Pharmaceutical Engineering Guide for New and Renovated Facilities

Introduction

Background

The design, construction, validation (commissioning and qualification) of water and steam systems for the pharmaceutical industry represent key opportunities for manufacturers, engineering proffesionals, and equipment suppliers. These systems required to meet current Good Manufacturing Practice cGMP regulations while remaining in compliance with all other governing codes, laws, and regulations.

The cost of bringing these systems on line is highly variable, owing to interpretation of regulatory requirements and overly conservative design approaches. This guide is intended to offer a practical consistent interpretation, while still allowing flexibility and innovation.

This guide was prepared by ISPE, with feedback from industry representatives from all areas and disciplines, and comments provided by FDA. It reflects ISPE's current thinking related to engineering of new water and steam systems.

It is recognized that industry standards evolve, and this document reflects the understanding of them as of the publication date.

This guide is intended for the design, construction, and operation of new water and steam systems. It is neither a standard nor a detailed design guide. The validation of water and steam systems which comprises commissioning and qualification activities, will not be discussed in-depth in this guide. But is covered in the commissioning and qualification baseline guide.

The purpose of this guide is to focus on engineering issues, and provide cost effective water and steam systems. Where non-engineering issues (e.g. microbiological topics) are covered, the information is included to stress the importance of such topics and the impact they have on water and steam system design. Such non-engineering topics, therefore, are not covered comprehensively and specific advice from QA departments and technical experts must be sought where technical input is required.

Scope of this Guide

This guide is intended primarily for regulatory compliance for the domestic United States (US) market, and follow US standards and references. European and other non-US standards and references may be incorporated in future revisions.

SOME APPLICABLE FDA CURRENT REGULATIONS AND GUIDES FOR PHARMACEUTICAL WATER SYSTEMS

Food and drug cosmetic act

The United States pharmacopoeia XXIV

Title 21 CFR, part 211

FDA guide to inspections of high purity water systems

KEY CONCEPTS

The following key concepts covered in this guide are:

Methodology for defining the required water quality and configuring a water delivery system

Critical process parameters

Good engineering practices

Design options

a) Methodology for defining the required quality and configuring a water delivery system:

Perhaps the most critical step in a new pharmaceutical water or steam system, from a regulatory as well as technical and financial standpoint, is the specification of water or steam quality required. The specification established is likely to have a larger impact on lifestyle costs of the system than any of the subsequent design decisions; in addition, regulated industries must consider the costs of noncompliance and water system failures. Therefore, it is essential for the designer to seek advice from the quality unit and technical experts early in the process.

One process water and/or steam requirements are determined; system design options need to be addressed. This guide presents alternative baseline water and steam system building blocks top permit reliable and consistent generation of the required water or steam quality.

b) Critical process parameters:

Critical parameters are defined as those parameters that directly affect the product quality. For example, since microbial quality cannot be directly monitored in real time, the parameters relied upon to control microbial growth is normally considered critical. These may include temperature, UV intensity, ozone concentration, circulating systems under positive pressure etc. in regard to chemical purity, the quality attributes themselves (properties of water produced), may be monitored at or after each process step and the proper performance of that operation confirmed directly. For a system producing compendial water, properties mandated in the official monograph obviously constitute critical parameters.

Critical instruments are those instruments that measure critical quality attributes. This concept is discussed in chapter 2 and used as a basis for subsequent chapter discussions where appropriate.

c) Good engineering practice (GEP)

GEP recognizes that all systems in a facility, whether they are water systems, steam systems, elevators, process reactors, safety valves, or rest rooms, require some form of commissioning and/or qualification.

Nearly all systems require documentation, inspection, and field testing. Good engineering practice capitalizes upon this practice suggesting that manufacturers engage all stakeholders (engineers, operators, quality assurance, and others) very early in the planning, design, construction, commissioning/qualification phases to ensure that systems are documented only once.

d) Design options:

The guide emphasizes that a water system can be designed in many different ways, yet meet the overall requirements of the system. It encourages a well-thought-out planned approach to the design with input from many areas of the organization including quality assurance.

Guide structure

The structure of the guide is shown in figure 1-1 below. The chapters have been organized to assist in a logical decision process to determine the type of water required and the system design needed to provide it.

KEY DESIGN PHILOPSPOPHIES

Introduction

Pharmaceutical water is the most widely used ingredient in drug manufacturing and the main component in equipment/system cleaning. Therefore, systems for the production of pharmaceutical water constitute a key component in every manufacturing facility. The nature of producing pharmaceutical waters is to minimize or eliminate potential sources of contamination. This guide considers this and the means by which engineers can design out, or ensure control of the risk.

The quality of pharmaceutical water and steam is not only critical from a regulatory point of view, but also from a financial point of view. The pharmaceutical water and steam specification has the largest impact on lifecycle costs of the system.

It must be demonstrated that all pharmaceutical waters (non-compendial and united states pharmacopoeia (USP) monograph compendia waters) can be produced consistently to specification. Establishing the level of microbial control needed in a pharmaceutical water and steam system used in manufacture of non-sterile product requires an understanding of both the use of the product and the manufacturing process.

Manufacturers need to define the appropriate water purity based upon sound process understanding and system equipment capability. They must determine the specific purification capability for each processing step, the limitations of the unit operation, and the critical parameters, which affect the specified water/steam quality-chemically, physically, or biologically. Expert QA advice should be sought to provide further details about this important area.

USP covers two compendial water qualities (USP purified water and USP water for injection). This guide supports both these water qualities plus additional non-compendial waters including “drinking water”. It is common practice to name non-compendial waters (exclusive of drinking water) used in pharmaceutical manufacturing by the final treatment step (i.e. Reverse osmosis/ro water, deionized water/di water. Etc.

Guidance on establishing specifications for monographs USP water is provided in the United States pharmacopoeia (USP). Additionally, the FDA guide to inspections of High purity water systems (which was developed for FDA personnel) also provides used information to the user.

UNITED STATES PHARMACOPOEIA (USP)

USP is a guide to producing medicinal products for consumption within the US. USP specify standards of quality, purity, packaging, and labeling for a number of waters including two bulk waters, “Water for injection” and “purified water” used in the preparation of compendia (USP) dosage forms. This guide is concerned with the production of these two compendial (USP) waters and does not address the other “packaged waters” monographed by the USP. USP 24 (and supplements) is the current version, at the time this guide was prepared

USP PURIFIED WATER

Official monograph requirements for “purified water” require that “purified water” Is obtained from water complying with the US environmental protection agency national primary drinking water regulations, or comparable regulations of the European union or japan, and will be referred to subsequently as “Drinking water” Contains no added substance.

KEY DESIGN PHILOPOHIES

Is obtained by a suitable process

Meets the requirements for water conductivity

Meets the requirements for total organic carbon (TOC)

USP WATER FOR INJECTION (WFI)

Official monograph requirements for “water for injection” require that ‘water for injection”

Meets all of the requirements for “purified water”

Is obtained by a suitable process and purifies by distillation or Reverse osmosis

Meets the requirements of the bacterial endotoxin test and contains not more than 0.25 USP endotoxin unit per ml

Is prepared using suitable means to minimize microbial growth

NON MONOGRAPHED BUT ACCEPTED REQUIREMENTS

The usp “general information” provides background information, which clarifies regulatory intent. The following information is included in chapter 11:

Purified water systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use

Water for injection is “finally subjected to distillation or Reverse osmosis”, implying that the still or RO unit is the last unit operation. “The system used to produce, store and distribute water for injection must be designed to prevent microbial and the formation of microbial endotoxins and it must be validated.

An action limit of 100 colony forming unite per mi * 10,000 CFU/100ml) for “purified water” is suggested.

An action limit of 10 colony forming units per 100ml (10cfu/100ml) for “water for injection” is suggested

Minimum sample sizes are 1 ml for USP purified water and 100 ml for WFI. (FDA Recommends 100 ml for purified water and 250 ml for WFI)

Note: “it should be emphasized that the above action guidelines are not intended to be totally inclusive for every situation where ingredient waters are to be employed. It is therefore, incumbent upon the

manufacturer to the supplement the general action guidelines to fit each particular manufacturing situation" [USP24 page 2163]. When designing a pharmaceutical or medical device water systems, it is critical for the designer to consult with the manufacturers technical experts to ascertain what purity levels must be achieved.

Three Stage Conductivity Testing

Stage	Method of measurement	Acceptance criteria
One	Use in-line or grab sample and measure the conductivity and operating water temperature	Use the stage 1 table from the latest revision to USP to determine the conductivity limit
Two	Retest at least 100ml of the stage 1 grab sample for conductivity after vigorous mixing and temperature normalization to 25 degrees C ±1 degrees C	When change does not exceed a net of 0.1 µs/CM over 5 minutes, measure the conductivity. If less than 2.1 µs/cm the water meets the requirements.
Three	If the stage 2 test does not meet the requirements, retest the sample within 5 minutes while maintaining temperature. Add 0.3 ml per 100 ml of saturated potassium chloride solution and determine the pH to the nearest 0.1 pH unit.	Use the stage 3 table from the latest revision to USP to determine the conductivity limit. If either the measured conductivity is greater than the limit value of the pH value is outside the range of 5 to 7, the water does not meet the requirements.

CONDUCTIVITY INSTRUMENT REQUIREMENTS FOR ACCEPTABLE REGULATORY MEASUREMENT

Temperature measurement	±0.25 degrees C accuracy	Resolution <±0.1 µS/cm
Conductivity cell constant	±2% degrees accurate	Reading accuracy <±0.1 µS/cm
Location of In-line meters	Must reflect the quality of the water used. Typically the optimum location in a distributed water loop is following the last "point of use" valve, and prior to the storage tank return connection.	
Instrument type	The above procedure is based on the use of a "dip" or "flow through" conductivity cell. Conductivity readings used to control USP compendial waters must be non-temperature-compensated measurements	

TOTAL ORGANIC CARBON (TOC) AND REQUIREMENTS FOR TOC CONTROL

TOC is an indirect measure, as carbon, of organic molecules present in high purity water. USP replaced the USP replaced by USP 22 “oxidizable substance” wet chemistry test with an In-line capable, TOC test. A limit was determined by USP to be 0.5ppm or 500ppb, based on the results of studies and an industry wide survey of pharmaceutical water systems.

SYSTEMS AVAILABLE FOR MEASURING TOC

instruments are available for measuring TOC in-line slipstreams and from grab samples manually removed from the water system. Automatic Off-line sample introduction systems are available for processing large numbers of grab samples. USP have not prevented acceptable technologies from being used, but limit the methods to the following instruments that are capable of completely oxidizing the organic molecules to carbon dioxide (co2) measuring the CO2 levels as carbon, discriminating between inorganic carbon (IC) and the CO2 levels generated from the oxidization of the organic molecules, maintaining an equipment limit of detection of 0.05 mg per liter, or lower, and periodically demonstrating an equipment “suitability”.

A number of acceptable methods exist for measuring TOC in high purity water. All share the same basic methodology, the complete oxidation of the organics to CO2 and the measurement of this CO2.

