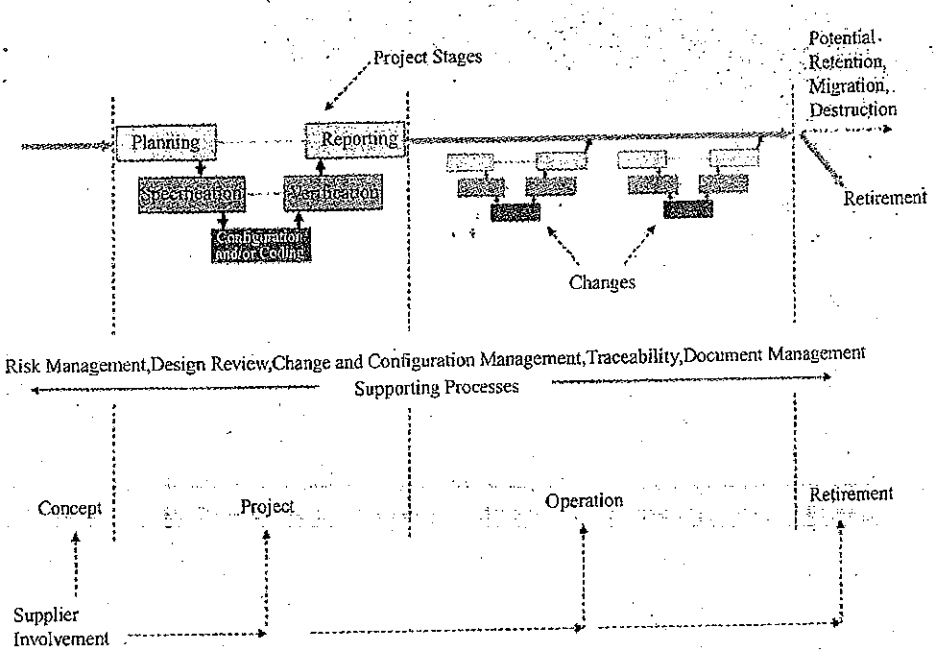


Fig 12.60 Project implementation phases and supporting processes

inherent important characteristic of the essence in controlled configuration and programming. All controllable items subject to review, approve or test should be under appropriate configuration management, and each controllable item should follow corresponding change management. During the system execution process, project change should be under control and documented. All components and its change of computerized system of the system should be under control. The accurate configuration of system hardware and software should be documented during the whole life cycle of the system. The level of formality of system configuration management in operation stage should be higher than that in the early development stage, but it should be same in principle. Configuration management should be applied in the system design stage as early as possible, the higher degree of formality of starting configuration management, the easier to form documents for the baseline configuration used for operation configuration management. Configuration management includes configuration identification, configuration control, configuration state record and configuration assessment.

The computerized system validation is used to verify whether the system meets the requirements of the regulatory documents. The validation of the system can include reviews and tests of multiple phases, e.g., code review, internal test, FAT, SAT, etc. The test strategy should confirm appropriate methods to test a specific system based on the following aspects: the result of the risk assessment, understanding of the system complexity and novelty and the result of the supplier assessment.

The system should be inspected and accepted in a system operating environment according to a controlled and documented process, and it should be released for operation. The acceptance and release of the system used in GxP regulated activities should be signed by the process owner, system owner and representative of the quality department.

The supporting process generally includes risk management, change and configuration management, design review, traceability and document management.

- Risk management. The risk management is based on a framework of assessment, control, communication and review consistent with the ICH Q9. The risk is specific to patient safety, product quality and data integrity. Risk assessment is the responsibility of the user, and supported by the supplier. The risk assessment is a continuous process, it should be performed in different phases of the system life cycle. Risk management has two aspects: the first one is to identify risk, propose control measures, and eliminate or reduce it to an acceptable level. The second one is to provide a type of flexible method for the regulated company to select appropriate life cycle activities specific to a certain system. Fig 12.61 shows a computerized system risk management process.
- Change and configuration management With the development of the system project, the degree of for-

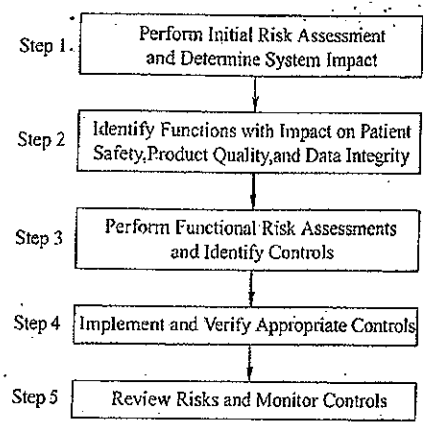


Fig 12.61 Risk management process

mality of change management is increased accordingly. This type of gradual change is reflected from informal project team meetings and discussions, to formally recorded project meetings and formal change management requests. The system project should define the method of implementing change management in the stage of project planning.

Design review. At suitable phases during the life cycle, planned and systematic design reviews of specifications, design, and development should be performed. Design reviews should evaluate the deliverables to ensure they meet the regulatory requirements. Corrective actions should be defined and implemented. The rigor of the design review process and the extent of documentation should be based on the risk, complexity, and novelty of the system.

• Traceability. A system defect should be identified and corrected at the early phase of system life cycle. Traceability helps to ensure the computerized system complies with the intended use, and reduce the cost of the whole project by identifying defects and solving problems at an early phase. Traceability can be used to ensure the user requirements are satisfied, and can be traced back to relevant function and design parts in the specification documents, ensuring the user requirements can be traced back to relevant verification activities. Traceability can promote assessment and change management in addition to demonstrating the contents and ranges of design and validation. Traceability should be focused on aspects critical to patient safety, product quality, and data integrity.

• Document management. Document standards should be agreed on by the enterprise and supplier at the stage of project planning to ensure the expectations of both parties are consistent. The documents should be evaluated on the basis applicability, accuracy and integrity. Documents are flexible in the aspect of acceptable format, structure and archiving. The document management includes preparation, review, approval, release, change, withdrawal and retention.

c. Operation. Once the system has been accepted and released for use, there is a need to maintain compliance and capability for intended use throughout its operational stage. This is achieved by the use of up to date documented procedures and training that cover use, maintenance, and management. As a part of preparing the final acceptance and formal transfer of the system to the user, the regulated company should ensure appropriate operation processes, procedures and plans have been executed and supported by relevant training. The supplier should participate during supporting and maintenance activities, meanwhile, the maintaining of the system compliance should cover many correlative activities.

d. Retirement. The system retirement includes the system withdrawal, system decommissioning, system disposal and migration of required data. The system retirement process should be documented in the system retirement plan.

Chapter 13

Validation

In *the Good Manufacturing Practice* (2010 *Revision*) validation is defined as a series of activities used to demonstrate that any operation procedures (or methods), production process, or system can reach its ranged quality. And qualification is described as a series of activities to prove that a facility or equipment can operate in a right way and serve its purpose. The US Guideline on *General Principles of Process Validation* (May, 1987) states that "*... establishing documented evidences which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes*". The ICH specifies qualification as: "*to verify and document that equipment or supporting systems are installed properly and used correctly and the expected results can be obtained. Qualification is a part of validation, but some individual qualification steps are not covered in process validation*". With the development of the modern pharmaceutical industry we can see that validation technologies have become core measures for supporting operations of pharmaceutical quality system (PQS). Validation technologies have penetrated into entire process and all details from design, research, development, trials, and large scale production of product.

Validation comprises validation management requirements, validation master plans (VMP), validation protocol and validation report. It is a series of repeated verification activities consisting of the testing of parameters, and a comparison work to see conformity level and practical outcome how far away from the expected targets. Compared with specified and acceptable criteria validation results would be audited and confirmed.

13.1 Basic Concepts

Validation is a process of establishing documented evidence to prove that aspecific process can consistently produce products meeting its specifications pre-defined by customer. In order to execute validation activities, a complete validation plan (VP) must be designed with effective testing methods and basing on life cycle of validation. A process that is completed through a series of studies is called a life cycle. Validation life cycle starts from making up user requirements, and goes through design, construction, installation qualification, operation qualification and performance qualification in order to verify system meet its prefixed aims. V-model is a commonly used model for validation life cycle (Fig 13.1).

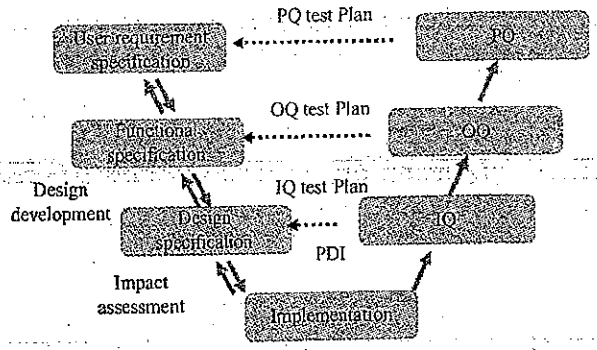


Fig 13.1 V-model of validation life cycle

13.1.1 Validation Plan

A validation master plan (VMP) is a safeguard verification file established for describing entire project and gathering all perspectives and methods of manufacturer. It is a high level document to ensure a sufficiency of validation. VMP provides t work procedure information and explains execution schedule of all alignment, including related responsibilities and statistical approach.

In VMP all required stuffing, equipment and other special requirements on completion of all validation activities must be assessed, including schedule for entire

project and detailed plans for sub-projects. The schedule can be included in validation matrix or prepared individually. Validation schedule needs to be periodically updated, and a Gantt chart generated by computer software is recommended. Once equipment list and system impact assessment completed, a more detailed schedule should be developed. And the sequence of system tests, the system dependencies and their supporting facilities should be determined. The schedule for qualification, overall construction, commissioning and startup activities should be leveraged when determining test sequences for a newly built or a renovated facility. The sequence must be determined based on assessment of each equipment, control process or system with the aim of minimizing any repeated activities and ensure that all the Good Engineering Practice activities and the related documentation required in order to support the qualification activities have been included in the executed procedures.

When preparing schedule, validation engineers need to consider milestones based on the information collected during early phase of VMP. When preparing this document, the attention should be paid to the validation prerequisites for each of systems. For example, the performance qualification (PQ) of WFI system and that of t pure steam system can only be started after the PQ for PW system has been completed, the operation qualification (OQ) of such pure steam using equipment as an autoclave can only start after the PQ for pure steam system has been completed, and the SIP process validation can only begin after the PQ for pure steam system has been finished. The preparation of validation plan is closed linked with validation equipment and execution engineers. It is necessary to have a full understanding and knowing about validation equipment and numbers of validation participants. A validation engineer's workload cannot be too long per day.

During the entire process starting from design to the operation of a pharmaceutical water system, project control is vital. The documents and records generated during the project execution process are going to be used as the bases for validation activities.

- Roles and responsibilities of the project team including participants from quality department and the various other departments.
- Engineering, change control management and deviation records.
- Schedule and cost control.
- Documentation, review and approval records.

13.1.2 User Requirement Specifications

The user requirement specifications (URS) describes the expected requirements for the use of equipment, facility and system proposed by the manufacturer based on its purpose, environment and uses. ISPE Baseline Guide Volume 3: *Sterile Manufacturing Facilities* specifies that the URS is generally the first of the series of specifications. It provides a high level description of the expected project scope from the customer emphasizing the product parameters and the process performance parameters.

13.1.3 Design Phase

Functional specifications (FS) describes how the requirements and targets described in URS are going to be achieved. It clearly specifies the expected system realization method. The FS is usually prepared by supplier, but it needs to be audited and approved by system user. FS elaborates equipment functions with meeting the requirements specified in URS. It is mainly used to describe all functions of equipment and can help user and system supplier to understand equipment functions.

Design specification (DS) is usually prepared by supplier. Supplier has the ownership of this document, and it is deemed as confidential. However, it also needs to be reviewed and approved by user. DS needs to describe accurately and in sufficient detail how the specific FS and URS requirements are going to be met. Through DS, user can know how an equipment is to be correctly installed, tested and maintained.

This document is composed of the standard documents from the supplier (such as User Manual) and is usually combined with the design qualification (DQ). For some simple equipment or a piece of equipment with a known detailed design, the FS and the DS can be combined into one document, the functional design specification (FDS).

The system impact assessment (SIA) is determines the scope of commissioning and validation. This process is used to determine which systems are to be validated in addition to commissioning following GEP and which systems only need to be commissioned following GEP. The SIA can be performed for each equipment/system to determine whether it is a direct

impact system, an indirect impact system or a non-impact system.

The component criticality assessment (CCA) can be performed based on design documents to determine which components of a system need to be qualified in addition to commissioning following GEP and which components of a system only need to be commissioned following GEP. CCA needs to be performed for direct impact systems to determine whether a component is critical or non-critical.

The risk assessment (RA) is a method for assessing and describing the critical areas of a system, equipment or process that form the bases for the preparation of the validation protocols. After critical components and functions are identified through assessment, a risk assessment is going to be performed on such critical components and functions and appropriate control methods are going to be determined. The failure mode and effect assessment (FMEA) or other risk assessment tools can be used to identify the effects of the possible failures in the critical components and functions.

The design qualification (DQ) provides evidences verifying that a facility, a supporting system, a utility system, a piece of equipment or procedure is designed following the GMP requirements. The first qualification step for a new facility or equipment is DQ. DQ is required in EU GMP, PIC/S and ICH. In the *Chinese GMP 2010*, DQ is specified and stressed and it is identified as the starting point of all the qualification activities. DQ is to provide documented evidences verifying that the proposed design of a facility, system or equipment is suitable for its intended use and can meet the GMP requirements. It uses scientific theories and actual evidences to prove the design results can meet the URS requirements. A complete DQ is the basis for ensuring the user requirements can be met and the equipment works normally. The approved DQ report is the basis for the subsequent qualification activities (such as IQ, OQ and PQ). The DQ is mainly used to verify the suitability of a selected equipment/system, technical specifications, technical parameters and drawings. It is performed through the verification of the various requirements specified in the URS for the equipment/system. It is also verified to see whether the equipment/system can meet the requirements of the product production process, the calibration requirements, the maintenance requirements and the cleaning requirements. And DQ is also used to provide useful information and necessary recommendations to facilitate manufacturing, installation and the validation of equipment/system.

13.1.4 Commissioning

In order to ensure that the production equipment/system conforms to user requirements, design, manufacturing and installation of equipment needs to be commissioned following GEP requirements. Commissioning is a well planed, documented and managed engineering approach to start up factory facilities, systems and equipment, then end user will work in a safe environment with functional equipment which meets established design requirements and stakeholder expectations. Commissioning activities are executed mainly following GEP. The project to be commissioned is tested and checked from the point of view of engineering. This is mainly concerning engineering requirements.

All the production equipment/systems need to be commissioned. The complete scope of commissioning activities includes three phases, the factory acceptance testing (FAT), the start-up and the site acceptance testing (SAT).

a. FAT. After the equipment has been manufactured based on t design, FAT shall be performed for equipment to be delivered at equipment manufacturing site and testing should be witnessed by customer before shipment to verify that equipment has been manufactured and assembled strictly following requirements. FAT testing is to be performed by the equipment manufacturer to check all documents and test each of equipment/system and the correct installation and functions, so that when any technical requirement cannot be met it can be more rapidly and effectively rectified to avoid any delay which can be caused when a problem is identified after the equipment has been shipped to user site. Personnel from the equipment manufacturer, the equipment user or an assigned qualified third party must witness the FAT. They shall offer signature and date on document after FAT is completed. The delivery of equipment can be arranged if all customer acceptance criteria are met with all parameters. FAT can cover some of the tests of IQ and OQ. All the tests which has no relationship with transportation or installation is allowed no repeat confirm during subsequent qualification phase if it is appropriately executed, verified and documented.

b. Start-up. Start-up must be performed after me-

chanical completion and before equipment is handed over to operation/maintenance department or validation team. Start-up must be performed by equipment/system manufacturer, and coordinated, approved and witnessed by the designated person from user part. The commissioning plan must be prepared by equipment/system supplier, and reviewed and approved by user before the commencing of testing. Data selected from the commissioning results that can meet the GMP documentation requirements can be used to support the equipment/system qualification and validation. It is acceptable not to repeat such tests during validation phase.

c. SAT. When the equipment arrives at the user site, the SAT must be performed. SAT is used to facilitate the commissioning activities. It can be performed together with the site commissioning activities. Similar with FAT, SAT is used to ensure that the equipment has been assembled and commissioned according to the requirements. So some of the SAT tests are the same as those of the FAT. The difference is that FAT is performed by the equipment manufacturer at the manufacturing site, and SAT is performed by the equipment user at the equipment use site. So an emphasis is put on the tests that cannot be performed at the manufacturer's site. They are going to be performed by the supplier after the equipment/system has been shipped to the use site to ensure that its documents, installation and functions are correct. They must be witnessed by user designated personnel. SAT include dynamic tests and static tests. The test activities will be performed at the site by the supplier before the equipment is handed over to the customer. Each of the SAT activities will be documented. The SAT protocol must be prepared by the equipment/system supplier and reviewed and approved by the user before commencing the testing. Data selected from the SAT results that can meet the GMP documentation requirements can be used to support the equipment/system validation. It is acceptable not to repeat such tests during the validation phase.

13.1.5 Installation Qualification

Installation qualification (IQ) is the documented verification that an installed or modified facility, utility or equipment can meet the approved design and manufacture recommendations and/or user requirements. IQ must be performed by an enterprise for any new or modified facility, equipment or system. IQ is to verify that the equipment received by the user can meet the requirements agreed by the two parties. The received equipment is to be verified based on the URS, the DS and the related documents. It is a data collection and archival process.

Power connection and action tests are normally not performed during IQ. The subsequent qualification activities can only be commenced after the equipment has been verified to be acceptable through IQ. IQ is used to verify that the major components of the equipment or system are correctly installed and are in compliance with the design requirements (such as standard specifications, contract and tender data package). The relevant supporting documents shall be available and the instruments shall be calibrated.

13.1.6 Operation Qualification

The operation qualification (OQ) is the documented verification that the installed or modified facility, system or equipment can operate as intended throughout all the anticipated ranges. OQ is used to verify through inspections and tests and by documented evidences that the equipment operation conforms to the equipment technical parameters, can meet the functional technical parameters defined in the equipment URS and DS. It is a series of activities to verify whether the various technical parameters of a system or equipment can meet the design requirements.

OQ is to verify that the facility/equipment/utility can operate normally within the specified limits and the tolerated ranges. OQ is performed for a system (including facilities, equipment and utilities) to verify the operation is within specified parameter ranges, such as temperature, pressure and flow rate. The OQ includes the verification of the parameters, which regulate process or product quality. Operations, indications, records, alarms and interlocks are to be verified. And they must be recorded during the OQ tests.

13.1.7 Performance Qualification

The performance qualification (PQ) is a series of inspections and tests used to verify that the equipment is working with loads within the design working parameter ranges following the defined operation procedures, it can produce products conforming to the predefined quality criteria. PQ must be commenced after the IQ and the OQ has been successfully completed. PQ can be described as an independent activity and in

some cases PQ and OQ can be combined together.

PQ can prove through documented evidences that the equipment, facility and other system can work effectively in a repeated way after they are connected together. The output of the tested facility and equipment is used to prove its correctness. For a piece of process equipment, PQ is actually using loaded production activities to assess the reliability of its operations, the stability of the critical process parameters and the quality homogeneity and reproducibility of final products.

PQ is used to provide documented evidences to verify that the system can operate effectively and repeatedly, either individually or in combination with other systems, based on the approved process methods and the product specifications. PQ is performed under the actual production conditions. The qualification data needs to be collected and recorded in the attached test reports. PQ is the last step of the formal testing. It provides the documented evidences to verify that the system can work normally before it is put into normal use for each of the systems identified as requiring PQ in the qualification requirement matrix. After the final PQ report is approved, the system can be put into use for normal production or for process validation.

13.1.8 Validation Summary Report

A validation summary report needs to be prepared after all the validation activities have been completed. This report provides a detailed summary on all the validation related activities mentioned in all the validation protocols. We can have a clear understanding of validation process and the validation conclusions from the summary of all the validation activities through validation report. The validation report needs to include, but not limited to, the following items:

- Design qualification summary, which describes the major conclusions of DQ and records any discrepancies with the validation protocol.
- Installation qualification summary, which describes the major conclusions of IQ and records any discrepancies with the validation protocol.
- Operation qualification summary, which describes the major conclusions of OQ and records any discrepancies with the validation protocol.
- Performance qualification summary, which describes the major conclusions of PQ and records any discrepancies with the validation protocol. If the release of the involved validation batches must follow the release method defined in PQ, the validation batches can be released only after the PQ report has been approved.
- Uncompleted tasks. The tasks specified in the validation protocol but have not been completed should be listed. These tasks must be minor or not GMP relevant. All the uncompleted tasks and the justifications why these uncompleted tasks will not affect the current validation conclusion should be listed.
- Deviations and changes. All the deviations or changes identified during the validation protocol execution process must be listed and it should be summarized as to whether these deviations or changes have been addressed.

13.1.9 Maintenance of Validated Status

The maintenance of the validated status is very crucial to ensure that the equipment, process or system is always "validated" and "under control". It is also required by the GMP. The validated status of a system must be maintained through the adoption of effective change control and other supporting procedures. This process will be achieved through GMP procedures and specifications. The major procedures involved include the approved procedures related to change control, calibration, preventive maintenance and training. The establishment and the use of these procedures are to ensure that the facility can consistently be in compliance with GMP requirements for a long term. These procedures must be reviewed and updated periodically, and there should be a relevant control system to ensure the validated status of all the equipment/systems. The maintenance of the validated status is the continuation of the validation.

13.2 Validation of a Pharmaceutical Water Systems

The purpose of the validation of a water systems is to investigate whether it can stably supply the pharmaceutical water conforming to the requirements in both quantity and quality under all kinds of situations that may occur in the future. And validation means providing the documented evidences in these areas. In order to complete this task, sample tests need to be performed during a rather long period of time during which the system can operate under different conditions.

13.2.1 The Life Cycle of a Pharmaceutical Water Systems

In order to better understand the validation life cycle concept, first we need to know the various phases of the life cycle of a pharmaceutical water or steam system and the relationship among the different sections of the life cycle. The ISPE Good Practice Guideline "*Commissioning and Qualification of Pharmaceutical Water and Steam Systems*" tries to integrate project management, commissioning and qualification and routine operations into the concept of validation life cycle. Table 13.1 describes in detail the various elements of the validation life cycle for water and steam systems.