Three general approaches, based on the above concept are used in a variety of commercially available instruments, which measure organic carbon in a water sample by completely oxidizing the organic molecules to carbon dioxide (CO2) and measuring the co2 levels as carbon. Four common oxidation methods and four common Co2 measurement methods are used in different combinations in these TOC analyzers. The total carbon (TC) result may be expected to include inorganic carbon resulting from dissolved CO2 and bicarbonate which must be subtracted from the TC to produce the Total organic carbon level in the sample. Some TOC analyzers remove the inorganic carbon (IC) by acidifying the samples and either gas stripping or vacuum degassing the CO2. In pharmaceutical waters the IC levels are generally very low and IC removal processes are not usually required

TYPES OF TOC ANAYLZERS

Laboratory instruments

In-line instruments

Laboratory instruments capable of operating in-line

When usp accepted the well-proven technology for measuring TOC, they apply laboratory quality control procedures to its application. While these techniques are common in a laboratory for setting wide range equipment for measurement over a specific range, they place unusual limitations on in-line TOC applications. TOC instruments must be:

Maintained calibrated to ensure reliable and consistent readings

Periodically checked for “suitability”

Standardized

May be used in-line or off-line

If installed in-line, the instrument must reflect the quality of water used

OUT OF RANGE EXCURSIONS

out of range readings may be experienced as the direct result of the above types of organic contaminations. Spikes may also occur as the result of extraneous electrical interference etc. all spikes must be identified and formally explained

Procedures to handle out of range spikes should be available. These procedures should address short duration spikes, which occur following continuous acceptable readings and are followed by similar acceptable readings, specifically in in-line applications. Procedures should list the potential sources and allow the acceptance of such a spike without further investigation if the spike is preceded and succeeded by a number of acceptable readings.

Unexplainable spikes may be minimized when using in-line batch sampling systems by extending the sample analysis period 30 to 60 minutes rather than using shorter analysis periods. This technique measures more sample in a longer time period, allowing the recorded result to be based on statistical analysis over the extended time period.

Table 2-1 IN LINE COMPARED WITH OFF LINE TOC MONITORING

	In –line	Off-line
Features	Monitor should include built in alarms and be programmable in respect to the “out of spec.” excursions should have convenient method of conducting limit response and suitability tests	Laboratory instrument should be capable of achieving robust oxidation levels and should include automatic off line sample introduction systems, for processing large numbers of grab samples. A generous supply of scrupulously clean polymer based sample containers is required. Laboratory instruments will require reagents and carrier gases
Installed cost	Medium, based on above features and a single installed unit. High, if multiple units are installed.	High, based on above features
Operating cost	Low to high, depending on instrument capability for suitability and limit respond	High

	testing and the number of instruments installed	
Recommended test frequency	4 to 48/day The recommended frequency is based on the specific system requirement for trending or concern for “out of spec”. excursions and their subsequent investigations. See paragraph on “special requirements”.	1/shift
Frequency of suitability and limit response	Based on documented history	1/shift

USP 23 MICROBIAL AND ENDOTOXIN TESTING

Microbial contaminants and endotoxins are traditionally sampled at the points of use in a water system.

USP 24 has made no changes in this area.

USP 23 pH TESTING

Testing water for compliance with the USP 24pH limits is required as part of the stage 3 off-line conductivity testing. (pH must be confirmed as being in the range of 5 to 7.) Testing may use calibrated off-line meters. Calibration should be performed using solutions of a known pH, covering the range of 5 to 7. The frequency of calibration should ensure that the levels of accuracy are maintained. Refer to manufacturer for specific recommendations on both method frequencies.

VALIDATED BACKUP INSTRUMENTATION

Failure of monitoring instrument should not be precluded when making decisions concerning type, location and the extent of validation. Since each excursion from the acceptable limits must be investigated, in-line installations should be supplemented with a calibrated laboratory instrument as backup. Validation should include the operation in off-line mode as a supplement or alternate to in-line instrumentation. Off-line laboratory testing should include a backup instrument to be maintained calibrated in case of failure of the primary unit.

SPECIFICATION OF PHARMACEUTICAL WATER QUALITY

Specifying water quality:

The quality of water supplied in any pharmaceutical process must be consistent with the quality required for the final product. It may not be sufficient to specify a water quality that meets the specification of the two compendial grades of water outline in the USP. These grades, USP Purified water and WFI, are minimum standards. A more stringent specification could be required depending on the intended use of the product and on the process used to manufacture that product. It is the responsibility of each drug manufacturer to establish the logic for their water quality specification based on the required quality of the end product.

Pharmaceutical water uses can be categorized as:

An ingredient in a dosage form manufacturing process

An ingredient in an Active pharmaceutical ingredient (API) process (the term API is used interchangeably with BPC, meaning bulk pharmaceutical chemical).

Equipment cleaning or rinsing

Water intended for use as a dosage form ingredient must be USP monograph water and must be produced consistently to specification. Evidence of control is required for all critical process parameters that may affect the final drug characterization. USP WFI water would be expected to be used for parenteral manufacture some ophthalmic and some inhalation products.

The monographs for USP purified and WFI compendial pharmaceutical waters stipulate the baseline requirements for water used in production, processing, or formulation of pharmaceutical activities.

For some applications where there are no requirements for compendial waters, the manufacturer may establish quality specifications equivalent to USP-WFI or purified waters, depending on the specific application.

Specifications for water used as an ingredient (exclusive of sterile bulks) in the manufacture of API or as the wash solvent in the wash or rinse cycles must be determined by the manufacturer. In some cases “drinking water” may be acceptable, or certain chemical or microbial or endotoxin quality specifications may be established, or one of the compendial waters may be used. The specification should be based on the potential for contamination of the final drug product. Any decision about water usage must be made with the approval of quality assurance.

With the appropriate justification, non-compendial pharmaceutical waters (including “drinking waters”) may be utilized throughout pharmaceutical operations including production equipment washing/cleaning as well as rinsing, laboratory usage and as an ingredient in the manufacture of formulation of bulk active pharmaceutical ingredients. Compendial water must, however, be used with preparation of (as an ingredient) compendial dosage forms. In both compendial and non-compendial waters, the manufacturer must establish an appropriate microbial quality specification per the FDA “guide to inspections of high purity water systems.” The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product and the nature of the product and the potential harm to the user. Manufacturers are expected to establish appropriate microbial alert and action levels for microbial counts associated with the types of pharmaceutical waters utilized. These levels must be based on process requirements and the historical record of the system in question. The US pharmacopoeia states action levels that are generally considered acceptable are 500CFU/ml for drinking water, 100 CFU/ml for purified waters, and 10 CFU/100ml for WFI, and may be more stringent depending on its use. Microbial system design considerations are discussed later (see chapter 8)

The user should consider whether microorganisms in pharmaceutical water could threaten product preservation or product stability, or whether water may contaminate product with pathogenic bacteria or endotoxins. Specific microbiological objectives and standards suitable to the needs of the products manufactured must be defined. A water system must see these objectives and a monitoring program must be established/implemented to document that the standards are consistently being met.

Engineers involved in water system design must understand the chemical and microbial quality attributes in the water delivered to use points.

The final quality of pharmaceutical water and steam is determined by the manufacturing process and end product, quality of feed water, pretreatment and final treatment sub-systems, storage and distribution system design and operator/maintenance procedures. Expert QA advice should be sought out to give further details about this important area.

CRITICAL PROCESS PARAMETERS

Critical parameters are defined as those parameters, which directly affect the water quality at, or after, a treatment step. For example, water temperature during a heat sanitization cycle has a direct effect on water quality.

Regarding chemical purity, the quality attributes may be monitored at or after each critical process step, and the proper performance of that operation confirmed directly. Since microbial quality cannot be directly monitored in real time, the parameters relied upon to control microbial growth are usually (depending on the system) considered critical, such as temperature, UV intensity, ozone concentration, circulation rate, sanitization procedures, positive pressure, etc.

For a system producing compendial water, properties mandated in the official monograph (including bio burden and endotoxins) constitute critical attributes. Critical instruments are those instruments, which measure critical attributes or parameters.

cGMP COMPLIANCE ISSUES

satisfying regulatory concerns is primarily a matter of establishing proper specifications, and using effective and appropriate methods to verify and record that those specifications are satisfied. Issues such as quality of installation, sampling and testing procedures, operating and maintenance procedures, record keeping, etc. often have a greater significance than the particular technologies selected to purify and distribute the water.

Fundamental conditions expected to aggravate a microbial problem typically include system design conditions such as stagnant conditions, areas of low flow rate, poor quality feed water etc.

- Measures to alleviate such problems include:
- Continuous, turbulent flow
- Elevated or reduced temperatures
- Smooth, clean surfaces that minimize nutrient accumulation
- Frequent draining, flushing or sanitizing

- Flooded distribution loop (maintenance of positive distribution loop pressures)
- Properly designed, installed and maintained system

While the control of chemical quality is important, the primary challenge in a pharmaceutical water system is maintaining the microbial quality. The industry and the regulatory community have recognized the effectiveness of maintaining a continuously recirculated system at high temperatures (65 degrees C-80 degrees C) in preventing microbial growth. Distillation has a long and well-documented history of success, but need not be the only technology considered for producing water with endotoxin limits. Reverse osmosis is the only other technology accepted by the USP for WFI. Ultrafiltration has been successfully used to produce waters with strict endotoxin limits that meet WFI attributes, but it cannot, by regulation, be used to produce compendial grade WFI>

Each pharmaceutical steam and water treatment system must be viewed in its entirety, as design and operational factors affecting any unit operation within the system can affect the whole system. It is useful to identify both quality parameters of water entering the system and the quality parameters of the water or steam to be produced. Water quality should be enhanced with each successive step. It does not necessarily follow that measures enhancing one quality attribute (such as conductivity, particulate level or color) will always enhance another (such as microbial population)

DESIGN RANGE VERSUS OPERATING RANGE

This guide recognizes the distinction between “Design Range” and “Operating range” and the impact this distinction has upon validation and facility system operation. These criteria are defined as:

Design Range: the specified range or accuracy of a controlled variable used by the designer as a basis to determine the performance requirements for an engineered water system

Allowable Operating Range: the range validated critical parameters within which acceptable product water can be manufactured

Normal operating range: a range which may be selected by the manufacturer as the desired acceptable values for a parameter (i.e. conductivity) during normal operations. This range must be within the allowable operating range.

a) While a water or steam system should meet all stated design conditions, the acceptability of the system for operation from a cGMP standpoint depends on operating within the allowable operating range.
b) Performance criteria for a pharmaceutical water generation system may require a final product water quality conductivity of 0.5 µS/cm. (2mohm-cm) or better as a design condition. The allowable operating range for this pharmaceutical water may, however allow for generation of water quality with conductivity of 1.3 µS/cm (o.77 mohm-cm) or better. The normal operating range for generating water may, in the end, be set by the manufacturer at conductivity value approaching 1.0 µS/cm. (1.0 Mohm-cm) or better to provide a comfortable environment for the operation.

c) Normal operating range cannot exceed the allowable operating range for the product water. The design condition selection should reflect good engineering practice.
d) It is also good practice for manufacturers to apply the concept of alert and action limits along the normal operating range. Alert and action limits should be based on the actual capability of the system. Alert limits are based on normal operating experience and are used to initiate corrective measures before reaching an action limit, which is defined as the process condition established by product acceptance criteria, the action limit deviations must be kept as a part of the batch record as they represent deviations from validated parameters.

Values of critical parameters for product water

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WATER OPTIONS AND SYSTEM PLANNING

INTRODUCTION

This chapter outlines basic water system design criteria, and along with subsequent chapters, aims to provide a better understanding of pharmaceutical water, how it is used, and how it can be provided. The primary goal of this chapter is to provide the user with a methodology for:

Evaluating water quality options for product manufacturing

Evaluating basic system configurations available to provide the water

Detailed information on unit operation design, maintenance and cost factors is addressed in later chapters.

The chapter also outlines the system planning effort for pharmaceutical water systems. This planning starts with the selection of water quality based upon product requirements, processing operating's, and end use. A decision tree concept is included to assist in selection of compendial and non-compendial waters for production, cleaning, and support. The program then provides steps to guide the user through a use-point and system analysis, to set-up the water system distribution strategy. Finally, evaluation points are provided for the selection of the primary system configurations.

WATER QUALITY OPTIONS

Quality requirements for water used in pharmaceutical manufacturing and product development are driven by the product characteristics, manufacturing processes, and the intended use of the product. To aid in the water selection process, the USP monographs define minimum requirements for general types of pharmaceutical water used in almost every pharmaceutical application. However, there is also the opportunity for a manufacturer to determine water quality requirements, different from those in the USP, based on specific product characteristics and processing operations. If this option is taken, the product manufacturer is responsible for assuring that water used to manufacture the product is appropriate, to reliably produce safe product.

Though water quality requirements are product specific, it is impractical to reliably produce special water that is specific to each situation. Manufacturing operations typically generate and distribute only a few, or perhaps just one, quality of water. Therefore, products and operations requiring similar water qualities are commonly grouped. The most common segmentation is that defined in the USP.

Manufacturers agree that in many if not most cases, the requirements defined in the USP are adequate for production of safe product. More stringent water quality specifications may be appropriate for some products and processes. Others may be appropriately less stringent. Typically more stringent requirements may apply to some processing operations involving significant concentration steps or products comprised of high water content, which may be applies in large volume doses. Likewise, processes involving reliable sterilization and purification steps which remove impurities, may in some

cases, not require water qualities as strict as those defined in the USP. Other process characteristics can affect water quality requirements as well.

In manufacturing operations with only one quality of water, the water system must be designed to meet the most stringent requirements of the most demanding product or process. With more than one quality of water, products and processes are often a function of volume of water consumed and variation of quality. Large consumers may find it economical to generate and distribute multiple grades of water, while small users often will general only one quality of water.

The three main categories of water used in pharmaceutical manufacturing are:

- Drinking water: meeting EPA national primary drinking water regulations. In figure 3-1 drinking water is included in the category suitable non-compendial
- Compendial water: meeting the compendial requirements for specific types of water in USP monographs (i.e., purified water USP, water for injection USP)
- "Suitable" non compendial process waters: meeting the requirements of drinking water, but with additional treatment to meet process requirements. It may, or may not, contain added substances for microbial control and does not have to meet full compendial requirements for USP water. In this guide, we name the non-compendial process waters used in manufacturing by the final/major process step (i.e., reverse osmosis-RO water, deionization-DI water etc.)

Non compendial water is not necessarily less critical, or less costly to produce or to qualify, than compendial water. It can enable the manufacturer to set product specific quality and/or test criteria that are appropriate for the specific product and processes.

Generally, more highly purified water is more expensive than less purified water. However, the specifics of each operation are different. For example, a plant with existing excess capacity of WFI might elect to use WFI over other grades even when unnecessary. In the example case, documentation defining water quality should identify the quality required for the product and why the WFI was used instead.

Figure 3-1 provides the framework of a diagram that can be developed by a manufacturer to show the requirements for water used in the pharmaceutical manufacturing processes. This diagram should be accompanied by documentation supporting the options chosen, with review and approval of quality assurance. The options chosen should be based on product and process specific requirements. Ultimately, water supplied to any process must meet or exceed requirements, as defined by the manufacturer, for the safe and reliable manufacture of that product.

Figure 3-1 provides an overall summary of water requirements for a manufacturer supported by the necessary justification for specific products, processes, and areas. It is almost impossible to provide one generic decision tree due to the diversity it would have to cover.

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Note: commitments made in drug applications override suggestions of this decision tree.

Notes:

1. By test procedure definition, some analytical methods require USP compendial waters. Quality should meet the needs of the analytical methods
2. Labs performing both cGMP and non-cGMP operations should follow the cGMP path.
3. Non-compendial water may be more highly purified than compendial water. Endotoxin and microbial quality is based on the process and quality standards of the product. Non-compendial water must at a minimum meet EPA (or comparable EU or Japanese standard) drinking water requirements for microbiological quality
4. Quality of final rinse water is determined by the type of product and subsequent processing steps. Where product contact surface is subsequently sanitized, final rinse with Suitable non-compendial water may be acceptable. Such practice may necessitate more stringent qualification criteria for the subsequent sanitization steps
5. Where product is purified downstream
6. More stringent endotoxin requirements (e.g., WFI quality) should be employed for water used in the final purification step for NON-sterile parenteral grade APIs

Figure 1-1 provides "baseline" requirements for most product contact water applications. Water quality criteria for pharmaceutical manufacturing and product development are driven by the product characteristics, manufacturing process, and the intended use of the product. Specific product and process characteristics may dictate that more or less stringent criteria than shown are appropriate. Figure above gives engineers some general guidance on selection of pharmaceutical water selection.

Once water needs are determined based on usage, table identifies common design options for various types of pharmaceutical water in the industry. The order of components and actual installed equipment varies widely throughout the industry. Primary criteria in evaluating the options are:

To have suitable specification for water criteria (i.e., it must be adequate for the process and product)

To produce water consistent in composition and quality

To monitor key performance indicators for assurance that specifications are met.

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COST IMPLICATIONS

Determining the economics of pharmaceutical/medical device water production is complex. Costs are quite predictable, but vary greatly depending on scale of operation, system design, actual usage, etc. the total operating cost to produce pharmaceutical waters is obtained by adding the cost of feed water to the costs of pretreatment (e.g., media filtration, carbon filtration, softening, and chemical addition) and final treatment (e.g., primary iron removal and polishing.)

Other significant costs should be anticipated for validation, ongoing QA/QC, as well as waste treatment and sewerage. In addition, regulated industries must consider the risks (cost) of noncompliance and water system failures. Municipal feed water ranged from $1-3 per thousand gallons with even wider

variations outside of the U.S. feed (surface or ground) water quality, generation technology and its associated capital cost, and product water specifications are then utilized to determine the total pharmaceutical water system net present value (NPV). The type of pharmaceutical water system design option selected is typically based on feed water total dissolved solids and hardness levels, organic and colloidal content, as well as anticipated water system utility costs (acid, caustic, and salt, power, and source water.) consideration should also be given to maintenance requirements and available resources.

Although water treatment systems for generating either compendial (USP purified) or non-compendial pharmaceutical process waters significantly vary in the system operational costs, NPV for each of these various types of process waters are quite similar. The only exception is DI process water generated through the use of a non-generable mixed bed bottle system, typically generated off site. However, membrane based systems do marginally produce the lowest net present values for pharmaceutical water generation. The NPV analysis is usually based on the water system capital cost and a five-year system operating cost. The period chosen has to be long enough to allow operating cost to be a significant factor, but short enough for reasonable analysis of operating cost returns versus increased capital expenditures.

Cost savings opportunities can be found in other places than just the quality of water and method of generation. Wastewater from the pretreatment or treatment systems can often be used for miscellaneous loads saw as lawn irrigation, humidification, boiler feed, etc. Each chapter of this guide also addresses cost savings issues based upon design criteria and approach for independent unit operations and systems.

SYSTEM PLANNING

High purity water and steam are the most widely used, and often the most expensive raw material or utility in a pharmaceutical facility. Improper sizing or selection of a steam or water system could limit or even shut down production if under sized; or comprise the reproducible quality and increase the capital cost If oversized however, system sizing is not the starting point in design. Proper definition of water quality requirements and usage can save construction as well as operation costs.

Figure 3-2 shows a graphic representation of the system boundaries, limitations, and restrictions the designer faces when planning a pharmaceutical water system. Initial system planning reveals primary boundaries that establish the cornerstone for design criteria. These primary system boundaries are water quality, use-point criteria, and system criteria.

During initial planning, the limits of each boundary need to be established. The arrows encircling each boundary represent limitations that establish more specific operating strategies and ranges. When documenting these limitations, the designer should always indicate ranges of acceptability, rather than a specific value or position. This allows more flexibility in final planning and detailed design decisions.

The reality of certain restrictions will sometimes force a specific strategy. As long as the decision leads to an answer that is within the limits of the system boundaries, this is perfectly acceptable. An example is a facility where the use-point criteria require non-compendial water with microbial control. However, there happens to be an oversized WFI system in an adjacent area, so the designer decides to provide

WFI to the use-point. In the example case, documentation defining water quality should identify the quality required for the product and why the WFI was used instead.

The primary emphasis of this section is to outline a systematic approach to planning a pharmaceutical water system. Figure 3-2 outlines a planning methodology that begins with the selection of water quality, given its own system and constraints and limitations. Then the use point criteria are established, followed by an initial system planning exercise. Often, these sequential steps are repeated as information in the design process iterates, and further criteria about the overall system boundaries are identified.

INSERT TABLE BRUCE

ESTABLISH WATER QUALITY

the first step in evaluation of water systems is the selection of water quality required for the specific product and process operation. Selection is based primarily on the dosage and form, and the microbiological and chemical purity criteria set for the product for which the water is used. The selection must consider underlying factors that have impact on quality control; installed and operating cost; maintenance and practicality

See section 3.2 in establishing possible water quality via development of the decision tree. Making notes as the water quality is designated for each use-point, indicating the basis for each decision. Simple annotations from the supporting documentation will be useful in later stages of the planning process. System design constraints may provide the motivation to challenge water quality or other criteria, particularly when it can be demonstrated that the change does not affect product quality or manufacturing controls.

CHARACHTERIZE USE POINT

Once the initial selection of water has been established, the operational criteria should be characterized for each use point. A matrix should be developed to outline the primary criteria required for system design.

Each use point should be annotated with the proper values for pressure, flow, and the temperature range of water entering unit operation, or process point from the water supply system. Establishing a range, rather than a fixed value, increases opportunities for a system optimization by allowing a more flexible approach to final design.

This data can be organized in many ways, but a well-planned spreadsheet can simplify the planning process and provide clear decision pathways for future detailed design activities. Table 3-1 shows an example of a spreadsheet used to characterize use-point flow and system demand. Flowrate is primarily used to size lines, whereas daily use leads to storage and generation decisions. The diversity factor is one way to level-out anticipated usage, assuming that not all loads happen every day or at the same time. This table indicated a clean in place (CIP) system and stopper-washer that are both likely to be used on the same day, but never at the same time. Therefore, only the higher flowrate is relevant to

loop sizing as show in the design flowrate column. Demand flowrates are eventually used for branch line sizing.