Table 13.1 Validation life cycle for water and steam systems

Engineering and validation project tasks	Project kick-off and conceptual design	Basic design and detailed design	Procurement and construction	Commissioning and qualification, and project completion	Routine operations
Project Control: • Organizing the project team • Determining the roles and responsibilities • Cost control and schedule • Project execution plan • Project validation plan	√				
Design Phase: • URS • P&ID verification • FDS • DDS • System safety design review • Component impact assessment • Assessment of critical quality attributes and critical process parameters (CQA & CPP) • Final design review		√			
Commissioning and Qualification: • Project commissioning and qualification plan • CCT verification		√			
Procurement and Construction: • System manufacturing and construction • Supplier documentation/delivery package • Verification of construction related operation procedures			√		
Commissioning: • FAT • Starting up • Commissioning activities • SOP and maintenance Guideline • Sampling				√	
Qualification: • IQ/OQ/PQ protocol preparation • IQ execution, OQ execution and PQ execution • Final report				√	

cont

Engineering and validation project tasks	Project kick-off and conceptual design	Basic design and detailed design	Procurement and construction	Commissioning and qualification, and project completion	Routine operations
Project completion and documentation hand over • Project close out and delivery				√	
Routine quality monitoring: • Chemical • Microbiology • Endotoxin • Factory specific quality criteria and parameters					√
Periodic quality review					√
Maintenance of validated status • The relevant measures shall be taken based on the project change and periodic quality review results • Position change, for which the URS may need to be developed					√

a. Design phase. The design phase is started after the information on a water and steam system project is collected and documented. The three kinds of documents that describe the tests performed during the qualification process, URS, FDS and detailed design specifications (DDS), are described in the validation life cycle V model. These documents can be combined depending on the strategy and the size of the project to be executed. However, the testing requirements are still divided into three phases. The requirements described in the documents should be considered with emphasis placed on different qualification phases. The other technical requirements proposed by the user, such as EHS or other requirements that will not affect the product quality, must also be tested and documented in records to meet the special requirements. All of these can be part of the commissioning test plan or report. The tests required by GMP must be included in the qualification protocol.

b. URS. The URS shall be generated during the conceptual design phase and continuously reviewed and updated during the entire project life cycle. If possible, the URS shall be finalized before the detailed design. Any changes to the URS shall be avoided after the qualification activities have been started to avoid wasting a large amount of time in revising the qualification protocols and repeating any tests. In the final DQ the URS shall be reviewed in detail to ensure that the design can meet the user expectations. The URS review results can be summarized in the final DQ report.

The URS shall describe the requirements on the pharmaceutical water and steam systems in the production and distribution system. Generally speaking, the URS shall describe the overall requirements and the performance requirements for the water and steam systems. These specifications will define the criteria for the critical quality attributes (CQA), including the specifications of water and steam quality, such as TOC, conductivity, microbes and endotoxin. The influences of the supply water quality and the seasonal changes shall be considered for the system design. The supply water quality shall be described in the FDS and the DDS.

The URS shall describe the uses that can directly impact water and steam systems. These items shall be tested and verified during PQ. The test requirements shall be noted. The URS is a simple and abstract like document. Each PQ part shall be described in the URS template. Any change in the performance criteria requirements in the URS shall be covered by the QA Change Control.

c. Function design specification (FDS). The FDS can be one or multiple documents, describing how the functional requirements of a direct impact water and steam system are going to be realized. Generally speaking, after procurement and installation, the functions de-

scribed in the FDS shall be tested and verified during commissioning and OQ. The FDS must include the following requirements:

- The volume and flow rate specified for the water and steam systems;
- The supply water quality of the pharmaceutical water generation system;
- Alarms and messages;
- The point of use requirements: flow rate, temperature and pressure;
- The sanitization method for the storage and distribution systems;
- The HMI pictures;
- The process control methods, including the inputs, outputs and interlocked structures;
- The storage of electronic data and the system safety.

d. Detailed design specification (DDS). The DDS can be one or multiple documents, describing a direct impact water and steam system is going to be built. Generally speaking, after procurement and installation, the DDS shall be tested and verified during IQ. The specific tests are as described below:

- The material of the constructed system, and how the water and steam quality is ensured; if these materials are not used, contamination, corrosion or leakage can be resulted.
- The functional specifications of the pumps, the heat exchangers, the storage tank and other components, including the critical instruments;
- The correct equipment installation; the incorrect installation of such components as the reverse osmosis (RO) unit and the electro-de-ionization (EDI) unit can cause problems in the system performance.
- System documentation requirements;
- The operation of the vent filter of the storage tank (such as electrically heated or steam heated);
- The description of the treatment system (such as the process flow diagram), and the influences of the supply water quality and the seasonal changes on the system;
- Electric wiring diagrams. These drawings can be used to system structure inspection and trouble shooting.
- Hardware specification, the structure and the specifications of the hardware of the automation system (please refer to GAMP5).

e. System impact assessment (SIA). Each system has its own functions. The system boundaries are defined based on the drawings according to their physical severability. It is very important to understand the differences among direct impact systems, in-direct impact systems and no impact systems. SIA shall be performed for all the defined systems. Direct impact systems include the whole set of water generation system using edible water as the raw water, the pharmaceutical water storage and distribution system, the pure steam generator, etc. Indirect impact systems are used to provide supports to the direct impact system, such plant steam system, chilled water system, e edible water system (the quality of edible water shall be supported by long term routine monitoring records). Non-impact systems have no effect on water system, such as janitor water system, the systems that support the equipment operation and have no impact on water quality, power system and instrument compressed air system.

f. Component criticality assessment (CCA) the components that constitute a system usually have their respective unique numbers in the P&ID drawing. The components can also be operation units or small equipment (such as a multi-media filter, a RO unit, a heat exchanger, a pump or a UV lamp). The critical components are those whose operations, contacts, control data, alarms or failures can have direct impacts on the water or steam quality. These components include:

- The RO/EDI units at the final process steps of a PW generation system;
- The temperature sensors (used for microbial control) in a WFI distribution system;
- On line TOC meters;
- On line conductivity meters.

Non-critical components are those whose operations, contacts, control data, alarms or failures can only have indirect impacts or no impacts on the water or steam quality. Although these components will not affect the final water quality, their operations can affect the service life of the downstream equipment. The non-critical components of a direct impact water and steam system generally include:

- The pressure gauge of the discharge line of the multi-media filter;
- The temperature probe of the supply water of the softeners;
- The on line filters of the pre-treatment system;
- The multi-media filter and the softener.

The non-critical instruments include non-critical

components. These instruments should be within the scope of GEP from design, to procurement and operation. For the non-critical instruments, their traceability, maintenance and calibration requirements are lower than those for the critical instruments. For non-critical components, the qualification activities to be performed generally include:

- The review of the instrument suitability, the technical parameters, the material and the internal structures;
- The calibration and maintenance management plan;
- The inspections, the traceability and the change management;
- The failure analysis (as appropriate);
- The importance of the instrument precision;
- The importance of the instrument precision after maintenance.

For a direct impact water and steam system, the various components of the system should be assessed on its impacts on the final water quality. All the process units or components with a "Component No." must be assessed. The risk analysis approach should be used for assessment. In a process step unit (such as the multimedia filter and the softener), all its components are considered as non-critical components. If the importance of a process unit in a system becomes increasingly high, the process unit will have more critical components.

g. Risk assessment (RA). The RA is used to identify all the potential risks and their influences on patient safety, product quality and data integrity. The potential risks in the pharmaceutical water and steam system during the entire drug manufacturing process must be assessed. The depth and the extent of the validation activities are based on the RA results. The critical risk factors that can affect the product quality are considered as the key areas of the validation activities. Such methods as appropriately increasing of the testing frequency, prolonging the test cycle or increasing the test challenge can be used to verify the safety, the effectiveness and the reliability of the system.

The FMEA approach can be adopted to perform the risk assessment for each system component or functional parameter, and measures can be taken to reduce the high level risks. Taking a WFI spray ball system as an example, the risk assessment can be as shown in Table 13.2.

Table 13.2 Example of risk assessment matrix for critical components/functions

Critical component/function	Descriptions/tasks	Failure events	Worst cases	Severity	Probability	Detectability	Risk priority	Recommended control measures
Spray ball	WFI returns to the storage tank through this spray ball	A wrong spray ball is selected	The spray bal cannot spray normally	High	Low	Medium	Medium	Perform the spray ball spraying test during OQ
		The construction material is not conforming to the requirements	The system is corroded and foreign matters can be shed, which can contaminate WFI	High	High	High	Medium	Check the material certificates during IQ
		The system is blocked after a long term of operation and iron chips can be shed after friction	Foreign matters can be shed, which can contaminate WFI	High	Low	Low	High	Specify in the maintenance SOP to inspect the spray ball periodically
		The return water pressure is not high enough and the spray ball cannot spray normally	There are cleaning dead leg within tank	High	High	High	Medium	Verify the return water pressure during OQ

The trend analysis of the data of the water system can be used as a part of the risk assessment. These data show that the direct impact water system is validated (these records can prove that the water quality is acceptably consistent). Abnormal or out of expectation water quality trends and changes in the actual data can all indicate that the system should be stopped (for SOP review and re-qualification) to correct the out of specification trend of the critical quality of the water quality.

13.2.2 Design Qualification

Before construction, the design documents of pharmaceutical water system (URS, FDS, DDS, etc.) needs to be reviewed one by one to ensure that system can fully meet all the URS and GMP requirements. DQ must continue during the entire design phase, from conceptual design to the commencement of procurement and construction. It should be a dynamic process. The forms of DQ are multiple and flexible. Such documents as meeting memos, parameter calculation sheets, technical communication records and emails can all be used as evidence documents for DQ. However, the normally adopted approach for DQ now is to prepare a DQ summary report, including a URS review report, after the design documents are finalized. The items that must be included in the DQ report for a pharmaceutical water system are described below.

a. Design document review. To verify that all the design documents (URS, FDS, PID, calculation sheet, equipment list, instrumentation list, etc.) for the generation and distribution systems are integrated and approved.

b. Generation system processing capacity review. To verify the selection of the generation system, the material balance calculation sheet, whether acceptable PW, WFI or pure steam can be generated with the supply water of certain quality, and whether the output can meet the requirements.

c. Storage and distribution system circulation capacity review. To verify the technical parameters of pumps and the calculation sheet of distribution loop to see whether the requirements at points of use for such parameters as flow rate, pressure and temperature can be met, and whether microbial growth can be prevented during the operation of distribution system.

d. Equipment and component review. To verify whether the structures and the materials of equipment and components used in generation and distribution systems can meet the GMP requirements. Examples of such requirements include whether the material and the surface finish of the metal parts in direct contact with water can meet the URS requirements, whether the RO membrane can tolerate pasteurization, whether the vent filter of the storage tank is a hydrophobic filter, and whether the material of the valve gaskets can meet the GMP or FDA requirements.

e. Instrument verification. To verify whether sanitary connections are used for the critical instruments of generation and distribution systems, whether material, precision and error can meet URS and GMP requirements, and whether calibration certificates and quality certificates can be provided upon delivery.

f. Pipeline installation verification. To verify whether the material and the surface finish of the pipeline of the generation and the distribution systems can meet the URS requirements, whether sanitary connections are used, whether the system slope can ensure the emptying of the system, whether there are any dead leg, whether an inspection plan has been prepared for welding, and whether the steam trap of the pure steam distribution loop is acceptable.

g. Sanitization method verification. To verify the sanitization method used for the system, whether it can ensure the sanitization of the entire system, including the storage tank, the components and the pipeline, and how the sanitization effect is ensured.

h. Control system verification. To verify whether the design of control system can meet the URS requirements, such as whether access control is reasonable, whether the critical parameters have alarms, whether the system operation requirements can be realized through the automation system, and whether the critical data can be stored.

13.2.3 Commissioning

Commissioning should be a well planned and documented engineering method for equipment and system start-up and handover to the final user. It should also ensure that the safety functions and the functional performances of the equipment and system can meet the design requirements and the user expectations. Qualification activities can provide documented records that will be reviewed and approved by the quality department. These records can demonstrate that the equipment or system received by the user can consistently

generate and distribute water and steam conforming to certain quality criteria.