Table 3.2. Use Point Criteria

Equipment name	Flow rate	Daily use					comments
	Demand	Diversity	Design	Demand	Diversity	Design	
	(lpm)	Factor	(lpm)	(lpd)	factor	(lpd)	
CIP washer cycle	40.0	1	40.0	1200	1	1200	Assume in a recirculating cycle in 4 steps for a total of 23 minutes
Stopper washer	20.0	0	0.0	460	1	460	Assume one cleaning cycle per day, 100 liters/rinse, 3 rinse/cycle, 1 overflow rinse/cycle @2 LPM for 80 mins

Once the location and qualities are finalized, the various properties can be charted on a requirements analysis histogram. This can be done with the aid of a computer and either simulation or spreadsheet software for larger systems, or done manually for small systems. At this point, basic process flow diagrams also provide a good pictorial view of the water qualities. Locations and the point-of-use properties.

(INSERT CHART HERE BRUCE)

ESTABLISH SYSTEM CRITERIA

Histogram analysis is beneficial for determining overall system peak demand(s), average demand, and the relationships between peak demand time periods and their flow rates. Figure 3-4 below shows a hypothetical storage tank profile using 24 hour demand profile from figure 3-3

There is no “rule of thumb” for minimum water level, or the optimum water level to turn on a still. However, these charts provide the tools for creating various scenarios to simulate recovery times from a failure, future expansion or reduction capabilities and analyze other factors that allow design of a properly sized water generation, storage and distribution system.

System planning and analysis also reveals other restrictions that influence design, and often lead the designer to re-evaluate the primary boundaries as discussed earlier. These restrictions might include items such as:

- Must the system be available at all times?
- What are the constraints on a shut down?
- Is the plant/personnel able to handle chemical’s properly? Are permits in place?
- Is production batched or continuous?
- Are the products dedicated or multiple product groups?

- How is campaigning between products handled?
- How much time is available for sanitization? Should redundancy be provided to allow adequate time for sterilization?

(Insert table here bruce) Figure 3-4 Storage Tank Level Chart

REVISIT WATER QUALITY

With all use points characterized for temperature range, and demand, the quality of water is revisited. A thorough review of use point criteria typically reveals a wide range of acceptable delivery conditions for the water. Since it is typically not practical to operate multiple water systems to provide the exact water conditions desired of the end product, compromises must be made. These compromises might include providing water of a higher quality than required to simplify the water treatment or delivery systems, or provisions for controlling water consumption at a use point to limit peak demands. Whatever compromises are made, water must be delivered at conditions within the boundary limits.

SYSTEM DESIGN

once the support areas, back up requirements, future growth, or expansion capabilities are established, detailed design of the system can begin. The processes requirements determine all the points of use (POU) on the distribution system. User locations determine how to distribute the system (e.g., central storage, multiple loops/branches, etc.) one or several of the use points may need either different qualities or other properties that single it out from the rest. In this case alternatives to the water system criteria are considered, such as using an ambient or cold distribution versus a hot system. Plant shift operating hours must also be considered since there may be an inability to perform regular heat sanitizations of cold systems, for example.

The boundaries, limitations, and restrictions that were identified in the initial planning stages should now be integrated into the design approach. Further considerations might include the physical area a system needs for support, one production area, one building, or multiple building on site. This could determine the size of the system and whether it is made up of multiple tanks, or multiple loop storage and distributed systems. For example, central systems are higher in initial capital, but lower in operation and maintenance and possible lower overall cost on unit basis. The capital is higher primarily due to the larger generation, storage, and distribution equipment or system. Alternatively, multiple generation systems may require less initially for each smaller system but more cost in terms of capital and operating and maintenance for the same total capacity.

All systems have a fixed capacity and will eventually have a failure. Therefore, if a piece of equipment fails a plan should be in place to deal with the down time. Having backup generation equipment for the critical components such as a still or deionization equipment, should be considered. The backup equipment can be used in a lead-lag type operation and/or to meet a specific duration of a peak demand.

More detailed descriptions of the alternatives for the various unit operations required for production of pharmaceutical grade water discussed in the following chapters. Rationale is provided for decisions that

will surface regarding quality, cost, performance, maintenance, and reliability as the system is developed in detail.

PRETREATMENT OPTIONS

INTRODUCTION

Pretreatment is all process steps or unit operations prior to the last (final) water treatment step. Pretreatment is a series of unit operations to modify the feed water quality so that it will be of adequate quality to be fed to a final treatment step. This final step may be reverse osmosis, ultrafiltration, multi or mixed bed deionization or distillation. These final steps are discussed in chapter 5 and 6

Reverse osmosis is unique since it can be a pretreatment step, in a addition to being a final treatment step. Reverse osmosis applications in pretreatment are discussed in this chapter and chapter 11., but reverse osmosis as a technology is discussed in chapters 5 and 6

The initial sections of this chapter discuss the process design (programming issues) for pretreatment design including feed water quality and output water quality from pretreatment. The chap then discusses the selection of treatment options (i.e. unit operations) for four groups of impurities:

- Control of foul—removal of turbidity and particulates
- Control of scaling—removal of hardness and metals
- Removal of organics and microbiological impurities
- Removal of microbial control agents

Pretreatment options are summarized in figure 4-1 at the end of the chapter

The final sections of the chapter discuss the importance of anion composition/concentration, ph, materials of construction, and pretreatment system control.

This discussion is based on the description of these technologies presented in chapter 11.

PROCESS DESIGN OF PRETREATMENT

Process design of the pretreatment system is the specification of the unit operations or process steps to treat the feed water. Typical information includes flow rates, temperatures, pressure, and composition of all streams. Detailed mechanical design of the equipment for a given unit operation or process step is beyond the scope of this guide

The process design (programming issues) for a pretreatment system may include:

a) Required quantity and quality of the water from the final treatment process
b) Treatment constraints on the water used in a pharmaceutical process and the approach to microbial control
c) The final treatment option that has been chosen, as this defines the required water quality leaving pretreatment

d) Quality of the feed water that is the input to the pretreatment system (water quality to be validated over a one year period)
e) Difference between input water quality and desired output water quality. the difference determines impurities that must be removed by the pretreatment system. The difference is determined by performing a material balance. Attention should be paid to impurities and minor components
f) Pretreatment options to provide the desired removal of impurities considering other factors such as capabilities of the labor force, economics, waste disposal, environmental considerations, validation, and the available space and utilities

In addition to defining the options for removal of impurities, the approach taken to microbial control is an integral part of the process design of the pretreatment system. Considerations include:

a) If the drinking quality of water to the pretreatment system comes from a municipality in the united states, it will typically contain chlorine, or chloramines, as a microbial control agent. In Europe ozone is the more common microbial control agent. The concentration of the agent should be sufficient to protect the initial steps of pretreatment.
b) If the quantity of microbial control agent is insufficient, additional microbial control agent may be added or provision made to periodically sanitize the initial equipment in the pretreatment system. This is likely if water comes from a source other than a municipality. Increased monitoring of feed water and the initial steps may be warranted
c) At some point in the pretreatment process, the microbial control agent must be removed before going to the final treatment. At this point, a means of either continuous or periodic sanitization needs to be selected for the treatment steps following this removal.

The USP requirement that compendial waters should contain “no added substances” eliminated addition of chemicals to “purified water” or water for injection. However addition of chemical agents is not prohibited in pretreatment. Substances are frequently added in pretreatment and subsequently removed in the pretreatment or final treatment. Some examples are:

- Chlorine (to control microbial growth, removed in later stages of pretreatment)
- Sodium ions (in softener with exchange for multivalent ions, removed in ion removal process)
- Acid (for degasification to remove carbon dioxide, counter ions, removed in a subsequent ion removal process)
- Sulfite (to reduce chloride to chloride, or chloramines, to ammonium and chloride while forming sulfate, removal by softening or ion removal process
- Sequestrates (to prevent scaling in final treatment, removed by RO in final treatment)
- PH control agent (removed in ion removal process)

Added substances are an issue if they result in an increase in microbial growth or endotoxins

A final consideration is the relationship between investment and operating dollars in pretreatment, and the performance and cost of the final treatment process. The following are generally true:

- A final treatment system will not operate reliably over the long term, without reliable operation of the pretreatment system.
- Inadequate operation in pretreatment (breakthrough of particulates, hardness, or chlorine) may not immediately affect water quality from final treatment, but it will be reflected in long term maintenance and operating reliability, and possibly in water quality.
- Investment in pretreatment capability and reliability can return many times the investment in final treatment maintenance costs.
- Pharmaceutical water systems are expected to generate water meeting final pharmaceutical product water standards. The system should be designed to control impunity spikes in the incoming water quality, or season impurity profile changes. A robust pretreatment system design handles impurity spikes detrimental to final treatment

There is no single "right" answer to the process design of the pretreatment system. Pretreatment system process design is a series of choices and options, each with advantages and disadvantages

FEEDWATER TO PRETREATMENT QUALITY: TESTING AND DOCUMENTATION

Compendial pharmaceutical water systems are required to use feed water complying with "drinking water" standards

Most pharmaceutical manufacturers utilize municipal water supplies. This water generally meets "drinking water" quality standards and is treated with a microbial control agent. Historically in the US, the microbial control agent is chlorine, but chloramine is now used with increasing frequency. Either feed water composition or microbial control agent concentration may be subject to occasional and seasonal variations. These variations may negatively impact water quality, and can be detected only by extensive sampling. In addition, water quality at the plant site may not be equivalent to that from a municipal treatment facility, due to potential for contamination or loss of microbial control agent in the distribution system. Documentation of feed water quality is recommended either by use of municipality testing (if applicable) supplemented by some testing at the plant side or by extensive testing of feed water quality.

Typical contaminants in feed water include:

- Particulates: silt, dust, pollen, pipe scale, iron and silica, undissolved minerals and organics
- Inorganics: calcium and magnesium salts, heavy metals (iron, aluminum, and silica) with their corresponding anions
- Organics: naturally occurring by products of vegetative decay, I.e., humic adic fulvic acids and "manmade organics" such as pesticides and auot motive pollution (oils)
- Bacteria: bacterial contamination and its byproducts, endotoxins, and pyrogens

Testing recommendations include:

- Documentation that feed water meets drinking water quality. this may be based on results of testing by the municipality, possibly supplemented by local or in-process testing. Frequency of

in-process testing will be affected by reliability of the municipality, importance of monitored variables, and company philosophy

- Monitoring for microbial control agent levels at the start of the pretreatment system. Chlorine level is affected by pH. A chlorine level of 0.2-1.0 ppm is generally considered adequate to control microbial growth and generally has negligible effects on pretreatment equipment and performance.
- Specific testing for contaminants known or suspected of being present in the feed water. This is to determine if data from the municipality is adequate; e.g., feed water from a surface source for pesticides in an agricultural area where fun off from farms may be seasonal

OUTPUT WATER FROM PRETREATMENT: QUALITY OF FEEDWATER TO FINAL TREATMENT

The goals for pretreatment are to provide water quality that minimizes the operating and maintenance problems in the final treatment equipment and to permit the final treatment step to product water meeting the desired specifications for final treatment.