Water system operators need to pay special attention to the commissioning and qualification plan. This plan can improve the commissioning and qualification efficiency and reduce the cost (in time, human resources and material resources). The commissioning and qualification plan must ensure that the qualification activities are thorough and without repetitions. For example, a good plan can leverage FAT or SAT to complete all the commissioning and qualification activities. For a water system, it may be beneficial to leverage FAT, SAT, commissioning and qualification activities. However, the commissioning and qualification activities that can be performed during FAT in a great extent depend on the capabilities of the supporting equipment and whether the required facilities are available. The approaches of FAT, SAT, commissioning and IQ/OQ/PQ for an entire project should be reasonably planned and the information accumulated during FAT and SAT should be referenced. The quality department should participate in the establishment of the commissioning and qualification plan. The design of a pharmaceutical water system comes from the user requirements on the average water consumption, the transient maximum water consumption and the water quality. The sampling results for the generation and distribution systems must conform to the design or specification requirements. A sampling plan must be developed for the commissioning and qualification plan to determine whether the URS requirements and the water quality requirements are met and provide support to the "process understanding".

Qualification activities are not just a simple repetition of the commissioning activities. More exactly, qualification activities are used to ensure that all the activities and items that can affect the water and steam quality are included in the project plan, executed following the plan and documented. A good commissioning plan with participation from the quality department can allow us to review, not simply repeat, the activities executed and documented at the time of commissioning, during the qualification process. The IQ and OQ protocols can simply review all the activities that can affect the water and steam quality executed at the time of commissioning (documented records). If there is a test that has not been performed at the time of commissioning, it must be described in detail in the qualification protocol and executed. With a good plan, the qualification activities can be executed during FAT and SAT. For a minor system change, it is acceptable not to commission it and it can be tested directly during qualification to see whether the requirements can be met. If it is the case, it should be noted on the qualification protocol that the system change is a minor change and the qualification is to be performed after approval by the quality department. It is very important for the quality department to be involved in the commissioning and qualification plan as soon as possible. This is beneficial to the review and approval of the documents and records and can also ensure that the subsequent qualification activities can be executed more easily and in compliance with the requirements.

13.2.4 Installation Qualification

The generation system and the storage and distribution system of pharmaceutical water are often separated for IQ. The documents required for IQ are as described below:

- The IQ protocol approved by the quality department;
- The as-built package. Process flow diagrams, pipe and instrument diagrams, component list, electric design documents, parameter manual, wiring diagrams, material certificates, necessary surface finish certificates, welding documents, pressure test records, cleaning and passivation records, etc.
- Technical parameters and calibration records of critical instruments;
- Calibration certificates and quality certificates of the instruments to be used during IQ.
- System operation and maintenance manual.
- System commissioning records, such as FAT and SAT records.

The test items of IQ are as described below:

- Verification of the as-built process flow diagrams, the pipe and instrument diagrams or other drawings. To verify whether the components shown on these drawings have been correctly installed and identified, and whether their positions, installation directions, the positions of the sampling valves, the positions of the on line instruments, the air gap to drain, etc. are correct. These drawings are very important for achieving and maintaining the water quality and any for subsequent system renovations. The isometric drawings of the system can help determine whether the system can be

emptied. If necessary, they should also be inspected.

• Component verification. To verify whether the models, the installation positions and the installation methods for the components are as specified in the design drawings and the installation instructions during IQ. For example, it should be verified whether the installation method of the heat changer of a distribution system, the model and the installation method of the RO units, the installation positions of the sampling valves, and the installation angles of the diaphragms valves are consistent with the instructions, whether the integrity test before shipment from the factory is acceptable for the vent filter of the storage tank, and whether the installation position of the steam trap of the pure steam system is correct.

• Calibration of instruments. To verify whether the critical instruments of the system and the instruments to be used for IQ are within their respective calibration due dates, and to verify the calibration of the non-critical instruments during IQ, if not verified and documented during commissioning.

• Component and pipe material and surface finish verification. To verify whether the material and the surface finish of the critical components of the system can meet the design requirements. For example, the RO units and the EDI unit can be inspected for the generation system while the mechanical filters, the active carbon filter and the softeners may only need to be inspected during commissioning. The material certificates and the surface finish certificates of the components must be traceable to the supplier, the batch No., the serial No., the heat No., etc. The material certificate of a pipe must also be identified to its corresponding heat No. and welding logs. For valves, the heat No., the serial No., and the quantity must be consistent with those specified in the mechanical component list and the actual installation.

• Documents of pipelines connected by welding or other methods. These documents include standard operation procedures, welder qualification certificates, welding inspection protocols and reports, welding point drawings, welding records, etc. For the welding inspections, it is preferred that they should be performed by the system user or a third party. If they are inspected by the constructor, they should be supervised and witnessed by the system user, who should sign and date the inspection records.

• Pipeline pressurization test and cleaning and passivation verification. The pressurization test and the cleaning and passivation need to be performed during commissioning. During IQ, it needs to be verified whether these activities have been completed and documented following the standard operation procedures.

• System slope and dead leg verification. The slope of the distribution loop must ensure that the system can be emptied at the lowest point, any dead leg should meet the $3D$ or higher criteria to ensure that there is no cleaning dead leg (please refer to the GEP related specifications for the dead leg of the pure steam system and the clean process air system).

• Utility verification. To verify the utility systems, including the power connections, the compressed air, the nitrogen, the plant steam, the cooling water, and the supply water systems, have been correctly connected and their parameters can meet the design requirements.

• Automation system verification. To verify the installation of the automation system, which generally include the hardware inspection, the wiring diagram inspection, the input and output test, the HMI operation picture inspection, the software version inspection, etc.

13.2.5 Operation Qualification

a. The documents required for OQ are as described below:

• The OQ protocol approved by the quality department.

• The FS and the system operation and maintenance manual provided by the supplier.

• The system operation and maintenance SOPs.

• The system IQ records and deviation report.

• The owner should provide the SOPs (at least the draft versions).

b. The test items of OQ are as described below:

• System SOP verification. To verify that there will be at least the drafted versions of the system (use, maintenance, and sanitization) SOPs before OQ, and verify their accuracy and suitability during OQ. They can be approved after the first phase PQ is completed.

• Testing instrument calibration verification. To verify the calibration of the instruments to be used during OQ, which mainly include the on line TOC and conductivity meters. If samples need to be taken for several consecutive days for testing, this verification

mainly includes the off line TOC and conductivity meters used in the QC labs.

• Storage tank vent filter verification. To verify whether the electric heating function (if available) of the vent filter of the PW or WFI storage tank can work effectively when the system is running, and whether the condensate can be smoothly drained. The condensate needs to be inspected especially after a sanitization/sterilization cycle is completed.

• Automation system verification:

-System access control verification. To verify the reliability of the different levels of users and their passwords, and whether the operation authorities of the corresponding levels can meet the design requirements.

-Emergency stop test. To verify whether the emergency stop is effective when the system is running at various operation statuses, whether the system is at a safe state after the system is stopped, and whether the stored data can be lost.

-Alarm tests. To verify whether the critical alarms of the system can be triggered correctly and whether the triggered actions and results are consistent with those specified in the design documents. Special care must be given to the alarms and the actions for failures in the utility systems.

-Data storage verification. To verify whether the data storage and backup are consistent with the design documents.

• Unit operation verification for the generation system, used to verify whether the operations of the various functional units are consistent with the design procedures. Please see the paragraphs below for the details.

-PW pretreatment and generation system verification. To verify that the level control of the raw water device, the mechanical filters, the active carbon filter, the softeners, the RO units, and the EDI unit can work normally, whether the rinsing procedures are consistent with the design, whether the sanitization cycle can be smoothly completed, whether the interlock between the water generation and the storage tank level is reliable, whether the frequencies of the raw water pump and the booster pump are acceptable, whether the water generation rates and the water quality are acceptable for each pass of RO, and whether the total water generation rate and the EDI water quality are acceptable.

• WFI generation system verification. To verify whether the preheating, the rinsing, the normal running, and the draining procedures are consistent with the design and whether the start and stop of the system and the interlock with the storage tank level are reliable.

• Generation system normal running verification. To verify whether there are any abnormalities in the system after it has been started and running at the normal production status, whether the on line production parameters can meet the URS requirements, whether there are any leakages, etc.

• The qualification tests for the storage and distribution system are as described below:

- Whether the interlock among the circulation pump, the storage tank level and the return loop flow rate can ensure that the return loop flow rate can meet the design requirements, such as no less than 1.0 m/s.

- Storage tank vent filter verification: to verify the integrity test of the vent filter.

- Storage tank spray ball efficacy verification. To verify the spraying efficacy of the spray balls (if this has been tested by the tank manufacturer during FAT, it is not necessary to repeat it if the same results can be obtained for the circulation capacity verification test described below, however, it should be noted).

- Circulation capacity verification. To verify whether there are any abnormalities in the distribution system when it is running normally, whether the on line data of such circulation parameters as flow rate, conductivity and TOC can meet the URS requirements an whether there are any leakages in the distribution loop.

- Peak demand verification. To verify whether the water supply of the generation system is sufficient when the water demand is maximum at the distribution system, whether the pumps are running normally, whether the loop pressure can be maintained normal and whether there are any leakages in the loop.

- Sanitization verification. To verify whether the system sanitization can be successfully completed, whether there are any sanitization deadlegs, and whether the temperature can meet the requirements.

- Water quality off line testing. It is recommended to test the water quality off line through samples taken at the water generation system, the main supply and the main return of the storage and distribution system.

13.2.6 Performance Qualification

The PQ for a PW or WIF system is generally divided into three phases. There must be no failures or performance deviations during PQ for the generation system and the storage and distribution system.

For the first phase, samples are taken continuously for 2 to 4 weeks and all the test items specified in the pharmacopoeia are tested. The purpose is to verify that the system can continuously generate and distribute acceptable PW or WFI. It also provides supports for the updating and the approval of the system operation, sanitization and maintenance SOPs.

For the second phase, samples are taken continuously for 2 to 4 weeks. The purpose is to verify that when operated following the relevant SOPs, the system can consistently generate and distribute acceptable PW or WFI. The sampling scheme is the same as that of the first phase.

For the third phase, the PW or WFI system is routinely monitored following the approved SOP. The test will last for one year starting from phase 1 to verify the long term reliability of the system and assess the influences of seasonal changes on the water quality.

The example sampling points and testing plan for the three phases of PQ for a PW system are as shown in Table 13.3. The example sampling points and testing plan for the three phases of PQ for a WFI system are as shown in Table 13.4.

Table 13.3 PW PQ sampling points and testing plan (example)

Phase	Sampling positions	Sampling frequency	Test items	Acceptance criteria
Phase 1	Generation system/raw water tank	Once a month	National criteria for edible water①	National criteria for edible water①
	Generation system/mechanical filters	Once a week	Silt density index(SDI)	<4②
	Generation system/softeners	Once a week	Hardness	<1②
	Generation system/product water	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
Phase 2	Generation system/raw water tank	Once a month	National criteria for edible water①	National criteria for edible water
	Generation system/mechanical filters	Once a week	Silt Density Index(SDI)	<4②
	Generation system/softeners	Once a week	Hardness	<1②
	Generation system/product water	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
Phase 3	Generation system/raw water tank	Once a month	National criteria for edible water①	National criteria for edible water①
	Generation system/mechanical filters	Once a month	Silt density index(SDI)	<4②
	Generation system/softeners	Once a month	Hardness	<1②
	Generation system/product water	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Samples to be taken every day and for every sampling points every month in rotation	Full item inspection	Pharmacopoeia or internal criteria

① Test reports provided by national inspection and quarantine authorities shall be used. If municipal water is not used, the treated raw water shall meet the criteria for edible water.