The impurities that must be removed in the pretreatment process to permit reliable operation of the final treatment step depend on the final treatment step selected and the tolerance of a final treatment step for the impurities. If pretreatment is inadequate, resulting problems can become very large in magnitude, as seen in table 4-1 below

Table 4-1

Magnitude of problems in final treatment caused by type of impurity	IMPURITY Fouling: caused by particulates	Scaling: caused by hardness and minerals	Corrosion: caused by chlorides	Degradation: cause by chlorine
Reverse osmosis	Large	Large	None	Large*
Other membrane processes	Large-moderate	Large-moderate	None	Large*
Single effect distillation	Moderate	Moderate	Moderate-large	Large
Multi-effect distillation	Large-moderate	Large-moderate	Moderate-large	Large
Vapor compression	Moderate	Moderate	Small	Large

*membrane dependent

Pretreatment requirements for feed water to the final treatment process usually include:

FOR MEMBRANES

The concerns are fouling by suspended solids (particulates) and scaling (precipitating solids) as water is removed. A typical goal for control in pretreatment might be a silt density index (SDI) of 3-5 and

hardness of <1 grain/gallon for on-site analysis. Membranes tolerate chlorides but only some membranes tolerate chlorine.

FOR DISTILLATION
the concerns are scaled formation due to hardness and corrosion due to chlorides. Typical water quality might be as high as 1.0 mohm/cm, which often requires additional treatment beyond pretreatment, i.e. RO or ultrafiltration. Distillation has no tolerance for chlorine due to corrosion and carryover to the product. Distillation has some tolerance for particulates.

Pretreatment generally has little effect on the other parameters indicative of water quality such as anions, microbial levels, conductivity, total organic carbons (TOC), and volatiles

Selecting pretreatment to reliably provide the required feed water quality to final treatment, in spite of spikes in feed drinking water quality, will reduce operating and maintenance costs in final treatment.

CONTROL OF FOULING: REMOVAL OF TURBIDITY AND PARTICULATES

The principal methods for removing particulates and reducing turbidity are:

- Clarification and the accompanying operations of flocculation, coagulation, and sedimentation
- Depth or media filtration including single and multimedia filtration (particles retained by the media)

The definitions, filtration mechanisms and typical removal processes for these are outline in chapter 11.

Clarification is not applicable as feed water sources are potable quality or better

Depth of media filtration is used in pharmaceutical water systems and is often the first step in a pretreatment system. Multi-sized sand is the most common media, but other media may provide better performance with some feed waters. Removal of particulates down to 10 microns is possible and depends on selection of media. Microbial growth is a key concern in a media filter, unless the feed water contains a microbial control agent. Otherwise, microbial control in the depth filter is required (e.g, periodic sanitization using either heat or a chemical sanitizing agent.)

CONTROL OF SCALING: REMOVAL OF HARDNESS AND METALS

when water is separated from its impurities in the final treatment process, those compounds with low solubility are concentrated to the point where they precipitate. This precipitation, or scaling, is the result of exceeding the solubility of the divalent and trivalent cations, usually as a sparingly soluble salt such as carbonate or sulfate. The methods of control are:

- Removal by ion exchange. These are principally calcium and magnesium and may include divalent and trivalent ions such as iron, aluminum and silica. Pretreatment is usually water softening, (exchanging the ions causing hardness and scaling for sodium ions)
- Removal of carbonate by acidification. Acidification converts the carbonate to carbon dioxide, which is removed by subsequent degasification.

- Removal of the offending compounding by a barrier filtration process such as Nano filtration. Water passes through the membrane and compounds are retained by the membrane and removed as a purge stream

These removal processes are detailed in chapter 11

Water softening ion exchange, which removes divalent and trivalent ions and replaces them with sodium, is a very common process used in pretreatment of pharmaceutical water. It is applicable for all flow rates and all hardness levels, and is well understood and easy to operate. It involves the handling of salt only, and produces a non-hazardous waste stream. However, the high total dissolved solids (TDS) in the waste stream may limit disposal options. Water softening is also easily controlled manually or with a PLC.

For large flow rates (>50 gpm or 0.18 m3/min) and high hardness (<50 ppm) degasification (after acidification) may be the progress of choice. The degasification process is often employed between the two stages of an RO and involves the handling of acid and base for two pH adjustments:

- Lowering of pH before first stage of RO
- Increasing of pH before second stage of RO

The principal advantage is that the carbon dioxide is released to the atmosphere rather than being a liquid waste stream requiring disposal.

Nano filtration is a membrane process that may be applicable with certain feed waters and specialized situations. The filtration is usually crossflow and involves a significant purge steam. It is much like RO, the differences being pore size in the membrane and the corresponding effect on ion removal. Removal of divalent ions can be greater than 98%

Chemical injection is an alternate method to control the ions or compounds that contribute to scaling. This process inject a compound (usually a proprietary organic compound) to the final treatment feed water. These compound are called sequestrates and act “to tie up and complex” the offending ions or compounds to form a complex, or compound, that is more soluble and will not precipitate in the final treatment process. Sequestrants are almost always proprietary compounds, which require testing to verify applicability and dosage level for the particular feed water, and analysis to verify removal in the final treatment process.

A key choice in the process design of the pretreatment system is location of the softener. The two options are either before or after removal of the microbial control agent (often chlorine) that is in the feed water, or which may have been added for control of microbial growth.

Softener located prior to removal of microbial control agent: the principal advantage is protection of the softener from microbial growth by the microbial control agent present in the feed water. If the microbial control agent is chlorine, it will have only a minor effect on resin life and efficiency at the chlorine levels typically encountered in chlorinated municipal feed waters (<1ppm)

Softener located after removal of microbial control agent: the advantage is better resin life and capacity (due to absence of chlorine, if it is the microbial control agent). However this must be balanced by the need to protect the softener from microbial growth and endotoxin load (I.e., by periodic sanitization with the associated cost of head or chemicals, labor, down time, and waste steam disposal.)

Removal of organics

The types of organics and microbiological impurities typically present in water systems and the methods for removal of them as discussed in chapter 11. The methods for removal of organics are:

- Ozone
- Strong base ion exchange
- Barrier filtration (microfiltration, ultrafiultration or reverse osmosis
- Polymer flocculant
- Carbon

Ozone is a powerful oxidant that controls microbial growth and reduces the concentration of organics due to oxidation, but requires compatible materials of construction.

Strong base ion exchange removes organics but results in a purge steam containing high concentrations of brine and organics, due to regeneration of the resin.

Barrier filtration, when appropriately sized, captures organics and microbial growth on the barrier and can be aided by addition of a polumer flocculant. A potential problem with barrier filtration is microbial growth “growing through the barrier” which results in microbial contamination on the downstream side of the barrier

Carbon is probably the most common method of reducing organics,. It is used because it provides multiple functions, including removal of organics as well as removal or reduction in the amount of chlorine and chloramines (if these are present and the carbon filter is appropriately designed.) the advantages of using carbon are that it is a frequently practiced technology, it performs multiple functions, and effectively “cleans up the feed water”, and microbial growth can be controlled by periodic sanitization. The disadvantage is that it is a source of microbial growth, as well as a source of nutrients.

SYSTEM DESIGN FOR CONTROL OF MIRCROBIAL GROWTH

the methods for control of microbial growth are summarized in chapter 11. The methods used in pretreatment to control microbial growth are:

- Microbial control agent such as chlorine or chloramine
- Periodic sanitization (heat or chemical)
- Ultraviolet light
- Avoiding dead legs and avoiding water stagnation

A common strategy is the design of the pretreatment system is to leave the microbial control agent provided by the municipality in the water through as many pretreatment steps as possible, in order to protect these steps from microbial growth.

However, at some point the microbial control agent (chlorine or chloramine) must be removed since it is not compatible with the final treatment processes. At this point, the only option is periodic sanitization, either with heat or a chemical disinfectant. This must be included in the design of the pretreatment system, along with the provisions for validation and monitoring its effectiveness via sampling and testing. If a chemical disinfectant is used, provisions to remove it and monitor its removal are also required.

Ultraviolet light (UV) is effective in inhibiting microbial growth but is only effective when the light is present. UV light is often used before a unit operation to minimize the microbial growth in the unit operation by controlling the microbial counts in feed water. The most common places for use of UV light are before reverse osmosis units and some filters.

REMOVAL OF MICROBIAL CONTROL AGENTS

At some point in pretreatment, microbial control agents must be removed because of their detrimental effect of final treatment equipment and performance. Chlorine causes deterioration of most Reverse Osmosis membranes and is corrosive in distillation. Chloramines can pass through pretreatment and decompose in the distillation process with an adverse effect on water quality

The methods for removal of chlorine and chloramines are similar and are detailed in chapter 11

For chlorine removal, activated carbon is a straightforward process for the absorption of chlorine. The carbon will reduce some of the chlorine to chloride ion, which is then removed in the final treatment ion removal process. Sulfite reduction is also straightforward, with sulfite being oxidized to sulfate and chlorine being reduced to chloride ion.

Chloramine removal is more complex. Chloramine adsorption on carbon occurs at a much slower rate than chlorine, necessitating longer contact times and lower hydraulic flow rates. The potential for dissociation of the absorbed chloramines into ammonium ion and ammonia is a problem. Ammonium is removed by reverse osmosis but decomposes to ammonia in a distillation process. Ammonia passes through both reverse osmosis and distillation processes in final treatment.

Sulfite reduction for chloramines results in ammonium and chloride ions. These can be removed by reverse osmosis. The ammonium partially decomposes to ammonia in the higher temperature distillation process, resulting in carryover and effect on the water quality.

Removal of ammonia (from chloramine) and carbon dioxide requires proper pH control to maintain these species as ions for removal in an RO. The equilibrium of carbonate, bicarbonate, and carbon dioxide is pH dependent, with alkaline conditions required to maintain the ionic species. The equilibrium between ammonium and ammonia is pH and temperature dependent, with acidic conditions required to maintain the ionic species. At no single pH point are these species all carbonate and ammonium ions.

Thus two pH adjustment steps followed by the appropriate removal technologies are required to remove both chloramines and carbon dioxide.

CHANGES IN ANION COMPOSITION/CONCENTRATION

Pretreatment systems typically remove non-ionic impurities and cations. Thus, any change in anionic composition or concentration is usually secondary. However, some distillation processes in final treatment are affected by chlorides, which can be removed by an RO prior to the final treatment step.

The pretreatment processes that affect anionic composition are:

- Deionization
- Degasification
- Carbon bed filtration for removal of chlorine and chloramine
- Reduction to remove chlorine and chloramine
- Barrier filtration (nanofiltration, ultrafiltration, reverse osmosis)

Ion exchange resins are designed to remove either cations or anions. An ion exchange resin that is designed to remove anions (anionic resin) will typically exchange the anions (chloride, sulfate, nitrate, and carbonate; and bicarbonate if the pH is appropriate) for the hydroxyl ion. The ion exchange may be in a single bed, mixed beds, or twin beds and will affect anionic composition if an anionic resin is present. Ion exchange is a deionization process to specifically remove anions is discussed in chapter 5.

Degasfication and the accompanying process of acidification, for removal of hardness, changed anionic composition. The water is acidified with a non-volatile acid (usually sulfuric, based on cost and ease of removal of the resulting anion i.e., sulfate) to convert carbonate and bicarbonate to dissolved CO2 which is removed by degasification. The net effect is replacement of bicarbonate and carbonate with sulfate, (see chapter 11).

As discussed above, carbon bed filtration adsorbs chlorine and chloramines from feed water. However, some of the chlorine is reduced to chloride and is removed in a subsequent ion removal process, usually in final treatment.

The removal of chlorine and chloramines by reduction, often with bisulfite, changed ionic composition, and concentration, as the bisulfite is oxidized to sulfate and the chlorine, or chloramines, are reduced to chloride and ammonium.

Some barrier filtrations (particularly nano filtration) remove some of the large anions. Reverse osmosis may be used to remove chloride ion prior to some distillation processes.

THE IMPORTANCE OF PH IN PRETREATMENT

The effect of pH on the equilibrium between carbonate, bicarbonate, and carbon dioxide is discussed in chapter 11.

EPA drinking water standards require a pH range of 6.5-8.5. in reality, the pH range of most drinking feed water is narrower, due to the corrosive nature of acidic water and the scaling potential of alkaline waters.

The pH of the feed water and its seasonal variations need to be known because of its impact on pretreatment and final treatment process design. The pH determines the form of the carbon dioxide, tis scaling potential and where carbon dioxide (carbonate) is removed (see chapter 11)

A complicating factor in pretreatment design is the potential presence of ammonia as a result of chloramine presence in the feed water. Ammonia is a dissolved gas at the pH values where carbon dioxide is an ion (carbonate), and exists an ion (ammonium) at pH values where carbon dioxide exists as a dissolved gas. Thus it is not possible remove both carbon dioxide and ammonia at one pH. If both are present, two pH adjustments steps are required:

- pH adjustment followed by removal of either carbon dioxide or ammonia
- A change in pH to remove the other compound

These operations may be part of pretreatment or final treatment

MATERIALS OF CONSTRUCTION AND CONTSTRUCTION PRACTICES

Piping to the pretreatment system may be copper, galvanized steel, or a suitable thermoplastic. Piping in the pretreatment system, where high temperatures are not encountered, is usually plastic (PV, CPVC, polypropylene, or other material) based upon cost and corrosion resistance. Leaching from some plastics such as PVC or CPVC may make these materials undesirable to the user. Vessels may be fiberglass, lined carbon steel, or stainless steel.

The piping and equipment in a portion of the pretreatment system may encounter high temperature (periodic heat sanitization) or high pressure (RO plus degasification). In these portions, piping is typically stainless steel or a plastic that can be heat sanitized, such as PVDF. Equipment designed for high pressure may be carbon steel, lines carbon steel, or stainless steel. Mill finish is satisfactory for these materials; electro polishing is unnecessary.

The cost of sanitary construction practices such a orbital welding and sanitary fittings may not be warranted in the pretreatment system. Use a plastic pipe that is solvent cemented or heat fused, stainless steel pipe that is welded or flanged with mill finish, or tubing with compression fittings is common. Ball or diaphragm valves predominate for flow diversion, with globe and needle valves for flow control. Selecting the minimum cost piping components that will not degrade water quality is an area for major cost savings.

Sample points should be provided upstream and downstream of each piece of equipment for monitoring and for troubleshooting. Points for field measurement of pressure and temperature are also useful for trouble shooting

PRETREATMENT SUMMARY

The philosophy of control selected for pretreatment can have a major impact on both investment and continuing operating cost. Reliable operation and control of pretreatment can significantly reduce operating and maintenance costs in a final treatment. The important process steps in pretreatment are:

- Removal of turbidity and particulates to minimize membrane and equipment fouling
- Removal of hardness and metals to prevent scale formation in final treatment
- Removal of organics and microbiological impurities
- Control of microbial growth and removal of microbial control agents to prevent degradation of final treatment

These process steps are important because of their immediate effect on water quality from final treatment or their long-term effect on final treatment equipment performance and hence, their indirect effect on water quality from final treatment

Pretreatment, like other parts of the water treatment system, should be subject to good engineering practices. Validation of pretreatment as a component of the water treatment system, is required as part of the entire water treatment system validation and should include microbiological monitoring.

INSERT TABLE HERE BRUCE Figure 4.1 Pre Treatment Diagram

Note: the order of unit operations may be different than shown.

FINAL TREATMENT OPTIONS: NON COMPENDIAL AND COMPENDIAL PURIFIED WATER

INTRODUCTION

This chapter discussed the final treatment technologies and basis system configurations related to the manufacturing process of USP purified water and non- compendial water.

Various system configurations are presented, and reflect a significant shift from ion exchange based systems to membrane based systems. Equipment and system materials, surface finish and other design factors are discussed to promote the use of good engineering practice for proper selection of components, piping, instrumentation, and controls.

USP purified water and non-compendial water can be produced by an almost unlimited combination of unit processes in various configurations. The most common pretreatment and final treatment technologies used in purified water production are shown in figure 5-1, figure 5-2, and table 5-4 at the end of the chapter. This chapter discusses the final treatment unit processes currently utilized, including ion exchange, reverse osmosis, electrodeionization, ultrafiltration, microfiltration, and ultraviolet light. These technologies as well as distillation (see chapter 6) are utilized in thousands of systems for the successful production of purified and non-compendial water.

Ion exchange based systems were the dominant systems for decades in purified water production and are still successfully utilized in facilities today. The last decade has seen the growth of reverse osmosis membrane based systems increase to the point where over 90 % of new systems employ primary reverse osmosis, with final polishing by continuous electrodeionization, ion exchange, or second reverse osmosis stage. Membrane based systems usage has increased due to chemical consumption reduction, contaminant rejection (ionized solids, organics, colloids, microbes, endotoxins, and suspended solids), reduced maintenance consistent operation, and effective lifecycle cost.

The various membrane based system configurations are compared with ion exchange and distillation in table at the end of this chapter.

Equipment construction is discussed for each unit process section to promote proper selection of materials, surface finishes, and other design factors. The total system capital cost is influenced more by equipment design details than by process selection. Many aspects of equipment can be overdesigned and hence, become unnecessarily costly. Proper thought must be given to the individual components function, location, required microbial performance, sanitization, and other factors, to optimize design. It is not necessary to construct every makeup system component with the same level of surface finish and detail as the distribution system for successful operation in most cases.

Many material selections are made erroneously to conform to cGMP requirements that do not actually dictate the details of construction for most final treatment compounds. Good engineering practice should be employed to optimize the system for consistent operation to specifications and lifecycle cost optimization. Part of the consideration is the need to replace system components (e.g., filters, RO membranes) at a frequency that meets GMP.

This chapter does not differentiate between compendial and non compendial water system equipment. Non compendial water is often manufactured and validated in a manner consistent with compendial water.

ION EXCHANGE

DESCRIPTION

Cation and anion exchange resins are regenerated with acid and caustic solutions, respectively. As water passes through the ion exchange bed, the exchange of ions in the water stream for the hydrogen and hydroxide ions, held by the resin, occurs readily and is driven by concentration. Thus the regeneration process is driven by excess chemical concentrations. The important parameters of this system include resin quality, regeneration systems, vessel linings, and waste neutralization systems. The operation of the system can be monitored by conductivity (resistivity) or the product water.

A two-bed ion exchange system includes both cation and anion resin tanks. Two-bed ion exchange systems often times function as the workhorse of a strictly deionization (DI) water system in terms of salt removal.

Mixed-bed ion exchange systems are typically used as a secondary or polishing system. Mixed-bed DI units consist of a single tank with a mixture of anion and cation removal resin. A cation bed can also be used as a “polishing” DI step, rather than a mixed-bed DI.

Ion exchange resins are available in on-site and off-site regenerable systems. On-site regeneration requires chemical handling and disposal, but allows for internal process control and microbial control. Off-site regeneration can be accomplished through new resin to be used on time, or through repeated regeneration of the existing resin. New resin provides greater capacity and some possible quality control advantages, but at a higher cost. Regenerated resin produces a lower operating cost, but may raise quality control issues, such as resin segregation, regeneration quality, and consistency.

Additional details on ion exchange can be found in chapter 11.

APPLICATION

The major purpose of ion exchange equipment in USP purified water systems is to satisfy the conductivity requirements of the USP. Deionization (DI) systems are often times used alone or in conjunction with reverse osmosis to product USP purified water. Typical ion exchange systems do not effectively remove other contaminants noted in the USP purified water specification. In the ion exchange process, salt ions, which are common to potable water, are removed from the water stream and replaced with hydrogen and hydroxide ions. Ion exchange systems are available in various configurations that include two-bed DI and mixed-bed DI. Both configurations are available in on-site and off-site regeneration systems.

PRETREATMENT REQUIRMEMENTS

Ion exchange systems require pretreatment to remove undissolved solids from the water stream and to avoid resin fouling or degradation. Although dechlorination is also recommended to avoid resin degradation by oxidation, the low levels of chlorine commonly found in most portable water supplies normally demonstrate only long-term effects on most ion exchange resins.

COST SAVING FACTORS

Most of the cost saving opportunities for these systems revolve around the correct choices in materials of construction, pretreatment options, instrumentation, and sizing of the DI system. Acceptable piping materials of construction can vary from PVC to 316L SS. A correctly designed system will minimize the equipment size and maximize the amount of time between regenerations, considering microbial control and maintenance. Choosing to monitor only the critical parameters such as conductivity (resistivity), flow pressure, etc., can minimize instrumentation.

There are also cost savings choices that will need to be made with respect to capital purchase and on-going operating costs. These choices will steer you towards DI off-site regenerable bottles, on-site regenerable DI vessels (with automatic or manual controls) or another water treatment unit operation

ADVANTAGES:

- Simple design and maintenance
- Flexible in water flow production

- Good upset recovery
- Low capital cost for single train DI systems
- Removes ionizable substances (ammonia, carbon dioxide, and some organics)

DISADVANTAGES:

- High cost of operations on high total dissolved solids (TDS) in-feed water
- Requires chemical handling for on-site regenerable DI (safety and environmental issues)
- Full on-site DI system can take significantly more floor space due to primary vessels, chemical storage, and neutralization system
- Off-site DI systems will require outside service and significant costs for regeneration services
- Off-site regeneration involves consequent loss of control over the use, handling, and care of DI vessels
- DI vessels are excellent places for microbial growth to occur between regenerations

SANITIZATION

All ion exchange resins can be sanitized chemically with various agents. The degree of resin attrition is a function of resin type and the chemical agent. Chemical cleaners include peracetic acid, sodium hypochlorite, and others. Some resins are capable of hot water sanitizations at temperatures between 65 degrees C to 85 degrees C. Ion exchange resins suitable for limited thermal sanitizations include: strong acid cation resin and standard polystyrene cross-linked with divinylbenzene type 1 strong base resin.