② The specific criteria can be from the use instructions from the generation system manufacturer.

Table 13.4 WFI PQ sampling points and testing plan (example)

Phase	Sampling positions	Sampling frequency	Test items	Acceptance criteria
Phase 1	Generation system supply water①	Once a week	Test items specified in pharmacopoeia	Criteria specified in pharmacopoeia
	Generation system outlet	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
Phase 2	Generation system supply water	Once a week	Test items specified in pharmacopoeia	Criteria specified in pharmacopoeia
	Generation system/product water	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
Phase 3	Generation system/product water	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at main supply and main return of storage tank and distribution system	Every day	Full item inspection	Pharmacopoeia or internal criteria
	Sampling ports at each points of use of the distribution system	Samples to be taken every day and for every sampling points every week in rotation	Full item inspection	Pharmacopoeia or internal criteria

① If the supply water is edible water, it shall be tested once a month. If the supply water is PW, the PQ of the WFI system can only be started after the phase 1 of the PQ of the PW system has been completed.

13.2.7 Validation of Non-pharmacopoeia Water Systems

Non-pharmaceutical water is not specified in the pharmacopoeia, such as deionized water, RO water and lab water. There are many types of such water. The quality criteria for these types of water can be lower or higher than the requirements for pharmacopoeia water according to the actual factory or lab requirements. For example, the water required for the production of a special kind of product may require the same chemical parameter requirements as those for PW, but with additional requirements for endotoxin control. This means the use of a type of non-pharmacopoeia water with higher criteria than those for PW specified in pharmacopoeia in production activities. In this case all the validation requirements must be met for this type of non-pharmacopoeia water and even stricter validation can be required based on the product properties and requirements. Although there are no clear criteria for non-pharmacopoeia water, for a pharmaceutical company, the quality of the non-pharmacopoeia water used is generally not inferior to that of drinking water.

The quality of other process water, such as deionized water, is generally inferior to the pharmacopoeia water requirements. However, because it is often used in some early process steps, the system also requires some simple validation. A risk assessment needs to be performed according to the process requirements to determine the depth and the extent of validation. Some of the water used in the lab during the research and development phase may also need to follow the GMP requirements. In this case the GMP management requirements need to be followed to decide which pharmacopoeia water is to be used and the relevant validation must be performed. If based on the GMP management requirements it is not necessary to use pharmacopoeia water or for water to be used for analyses in labs, appropriate non-pharmacopoeia water should be used in-

stead. Because of the special requirements of lab analyses, low endotoxin non-pharmacopoeia water should be used, such as the water to be used for endotoxin tests. Reasonable purification measures and quality monitoring measures are required for such special non-pharmacopoeia water. A risk assessment must be performed by the users to determine the depth and the extent of validation.

13.2.8 Routine Monitoring of a Pharmaceutical Water Systems

After completing PQ, the system should be comprehensively assessed and a routine monitoring plan must be established based on the phase 3 test results. For the routine sampling and monitoring phase, the sampling frequency at a point of use (usually some minimum frequencies) is usually lower than the sampling frequency used during PQ. For a WFI system, it must be ensured that all the points of use can be tested every week. Under these conditions, the number of samples to be taken each day can be determined through assessment. The routine monitoring of the critical sampling points should be determined according to the process requirements. Therefore, for a larger distribution system, samples can be taken from different sampling points in rotation to ensure that samples can be taken from each sampling point every week. For a PW or pure steam system, the system impact risks are lower, so the routine monitoring frequency can be lowered as appropriate compared with that of a WFI system. The sampling plan related to all these routine monitoring activities must be recorded in a SOP.

A quality review must be performed for a water system at least once a year. The annual review of the system can help the user understand the trend of changes in the system with time and can help adjusting the set alert limits and action limits, even the relevant SOPs based on the analysis of the data. The system quality review cannot be restricted to only the water quality test results obtained by sampling testing, it should be a comprehensive review of the system, including:

- Review of the system drawings and the relevant SOPs;
- Review of the qualified and validated status of the system;
- Review of the preventive maintenance and trouble shooting records of the system;
- Review of the critical deviations and alarms of the system;
- Review of the routine monitoring data and their trends;
- Review of the sanitization cycles of the system;
- Review of the relevant training records related to the system.

13.2.9 Periodic Maintenance of a Pharmaceutical Water Systems

A pharmaceutical water system must be maintained according to the system maintenance procedures, which must define the system maintenance frequency, the maintenance methods for different components, the maintenance record, the control of acceptable spare parts, etc. After a system is maintained periodically, the revalidation of system is not necessary. If necessary, only continuous water quality monitoring is sufficient. The typical maintenance activities for a pharmaceutical water system include:

- Periodic cleaning of the storage tank;
- Periodicre placement of such wear parts as valves, gaskets and vent filters;
- Pressurization test, cleaning and passivation of the pipeline system;
- Thorough cleaning or replacement of the multimedia filter, the active carbon filter and the RO membrane of a PW generation system;
- Inspection, testing and replacement of instruments.

13.2.10 Periodic Validation of a Pharmaceutical Water Systems

In order to ensure that a pharmaceutical water system can be running satisfactorily within the entire service cycle, periodic revalidation of the system is required after the system has been running for a certain period of time, which include the periodic assessment of the system performance, the nature and the extent of system changes, the expected changes in the use of the system in future, and the appropriate quality system of company. The items to be considered in plan include:

- Maintenance. Revalidation is generally not required for the routine maintenance activities of the system, such as component replacement and cleaning.
- Renovation. Renovation activities can include

• Automation system verification. To verify the installation of automation system, which generally includes hardware inspection. e wiring diagram inspection, input and output test, HMI operation pictures and software backup inspection, etc.

13.3.3 Operation Qualification

a. The documents required for OQ.

• OQ protocol approved by quality department.

• FS and the operation and maintenance manual of system provided by supplier.

• Operation and maintenance SOPs of system.

• System IQ records and deviation report.

b. The test items of OQ.

• System SOP verification. To verify that there will be at least the drafted versions of system (operation and maintenance SOP, etc.) SOPs before OQ, and verify their accuracy and suitability during OQ. They can be approved after the first phase PQ is completed.

• Instrument calibration verification. To verify whether the instruments used for water quality testing during OQ are within their calibration due dates.

• Qualification of the automation system of a pure steam generator.

- System access control verification. To verify the reliability of different levels of users and their passwords, and whether the operation authorities of corresponding levels can meet design requirements.

- Emergency shut down test. To verify whether emergency shut down is effective when system is running at various operation statuses, whether system could state with safety after downtime, and whether there is possibility to lose stored data.

- Alarm tests. To verify whether the critical alarms of system can be triggered correctly and whether the triggered actions and results are consistent with those specified in design documents. Special care must be given to alarms and the actions for failures in utility systems.

- Data record verification. To verify whether stored data and the backed up data are consistent with those in design document, and whether printing function works well.

• System operation parameter verification. To start system and allow it to run in normal production conditions, and check whether the on-line production parameters are stable, whether there are any leakages, and whether URS requirements are met with.

• Distribution system verification. To verify, under normal production conditions, whether the pressure at each point of use can meet e process requirements, whether the supply pressure is stable during the peak demand period, and whether steam trap can have good function.

• Steam quality verification. To verify whether steam quality from pure steam generator and each point of use of distribution system can meet URS requirements (for non-condensable gases, dryness and the degree of superheat). The tests can be performed on-line or through special off-line sampling tubes. Samples shall be taken from a point as close as possible to point of use. It is not recommended to perform test only at one position of system unless has good reasons.

13.3.4 Performance Qualification

Generally speaking, PQ for a pharmaceutical steam system adopts the same three-phase sampling cycle as for PW and WFI systems. However, it also has its special features.

a. PQ of a pure steam system. For the PQ of a pure steam system, it is generally required to take samples at the outlet of pure steam generator and at each point of use. For a non-critical point of use, it is acceptable to take samples at a downstream point of use only based on risk assessment and with proper justifications. Usually the pure steam is cooled to liquid with a portable condenser to verify the quality of the pure steam. The acceptance criteria are the quality requirements specified in Pharmacopoeia for WFI. The PQ for a pure steam system is preferred to be performed following the three-phase approach used for WFI systems. However, other qualification cycles can also be used because of the special features of pure steam system. Table 13.5 and Table 13.6 show two examples of sampling plan for the PQ of a pure steam system.

b. PQ of plant steam system. Generally speaking, the condensate of plant steam needs to conform to the criteria for drinking water. TOC and conductivity testing can be used to determine whether the system is contaminated. These criteria can be established during PQ and assessed during routine monitoring. The PQ can also follow the three-phase model.

Table 13.5 Example sampling plan for PQ of a pure steam system (1)

Phase	Sampling cycle	Frequency of sampling
Phase 1	Three days	At least one sample is taken at each point of use and at least one sample at each outlet of a pure steam generator
Phase 2	One week	At least one sample is taken at each sampling point and more than one samples at each outlet of a pure steam generator
Phase 3	Four weeks	At least one sample is taken at each point of use within one week and one sample at each outlet of a pure steam generator

Note: 1. Test methods shall be clearly defined in PQ protocol.

2. Sampling plan for each point of use can be determined through risk assessment.

Table 13.6 Example sampling plan for PQ of a pure steam system (2)

Phase	Sampling cycle	Sampling of frequency
Phase 1	One week	Samples are taken continuously for one week at pure steam generator outlet and all the points of use
Phase 2	One year	Samples are taken once a week at pure steam generator outlet and at least once every month at each point of use

Note: 1. Test methods shall be clearly defined in PQ protocol.

2. Sampling plan for each point of use can be determined through risk assessment.

• Phase 1. Generally speaking, this phase is only used for collecting the quality information of system. The criteria for determining whether the system is contaminated can be assessed and determined during phase 2. If the user has established the criteria, the phase 2 can be started directly.

• Phase 2. Samples must be taken for no less than 3 times for this phase of the PQ. And the sampling interval must be no less than 24 hours and no more than 7 days.

• Phase 3. This is the routine monitoring phase and samples must be taken at least once a month.

13.4 Application of Quality Risk Management in Pharmaceutical Water Systems

The internal and external risk environments of a pharmaceutical company are becoming more and more complicated, and the risk management technologies are improving continuously. With strong promotion by international organizations and risk management associations of different countries, effective risk assessment has become a prerequisite for good business operation and development of each enterprise.

For pharmaceutical water systems, appropriate risk management processes should be followed throughout the whole life cycle in order to manage the identified risks and to confirm the rigidity and range of activities required for each phase of the life cycle. Risk assessment approaches should be used to eliminate or reduce the hazards of a system or a piece of equipment from product quality and the safety of operators, and certain measures should be taken into consideration to lower existing risks to some acceptable level. Major risk management procedure includes risk identification, risk analysis and risk assessment.

13.4.1 Risk Identification

Risk identification means understanding the process flow of a system or equipment and identify any potential risks their causes and consequential effects. An enterprise can determine the scope of risk identification through system impact assessment. The systems are classified to direct impact systems, indirect impact systems or no impact systems by assessment. A water system has direct effect on product quality, so the system is a direct impact system. The design and the implementation of this system must conform to both GEP requirements and qualification management regulations. The risk identification methods mainly include flow charts, the causal loop diagrams (also known as "brainstorming"), the failure mode and effect analysis, fault tree analysis, hazard analysis and critical control points.