INSERT TABLE Figure 5.1 Comparison of Ion Exchange Unit Operations

Note: having the DI bottles regenerated by an outside service does not relieve the manufacturer of the responsibility to have quality control of their ion exchange system.

INSERT TABLE Figure 5.2 LIMITS OF OPERATION AND EXPECTED PERFORMANCE

CONTINOUS ELECTRODEIONIZATION (CEDI)

DESCRIPTION

Electrodeionization removes ionized and ionzable species from water using electrically active media and an electrical potential to effect ion transport. Electrodeionization is distinguished from electrodialysis or oxidation/reduction processes by the use of electrically active media, and is distinguished from other ion exchange processes by the use of an electrical potential

The electrically active media in electrodeionization devices functions to alternately collect and discharge ionizable species and to facilitate the transport of ions continuously by ionic or electronic substitution mechanisms. Electrodeionization devices may comprise media or permanent or temporary charge and may be operated batchwise, intermittently, or continuously. The devices can be operated so as to cause electrochemical reactions specifically designed to achieve or enhance performance and may comprise electrically active membranes such as, semi-permeable ion exchange or bi polar membranes

The continuous electrodeionization (CEDI) processes are distinguished from the collection/discharge processes (such as electrochemical ion exchange or capacitive deionization) is that the process is continuous rather than batch or intermittent, and that the ionic transport properties of the active media are a primary sizing parameter, as opposed to ionic capacity. Continuous electrodeionization devices typically comprise semi-permeable ion exchange membranes. Permanently charged media, and a power supply that can create a DC electrical field.

A continuous electrodeionization cell is formed by two adjacent ion exchange membranes or by a membrane and an adjacent electrode. CEDI units typically have alternating ion depleting (purifying) and ion concentrating cells that can be fed from the same water source, or different water sources. Water is purified in CEDI devices through ion transfer. Ionized or ionzable species are drawn from the water passing through the ion depleting (purifying) cells into the concentrate water stream passing through the ion concentration cells.

The water that is purified in CEDI units passes only through the electrically charged ion exchange media, and not through the ion exchange membranes. The ion exchange membranes are permeable to ionized or ionzable species, but not permeable to water

The purifying cells typically have permanently charged ion exchange media between a pair of ion exchange membranes. Some units incorporate mixed (cationic and anionic) ion exchange media between a cationic membrane and an anionic membrane to form the purifying cell. Some units incorporate layers of cation and anion ion exchange media between ion exchange membranes to for the purifying cell. Other devices create single purifying cells (cationic and anionic) by incorporating sing ion exchange medium between ion exchange membranes. CEDI units can be configured with the cells in a plate and frame, or spiral wound configuration.

The power supply creates a DC electric field between the cathode and anode of the CEDI device. Cations in the feed water steam passing through the purifying cell are drawn to the cathode. Cations are transported through the cation exchange media and either pass through the cation permeable membrane or are rejected by the anion permeable membrane. Anions are drawn to the anode and are transferred through anion exchange media and either pass through the anion permeable membrane or are rejected by the cation permeable membrane. The ion exchange membranes are oriented in a manner which contains the cations and anions removed from the purifying cells in the concentrating cells so that the ionic contaminants are removed from the CEDI unit. Some CEDI units utilize ion exchange media in the concentrating cells, while others do not.

As the ionic strength of the purified water stream decreases the high voltage gradient at the water-ion exchange media interfaces can cause water decomposition to its ionic constituents (H+ and OH*) the H+ and OH* ions are created continuously and regenerate the cation and anion exchange media, respectively, at the outlet end of the purifying cells. The constant high level of ion exchange media regeneration level allows the production of high purity water (1 to 18 mohm-cm) in the CEDI process.

APPLICATION

In some cases, where drug microbiological quality is of lesser concern, CEDI units may be utilized downstream of reverse osmosis (RO) units in production of USP purified water or non-compendial water to increase the life of the CEDI units. For USP WFI water, the CEDI units are utilized up stream of reverse osmosis (RO) units

LIMITATIONS

CEDI units cannot remove all contaminants from water. The principal removal mechanism is for ionized or ionizable species. CEDI units cannot purify 100% of the feed water stream, as a concentrate stream is always required to remove the contaminants from the system. CEDI has temperature limitations for practical operation. Most CEDI units are operated between 10-40 degrees C (50-104 degrees F)

PRETREATMENT REQUIREMENTS

CEDI units must be protected from scale formation, fouling and thermal or oxidative degradation. The RO/pretreatment equipment typically reduces hardness, organics, suspended solids, and oxidants to acceptable levels.

PERFORMANCE

CEDI unit performance is a function of feed water quality and unit design. Ionized solids reduction is generally greater than 99% allowing production of 1-18 mohm-cm quality water from reverse osmosis feed water. Organic rejection typically varies from 50% to 95% depending upon the type of organic material present in the feed stream. Ultraviolet light (185 NM) upstream of CEDI units can substantially increase organic rejection. Dissolved carbon dioxide is converted to bicarbonate ion and removed as dissolved ion. Dissolved silica removal is in the range of 80-95%, dependent upon operating conditions.

COST SAVING FACTORS

most of the cost savings opportunities revolve around the correct choices in materials of construction, instrumentation, and post-treatment equipment selection. Acceptable materials of construction for piping can vary from PVC to 316LSS. Choosing to monitor only the critical parameters, such as resistivity, flow, and pressure can minimize instrumentation. Many applications for purified water require no post=treatment after electrodeionization. Some systems incorporate ultraviolet light and/or sub micron filtration to either reduce santization requirements or to provide microbial levels well below those allowed for purified water production as outlined in the USP

ADVANTAGES AND DISADVANTAGES

ADVANTAGES

- Attainment of stage 1 conductivity
- Elimination of chemical handling
- Elimination of outside service (off-site regenerated resin)
- Electric field in membrane/resin module provides some bacterial control
- Removal of ionizable substances (e.g. Carbon dioxide, ammonia, and some organics)

Disadvantages:

- Does not remove non-ionic contaminants
- Unique designs for each manufacturer (modules are not interchangeable)
- May require UV, sub-micron filtration, or reverse osmosis (RO) for further bacterial reduction
- May require reverse osmosis pretreatment
- Rinse up after chemical sanitization may take hours to reach peak resistivity and TOC

SANITIZATION

Cedi units are typically chemically sanitized with a number of agents including: peracetic acid, sodium percarbonate, sodium hydroxide, hydrogen peroxide, and others

REVERSE OSMOSIS

DESCRIPTION

Reverse osmosis (RO) is a pressure driven process utilizing a semi-permeable membrane capable of removing dissolved organic and inorganic contaminants from water. A semi-permeable membrane is permeable to some substance such as water, while being impermeable to other substances such as many salts, acids, bases, colloids, bacteria, and endotoxins.

RO membranes are produced commercially in a spiral wound configuration for pharmaceutical water production. Membranes are available in two basic materials; cellulose acetate and thin film composite (polyamide) all of the membrane types have advantages and disadvantages. Membrane operatin parameters are shown in table 5-3, below.

RO membranes without leading edge brine seals, allow controlled flow between the membranes and pressure vessels to minimize bacterial growth.

INSERT TABLE Table 5.3 RO membrane Operating Parameters

APPLICATION

Reverse osmosis can be successfully implemented in pharmaceutical systems in several ways. RO units can be utilized upstream of regernerable deionizers, or off-site regenerated deionizers, to redue regenerant acid and caustic consumption, or to minimize resin replacement costs. Two-pass RO units (product staged) with proper pH control are generally capable of producing water that meets the requirements of the USP for TOC conductivity.

LIMITATIONS

Reverse osmosis cannot remove 100% of contaminants from water and has very low to no removal capacity for some extremely low molecular weight dissolved organics. RO, however, quantitatively reduces bacteria, endotoxins, colloids and high molecular weight organics from water.

RO cannot purify 100% of a feed water stream. A concentrate flow is always necessary to remove the contaminants that are rejected by the membrane. Many users of RO utilize the waste stream from the RO unit for cooling tower make-up water or compressor cooling water, etc.

Carbon dioxide passes directly through the RO membrane and CO2, will be in RO product stream at the same level that present in the feed water stream. Excess carbon dioxide in the RO product stream may increase the product conductivity beyond the USP stage 1 limit. Carbon dioxide contributes to the loading of anion resin, which may be downstream of the RO units

Reverse Osmosis has temperature limitations for practical operation. Most Ro systems operate on feed water between 5 and 28 deg C.

Pretreatment Requirements

Reverse osmosis membranes must be protected from scale formation, membrane fouling, and membrane degradation. Scaling is possible since the contaminants present in the feed water stream are being concerntrated into the water stream, which is an average of 25% of the feed stream. Scale control is normally prevented by the use of water softening upstream of the membranes, the injection of acids to lower the pH of the feed water stream, or an anti-scalant compound to prevent precipitation.

Reverse osmosis membrane fouling is reduced through the use of back-washable and multi-media filters or cartridge filters for suspended solids, green and filtration or softening for colloidal iron removal, and various microbial control pretreatment methods to reduce biological fouling,

The principal causes of membrane degradation are oxidation of certain membrane materials and heat degradation. Membranes, which cannot tolerate chlorine normally, incorporate activated carbon or injection of various microbial control pretreatment methods to reduce biological fouling.

The principal causes of membrane degradation are oxidation of certain membrane materials and head degradation. Membranes, which cannot tolerate chlorine normally, incorporate activated carbon or injection of various sodium sulfite compound for dechlorination. Protection against high temperature is normally incorporated where the feed water is preheated and the membrane material connot tolerate high temperature.

The reverse osmosis pretreatment unit operations are reviewed in chapter 4

PERFORMANCE

A single stage of reverse osmosis elements typically reduces the level of raw water salts, colloids, organics, bacteria, and endotoxin by 90-99%. Single stage reverse osmosis product water does not normally meet the requirements of the USP without further purification steps. Some two-pass units (two sets of RO membranes in series) produce water that can pass the USP 24 stage 1 conductivity requirements, allowing on-line testing. Those units that do not meet the stage 1 requirement normally meet stage 2 or 3. Membrane selection should be based upon pretreatment requirements, operating performance characteristics, sanitization options, warranties, capital and operating costs, and the feed water source.

Advantages and Disadvantages

ADVANTAGES

- Reverse osmosis units eliminate or significantly reduce chemical handling and disposal, relative to regenerable ion exchange systems
- Generally, RO has more effective microbial control than ion exchange systems
- Integrity testing can be accomplished by salt challenge and measurement of differential conductivity
- RO removes a wide variety of contaminants including ionized solids and non-ionic maters (e.e. colloids, bacteria, endotoxin, and some dissolved organics

DISADVANTAGES

- Water consumption can be significantly higher than ion exchange systems unless the wastewater is reused
- Energy consumption is generally higher than ion exchange and less than distillation
- No removal of dissolved gases (e.g., carbon dioxide and ammonia)

COST SAVING FACTORS

Capital costs can be minimized by reducing membrane area to the minimum suitable for feed water quality and membrane selected. Piping material and finish significantly impact capital cost. Some systems incorporate PVC low-pressure piping and welded mill finish stainless steel high-pressure piping, instrument costs can be minimized by appropriate selection of critical and non-critical parameters of operation. These parameters include:

- Flow
- Pressure
- Temperature
- Conductivity

WASTE WATER REUSE

RO wastewater is frequently used as cooling tower make-up, or for non-contact cooling for compressors, or other heat loads. Wastewater is sometimes re-purified in a wastewater reverse osmosis unit for reintroduction as system feed water. RO wastewater is sometimes used for filter backwas. The wastewater from the second pass of a two pass RO is normally returned to the feed water stream of the first pass RO

SANITIZATION

All RO membranes can be sanitized with some chemical agents that vary as a function of membrane selection. Specifically constructed membranes are available for hot water sanitization at 60 degrees to 80 degrees C.