13.4.2 Risk Analysis

Risk analysis means the analysis of identified risks and their events to determine the probability of occurrence of the events, and whether an occurred event and possible consequences can be timely detected. Through analyzing severity and the possibility of occurrence of each risk, a risk can be described in depth and then the

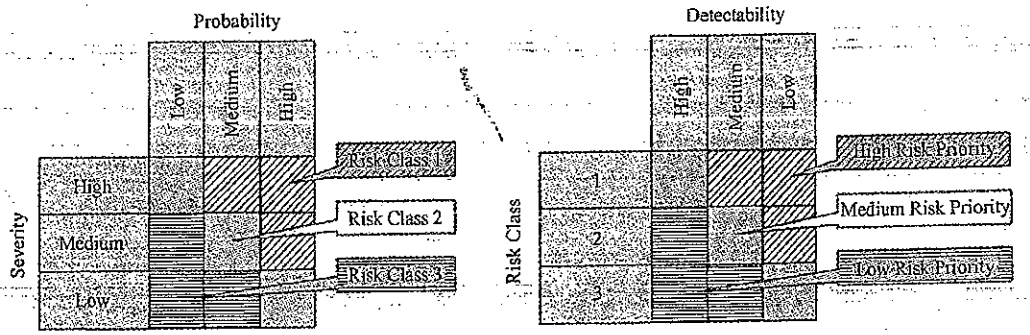
level of the risk can be determined considering the above factors during risk assessment. During risk analysis process, the chance of occurrence and the severity of quality hazards can be described qualitatively or quantitatively. The major tools that can be used includes formal management tools and informal management tools.

With informal management tools risk analysis is performed based on historical data, such as product quality trend analysis, deviation handling, corrective action and preventive action (CAPA), etc. Formal management tools can be used to quantitatively or semi-quantitatively perform risk management with support from sufficient data. They are mainly used for production process control, facility and equipment validation, critical production process parameter definition and quantification.

13.4.3 Risk Assessment

Risk assessment is to compare and distinguish the identified and analyzed risks following specified risk criteria, so as to manage the risks considering the severity and the probability of occurrence of risks. The purpose of risk assessment is to identify and rank all the possible hazards of a component. Fig 13.2 shows a commonly used risk assessment method.

Risk assessment can help an enterprise to focus on the areas of the company that are most vulnerable to hazards. This should be considered in combination with the risk tolerance. Different enterprises have different risk priorities and different risk tolerances, for different enterprises have different products and are subject to different regulatory requirements. It should be noticed that that if there would be a change in detailed design, the criticality assessment for system, functions and components must be fulfilled again following risk assessment method. Taking a PW distribution system as an example, Table 13.7 shows an example criticality assessment matrix, Table 13.8 shows an example risk assessment matrix, and Table 13.9 shows an example critical component risk control matrix.



Severity=Impact on patient safety,product quality, and data integrity (or other harm)
Probability=Likelihood of the fault occuring
Risk class=Severity×Probability

Detectability=Likelihood that the fault will be noted before harm occurs
Risk Priority=Risk class×Detectability

Fig 13.2 Risk Assessment Method

Table 13.7 Criticality assessment matrix

No.	Functions/components	Descriptions/tasks	Critical?
PW storage tank			
1	Tank body	PW storage tank	Y
2	Spray ball	Spraying and cleaning of tank internal wall	Y
3	Vent filter	Preventing contaminants in the air from entering storage tank	Y
4	Level transmitter	Monitoring the level in storage tank	Y
5	Temperature sensor	Monitoring the temperature in storage tank	Y
6	Pressure gauge	Monitoring the pressure in PW storage tank	Y
PW distribution loop			
1	Circulation pump	Transferring PW to points of use	Y
2	Pressure gauge	Monitoring the pressure in PW distribution loop	Y

cont

No.	Functions/components	Descriptions/tasks	Critical?
3	Flow meter	Monitoring the flow in loop	Y
4	Temperature sensor	Monitoring the temperature in PW storage and distribution system	Y
5	Conductivity sensor and meter	Monitoring the conductivity in the return line of loop	Y
6	TOC sensor and meter	Monitoring the TOC in the return line of loop	Y
7	Heat exchanger	Increasing the PW temperature to the pre-set sanitization temperature	Y
8	UV lamp	Controlling the microbial growth in PW	Y
9	Pipes and valves	Components of PW storage and distribution system	Y
Plant steam pipes			
1	Check valves	Components of the plant steam distribution system	N
2	Y filter	Filtering plant steam	N
3	Ordinary pressure gauges	Monitoring plant steam pressure	N
4	Angle seat valves	Components of plant steam distribution system	N
5	Steam trap	Draining any condensate from the plant steam system	N
6	Pipes and valves	Components of the plant steam distribution system	N
Cooling water pipelines			
1	Pipes and valves	Components of cooling water distribution system	N
Automation systems			
1	PLC control systems	Controlling t equipment operation	Y
2	Human machine interface	Allowing the interactions and the information exchange between system and users	N
3	Electric cabinet components	Protecting the normal operation of components	N
4	Frequency converter	Changing the power frequency to another frequency	N
5	Earthling	Ensuring the power supply safety	N

Table 13.8 Risk assessment matrix

No.	Functions/ critical components	Descriptions/ tasks	Failure events	Worst case effects	S	P	D	Risk priority
PW storage tank								
1	Tank body	PW storage tank	The construction material is not conforming to the requirements and the rusting of the tank body is resulted	Foreign matters can drop off and contaminate PW	H	L	M	M
			The welding is not conforming to the requirements and the welded parts are not smooth, dead legs are resulted and it is vulnerable to corrosion	The cleaning cannot be performed thoroughly and thus cause cross-contamination	H	L	L	H
			The surface roughness is not acceptable	The cleaning cannot be performed thoroughly and thus cause cross-contamination	H	L	M	M
			The passivation does not conform to the requirements, the product contact surfaces are influenced and residues may be resulted	Foreign matters can drop off and contaminate PW	H	L	L	H

cont

No.	Functions/ critical components	Descriptions/ tasks	Failure events	Worst case effects	S	P	D	Risk priority
			The construction material is not acceptable and impurities may be introduced	PW contaminated	H	L	M	M
2	Spray ball	Spraying and cleaning of the tank internal wall	The spray ball is faulty and cannot spray normally. The cleaning cannot cover the entire surface of the tank	The cleaning effect cannot be reached and thus contaminating the PW in tank	H	L	M	M
			The construction material is not conforming to the requirements and the rusting of the tank body is resulted	Foreign matters can drop off and contaminate PW	H	L	M	M
3	Vent filter	Preventing contaminants in the air from entering the storage tank	Installation error/integrity failure or blockage	The contaminants in the air enters the storage tank and contaminating PW	H	L	M	M
			The construction material is not conforming to the requirements	The impurities can drop off and contaminate the products in tank	H	L	M	M
4	Level transmitter	Monitoring the level in the storage tank	The setting is not correct and the measurement is wrong	The insufficient PW level can cause insufficient water supply at points of use	H	L	M	M
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW within tank	H	L	M	M
5	Temperature sensor	Monitoring the temperature in the storage tank	Transmitter/probe damages, causing instrument malfunction	Temperature measurement inaccurate, affecting sanitization effect	H	M	H	M
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate the PW within tank	H	L	M	M
6	Pressure gauge	Monitoring the pressure in the PW storage tank	Measurement errors can cause pressure indications inaccurate	Storage tank pressure too high or too low can cause physical damages to tank	M	L	H	L
PW distribution loop								
			The construction material is not acceptable and impurities may be introduced	Foreign matters can drop off and contaminate PW	H	L	M	M
1	Circulation pump	Transferring PW to the points of use	Circulation capacity insufficient	Point of use demand cannot be met	H	L	H	L
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
2	Pressure gauge	Monitoring the pressure in the PW distribution loop	Measurement errors can cause pressure indications inaccurate	System pressure too high or too low can cause physical damages to the pipeline	M	L	H	L
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
3	Flow meter	Monitoring the flow in the loop	The setting is not correct and the measurement and indication are wrong	The insufficient flow can result in microbial growth and insufficient water supply	H	M	H	M
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
4	Temperature sensor	Monitoring the temperature in the PW storage and distribution system	The setting is not correct and the measurement and indication are wrong	Inappropriate temperature can result in microbial growth	H	M	H	M
			The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
5	Conductivity meter	Monitoring the conductivity in the return line of the loop	The setting is not correct and the measurement and indication are wrong.	Conductivity measurement errors may result in unacceptable PW used at a point of use	H	M	H	M

cont

No.	Functions/ critical components	Descriptions/ tasks	Failure events	Worst case effects	S	P	D	Risk priority
6	TOC meter	Monitoring the TOC in the return line of the loop	The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
			The setting is not correct and the measurement and indication are wrong	TOC measurement errors may result in unacceptable PW used at a point of use	H	M	H	M
7	Heat exchanger	Increasing the PW temperature to the pre-set sanitization temperature	The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
			Insufficient heat exchange capacity	The sanitization effect cannot be reached and microbial growth can be resulted	H	L	H	M
8	UV lamp	Controlling the microbial growth in the PW	The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
			UV light intensity not sufficient	Microbial control can be results in PW	H	M	H	M
9	Pipes and valves	Components of the PW storage and distribution system	The construction material is not conforming to the requirements	Foreign matters can drop off and contaminate PW	H	L	M	M
			The design and the installation of the pipeline are not reasonable and with deadlegs	The system cannot be cleaned satisfactorily, contaminating PW	M	M	M	M
			The surface roughness is not acceptable	The cleaning cannot be performed thoroughly and thus cause cross contamination	H	L	M	M
			The welding is not conforming to the requirements and the welded parts are not smooth, deadlegs are resulted and it is vulnerable to corrosion	Foreign matters can drop off and contaminate PW	H	L	L	H
			The valve leaks	It can contaminate PW	H	L	M	M
Automation systems								
1	PLC control systems	Controlling the equipment operation	Hardware damaged	The equipment cannot run normally	H	L	M	M
			Communication error	The equipment is out of control	H	L	M	M
			Software error	The equipment operation is abnormal and the expected effects cannot be reached	H	L	M	M
			User access levels are out of control and the configuration is not reasonable	A critical process parameter is changed by a user without proper authorization and the product quality can be affected	H	M	M	H

Table 13.9 Risk control matrix

No.	Functions/ critical components	Failure events	Risk priority	Recommended measures	S	P	D
PW storage tank							
1	Tank body	The construction material is not conforming to the requirements and the rusting of the tank body is resulted	M	Check construction material during IQ	H	L	H
		The welding is not conforming to the requirements and the welded parts are not smooth, deadlegs are resulted and it is vulnerable to corrosion	H	Check welding during IQ	H	L	H

cont

No.	Functions/ critical components	Failure events	Risk priority	Recommended measures	S	P	D
1	Tank body	The surface roughness is not acceptable	M	Check surface roughness during IQ	H	L	H
		The passivation does not conform to the requirements, the product contact surfaces are influenced and residues may be resulted	H	Check the passivation during the IQ	H	L	H
2	Spray ball	The construction material is not acceptable and impurities may be introduced	M	Check construction material during IQ	H	L	H
		The spray ball is faulty and cannot spray normally. The cleaning cannot cover the entire surface of the tank	M	Establish maintenance SOP and check periodically Verify the spraying effect during OQ	H	L	H
3	Vent filter	The construction material is not conforming to the requirements and the rusting of the tank body is resulted	M	Check the construction material during IQ	H	L	H
		Installation error, integrity failure or blockage	M	Check the installation and the integrity test report during IQ. Perform the integrity test periodically	H	L	H
4	Level transmitter	The construction material is not conforming to the requirements	M	Check the construction material during IQ	H	L	M
		The setting is not correct and the measurement is wrong	M	Check the availability of the calibration report during IQ Check the monitoring level and alarming functions during OQ. Calibrate periodically	H	L	H
5	Temperature sensor	The construction material is not conforming to the requirements	M	Check construction material during IQ	H	L	M
		Instrument indication out of work or transmitter damaged	M	Check calibration certificates and perform loop tests during IQ. Establish an instrument testing and calibration SOP and check calibration of sensors and transmitters regularly	H	L	H
6	Pressure gauge	The construction material is not conforming to the requirements	M	Check construction material during the IQ	H	L	M
		Measurement errors can cause pressure indications inaccurate	L	Check certificates during IQ Check the availability of t original calibration report Calibrate periodically	N/A	N/A	N/A
PW distribution loop							
1	Circulation pump	The construction material is not acceptable and impurities may be introduced	M	Check the construction material during IQ	H	L	H
		Circulation capacity insufficient	L	Check technical parameters during IQ Check circulation capacity during the OQ	N/A	N/A	N/A
2	Pressure gauge	The construction material is not conforming to the requirements	M	Check construction material during the IQ	H	L	M
		Measurement errors can cause pressure indications inaccurate	L	Check certificates during IQ Check availability of original calibration report Calibrate periodically	N/A	N/A	N/A
3	Flow meter	The construction material is not conforming to the requirements	M	Check construction material during IQ	H	L	M
		The setting is not correct and the measurement and indication are wrong	M	Check calibration certificates and perform loop tests during IQ. Establish an instrument testing and calibration SOP and check calibration of instruments and transmittersregularly	H	L	H

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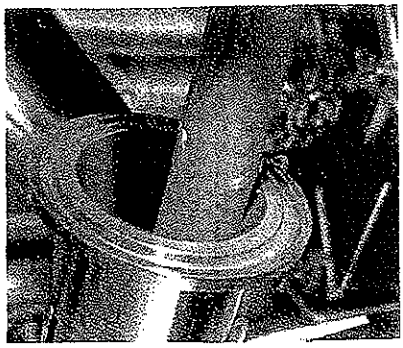
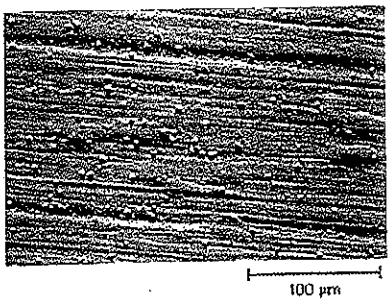


Fig9.1 Rouge



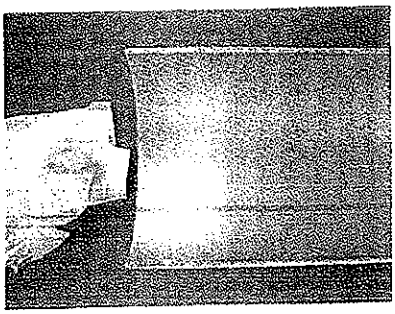


Fig9.2 Class I rouge



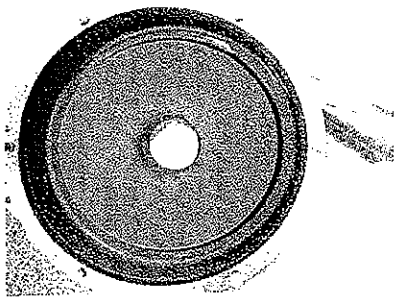


Fig9.3 Class II rouge

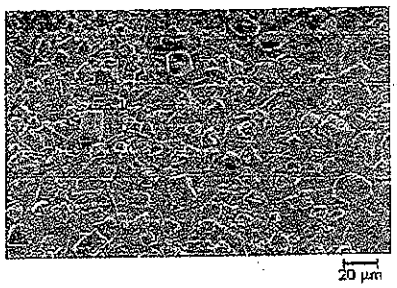


Fig9.4 Class III rouge



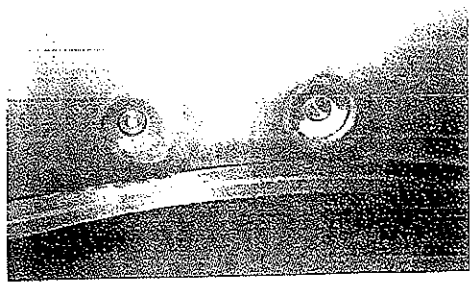


Fig9.10 Rouging due to chloride ion corrosion

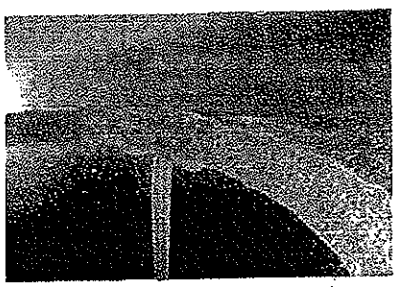


Fig9.11 Internal surface after derusting with the nitric acid method



Fig9.13 Residual liquid inside the pump cavity after halting

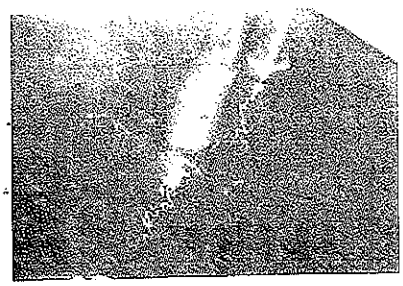


Fig9.14 WFI tank with a too high liquid level

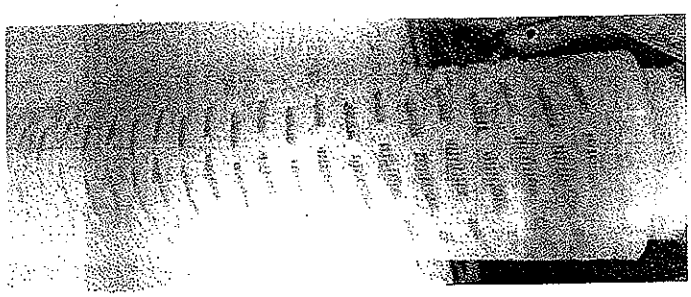


Fig9.17 Rouging on filter element

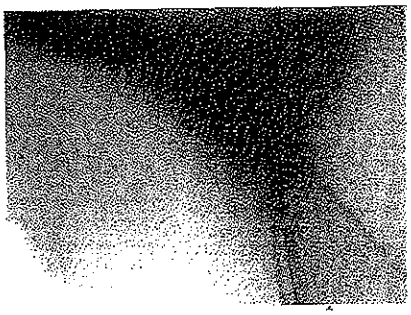


Fig9.19 Rouging in the Interior of a water distiller

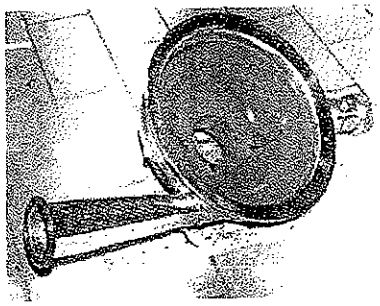


Fig9.20 Rouging of the pump cavity

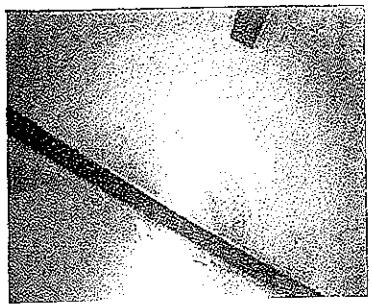


Fig9.21 Rouging of the sprayer

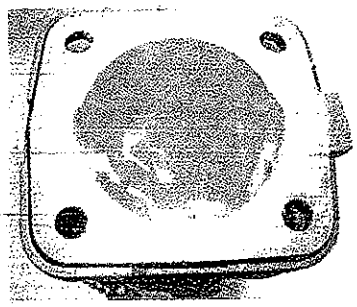


Fig9.22 Rouging of the diaphragm

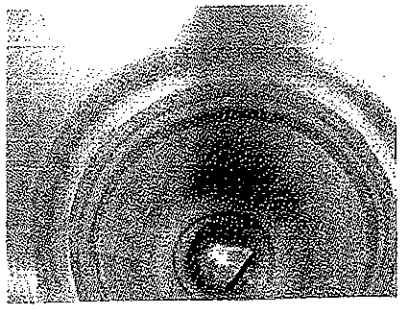


Fig9.23 Rouging of a pipe

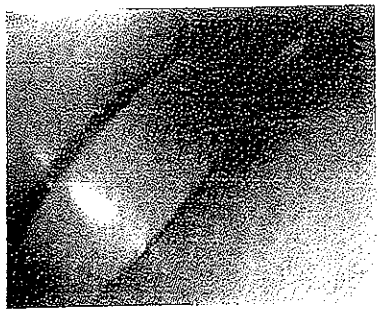


Fig10.13 Rouge remediation and passivation effects of citric acid



Fig10.14 Rouge remediation with hydrofluoric acid

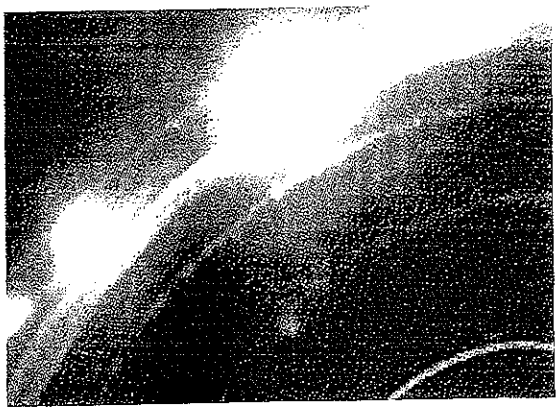


Fig10.15 Rouge remediation by CIP200



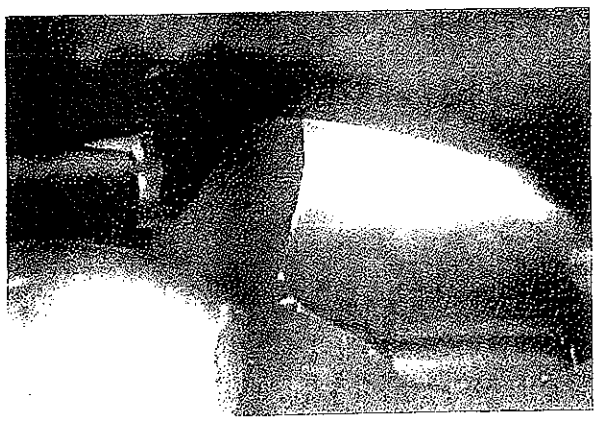


Fig10.20 Centrifuge pump chamber rouge remediation effects (water system)

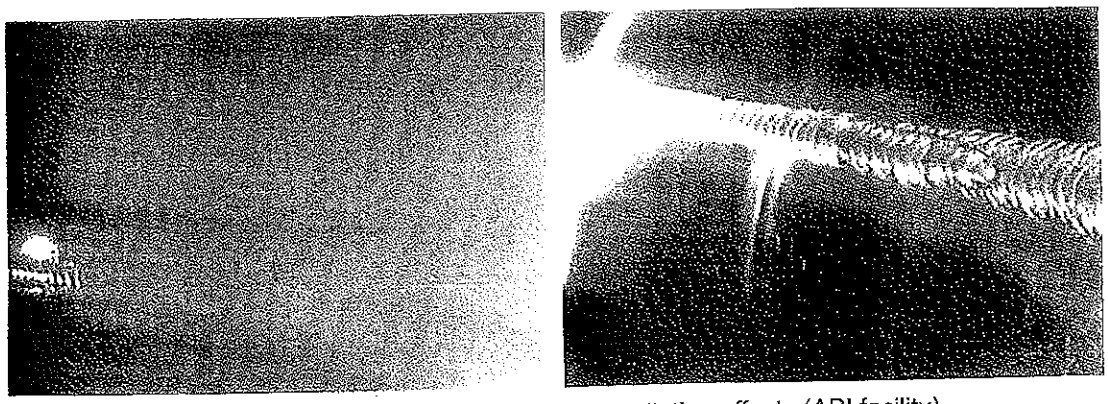


Fig10.21 User point loop rouge remediation effects (API facility)

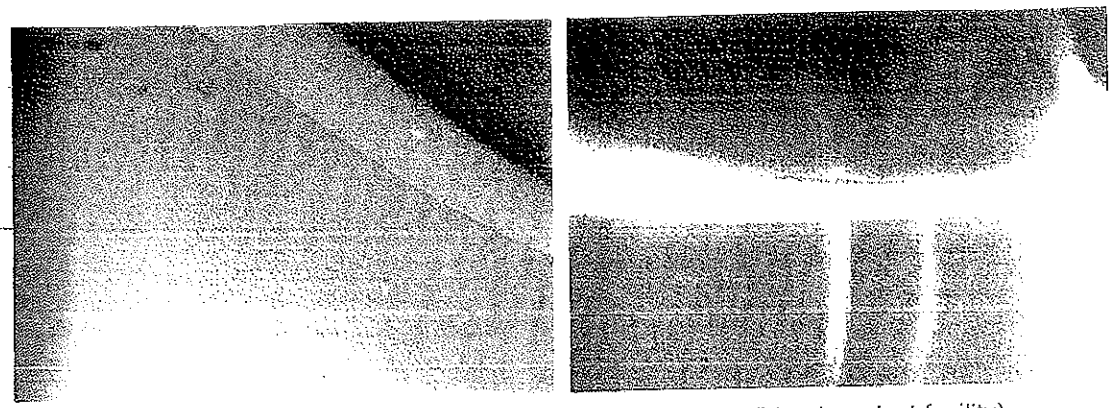


Fig10.22 User point loop rouge remediation effects (blood product facility)

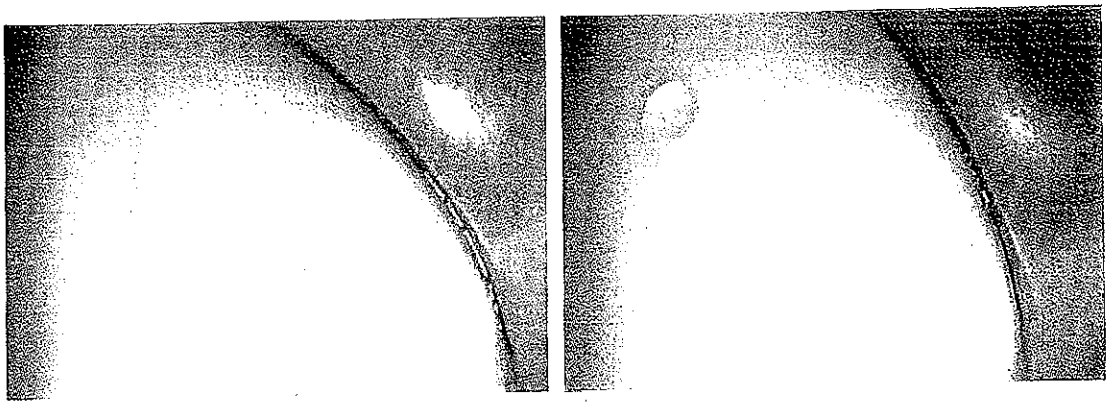


Fig10.23 Diaphragm valve diaphragm rouge remediation images

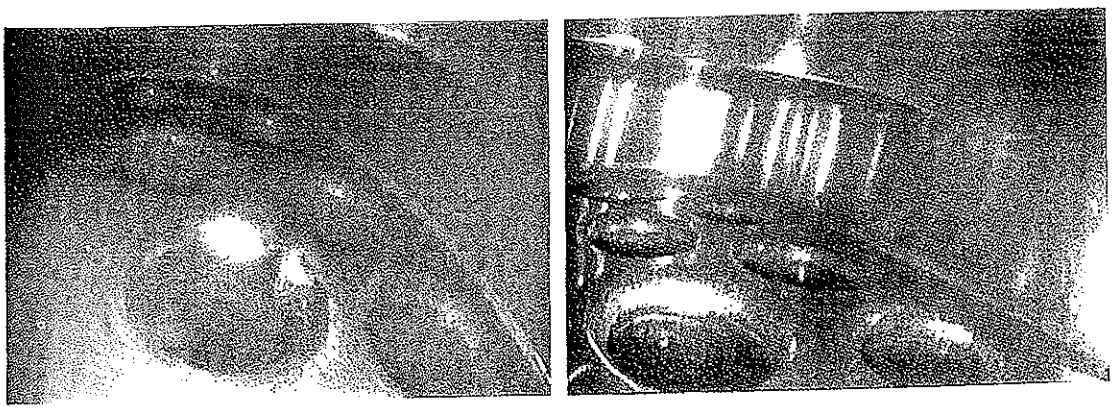


Fig10.24 Heat exchanger rouge remediation images

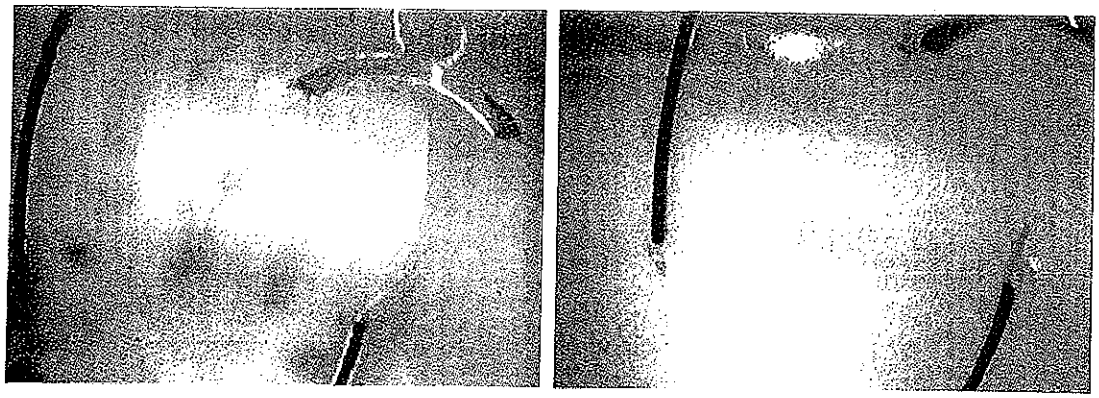


Fig10.25 Sprayer rouge remediation images

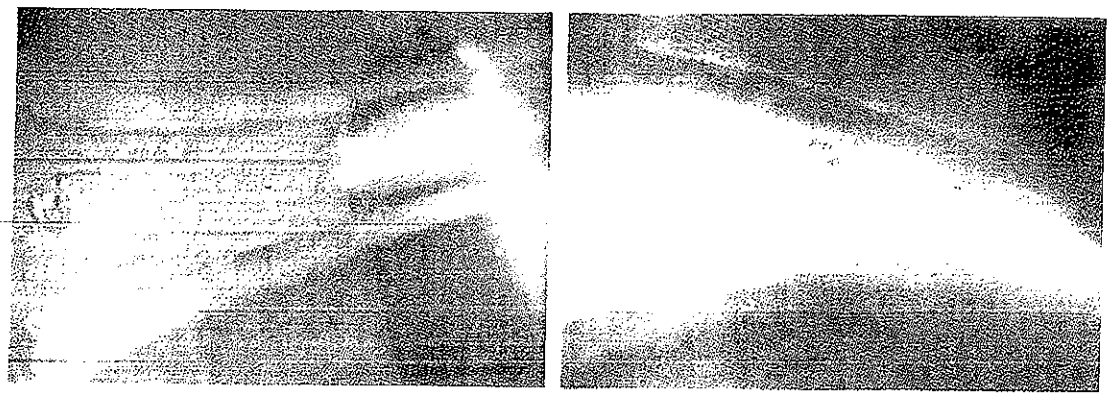


Fig10.26 Images of rouge remediation by the soaking method (pure steam system)

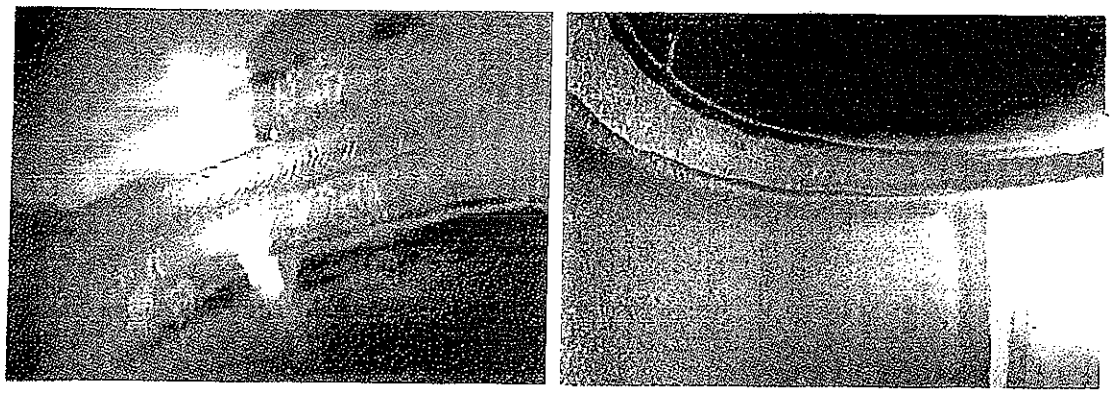


Fig10.27 Images of rouge remediation by the common circulation method (pure steam system)

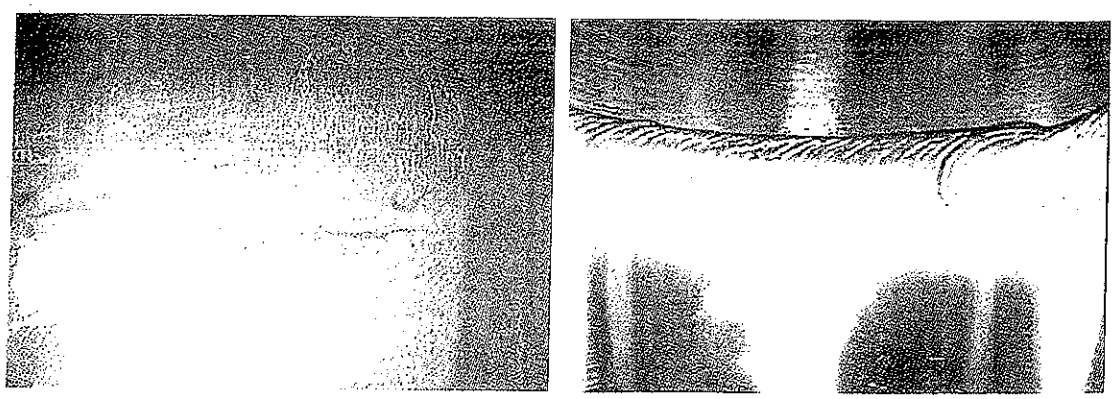


Fig10.28 Images of rouge remediation using the whole loop circulation method (pure steam system)

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