Polishing Components – non Ionic Contaminants Reduction

ULTRAFILTRATION

Ultrafiltration (UF) is a cross-flow process similary to reverse osmosis (RO). A pressurized feed stream flows parallel to a porous membrane filtration surface. A pressure differential forces water through the

membrane. The membrane reject particulates, organics, microbes, pyrogens, and other contaminants that are too large to pass through the membrane. UF does not reject low molecular weight ionic contaminants, as does reverse osmosis.

Membranes are available in both polymeric and ceramic materials. Polymeric membrane elements are available in spiral wound and hollow fiber configurations. Ceramic modules are available in single channel and multiple channel configurations.

APPLICATION

Ultrafiltration is utilized in several ways in purified water systems. UF is frequently used down stream of ion exchange processes for organic, colloidal, microbial, and endotoxin reduction. Purified water with low endotoxin levels (<0.25 Eu/ml) is utilized by some manufacturers in ophthalmic solutions, topicals, and bulk pharmaceutical chemicals that will be utilized in parenteral manufacturing and other applications.

Ultra filtration is utilized in several ways in purified water systems, in combination with ion exchange, to limit the endotoxin and colloida silica feed levels to the still.

LIMITATIONS

Ultrafiltration cannot remove 100% of contaminants from water. No ionic rejection occurs and organic rejection varies with the various membrane materials, configuration, and porosity. Many different nomial organic molecular weight rejection ratings are available. Dissolved gasses are not rejected by UF.

Most ultrafilters require a waste system to remove the contaminants on a continuous basis. The waste stream varies, but is usually two to ten percent. Some UF systems run dead-ended.

PRETREATMENT REQUIREMENTS

Pretreatment can include multimedia filters, activated carbon filters, ion exchange, membranes, or others. The UF flux rate and cleaning frequency vary widely as a function of feed water and pretreatment. Most UF membranes are chlorine tolerant and do not require dechlorination of the feed water.

PERFORMANCE

UF is utilized to remove a variety of contaminants. The proper UF membrane must be selected to meet the performance requirements. Organic molecules can be rejected well, but the rating of UF membranes varies in molecular weight cutoffs from 1,000 to 100,000. Reduction of typical raw water organics is not as effective as reverse osmosis. Pressure drops vary with membrane selection and operating temperature. Some UF membranes are capable of continuous operation at temperatures up to 90 degrees C, to provide excellent microbial control.

UF reduction of endotoxin (pyrogens) varies from log 10 to 4 log 10 as a function of membrane selection. UF has been shown to be capable of consistent production of water meeting the USP WFI endotoxin limit of 0.25 Eu/ml in typical system applications. UF produces excellent microbial reduction with typical ratings of 3log 10 to 4 log 10 reduction.

UF produces excellent particle reduction and is frequently used in other applications, such as semiconductor production when particle control is far more critical than pharmaceutical water.

Advantages and Disadvantages

ADVANTAGES:

- UF can remove some contaminants, such as endotoxin and organics, better than microfiltration
- UF can have more effective operating costs than microfiltration, in high particle loading applications.
- Some UF elements can tolerate more rigorous sanitization procedures using steam or ozone, than some other membranes filters (MF OR RO)
- The waste stream is generally much less than waste from reverse osmosis units
- Ultrafiltration is generally less energy intensive than reverse osmosis

DISADVANTAGES

- UF cannot remove ionic contaminants, where reverse osmosis can
- UF generally requires a waste stream, which can be a significant cost factor
- UF membranes are sometimes more difficult to integrity test than microfiltration cartridges

COST SAVING FACTORS

Capital costs can be influenced by the optimum sizing of membrane area and membrane selection. Piping material and finish significantly impact capital cost. Some systems incorporate various plastic piping materials while others utilize sanitary 316LSS. The sanitization method selected is a major factor in material selection. Instrument costs can be minimized by appropriate selection of critical and non-critical parameters of operation.

SANITIZATION

UF membranes are sanitized in many different ways. Most polymeric membranes are tolerant of a wide variety of chemical sanitizing agents such as sodium hypochlorite, hydrogen peroxide, peracetic acid, sodium hydroxide, and many others. Some polymeric membranes can be hot water sanitized and some can even be steam sanitized.

Ceramic UF elements can tolerate all common chemical sanitizing agents, hot water, steam, and ozone in santiziation or sterilization procedures.

WASTE WATER RECOVERY

Most pharmaceutical UF units are fed deionized water for USP purified water production or special non compendial water applications. The wastewater is therefore still low conductivity water that can be recycled upstream to reverse osmosis units or fed directly to boilers, cooling towers, or other uses.

MICROFILTRATION

DESCRIPTION

Microfiltration is a membrane process utilized for the removal of fine particles and microorganisms. No waste stream is generally employed in microfiltration processes. Virtually all microfiltration cartridges are disposable and are available in a wide range of materials and pore sizes. In final filtration the filters general range from 0.45 microns down to 0.04 microns. Microfilters are used in a wide range of applications, including aseptic filling of pharmaceutical products, which are not tolerant of terminal sterilization.

Microfilters are generally employed in purified water systems for microbial retention downstream of components where some microbial growth may exist. Microfilters can be extremely effective in this area, but operating procedures must be in place to assure filter integrity during installation and membrane replacement to insure proper performance. Microfilters are most appropriately employed in central purified water production systems and their use is discourage in distribution systems. The filters should not be the only microbial control unit operation in the system. They need to be a part of comprehensive microbial control plan. Minimizing the number of locations of microfiltration makes proper maintenance easier. (see chapter 8)

Advantages and Disadvantages

ADVANTAGES

- Simple design and maintenance
- Flexible in water flow production
- No waste stream
- Cartridges are integrity testable
- Heat and chemical santization of microfilters

DISADVANTAGES

- Can only be used as a safety net for microbial production
- No ion or endotoxin removal
- Shorter life due to dead head design, so replacement is required
- Not recommended for use in distribution piping

PERFORMANCE

Microfiltration can be as effective as ultrafiltration in microbial reduction and can minimize water consumption, as no waste stream is necessary. Microfiltration, however, cannot reduce dissolved organic levels as ultrafiltration can, and microfiltration cannot remove particles as small as ultra-filters can, due to the difference in pore size. Heat and chemical sanitization of micro filters is possible with the proper selection of material.

ULTRAVIOLET LIGHT TREATMENT

DESCRIPTION

ultraviolet light rays strike microorganisms (bacteria, virus, yeast, mold, or algae) and break through their outer membrane to modify the DNA. The modified DNA code brings about the destruction of the organism. The ultraviolet radiation is a point of use application with no residual radiation characteristics. Proper prefiltration should be implemented to keep particulate from shielding organisms from UV light. (see chapter 8)

Advantages and Disadvantages

ADVANTAGES

- Simple design and maintenance
- 254 nm design for microbial reduction
- 185 nm design for TOC reduction
- No waste stream
- Heat, ozone, and chemical sanitization are possible
- **DISADVANTAGES**
  can be used only as a safety net for microbial production
- No Ion or endotoxin removal
- No disinfection residual
- Particulate can shield organisms from UV light

PERFORMANCE

the UV light is used as a final treatment step to address microbial control and TOC reduction (where necessary), after deionization processes.

(insert 3 tables)

FINAL TREATMENT OPTIONS: WATER FOR INJECTION (WFI)

INTRODUCTION

This chapter addresses the USP approved final treatment methods for the production of compendial WFI. WFI is the purest grade of bulk water monographed by the USP and would be expected to be used for the manufacture of parenteral, some ophthalmic and inhalation products, and for finishing steps of parenteral grade active of pharmaceutical ingredients (API'S)

Recommend systems include either distillation or RO as the final processing step, but may also include ultrafiltration (UF), deionization (DI) and/or ion exchange (IX), to compliment the RO or distillation unit operation.

The technology, operation, maintenance, and relative cost issues for the approved process methods are discussed. This chapter includes USP monograph information, regulatory issues, and subsections that cover the unit operations:

- Single effect (SE) distillation
- Multi effect (ME) distillation

- Vapor compression (VC) distillation
- Reverse osmosis (RO)

Feed water pretreatment is covered along with economic factors such as construction materials, surface finishes, and instrumentation and controls. A comparison table on USP-WFI final treatment options and relative attributes is provided

US PHARMACOPOEIA ISSUES

The united states pharmacopoeia (USP) allows WFI to be "purified by distillation or by RO" this statement does not imply that the regulated process step is the only process step, but the USP advisory section does not imply that it is the final step in the process.

- Only distillation may be used to produce WFI under current European regulations
- Distillation, RO, and UF are allowable methods to produce WFI under the Japanese regulations

There are few regulations, which govern the design and construction of pharmaceutical water purification systems. There are no existing regulations governing materials of construction, type, or level of instrumentation, surface finish, or operating temperatures. Most practices commonly followed with respect to these and other issues, have been adopted based on many factors

Among US government publications including the code of federal regulations (CFR) and the FDA guide to inspection of high purity water systems, there are few stipulations related to design and construction of WFI processing equipment. Two notable stipulations are:

- "heat exchangers, other than the double concentric tube type or double tube sheet type, must employ a pressure differential and a means for monitoring the differential."
- "all stills and tanks holding liquid requiring microbial control shall have air vents with non-fiber releasing sterilizable filters capable of preventing microbial contamination of the contents."

DISTILLATION

The pharmaceutical still chemically and microbiologically purifies water by phase changes and entrainment separation. In this process water is evaporated, producing steam. The steam disengages from the water leaving behind dissolved solids, non-volatiles, and high molecular weight impurities. However, a low molecular weight impurities are carried with the water mist/droplets, which are entrained in the steam. A separator removes fine mist and entrained impurities, including endotoxins. The purified steam is condensed into WFI. Distillation systems are available to provide a minimum of 3log 10 (99.99%) reduction in endotoxin concentration. Specific endotoxin loading limits should be reviewed with the manufacturer.

A variety of different designs are available including single effect (SE), multi effect (ME), and vapor compression (VC). The distilled water quality expected from an SE still is equivalent to an ME design, by virtue of the fact that water is distilled only once in both systems. The benefit to the use of ME versus SE distillation are the significantly lower operating costs associated with utilities

In an ME system, purified steam produced by each effect is utilized to heat water and generate more steam in the subsequent effect. Due to this staged evaporation and condensation process, only the first effect requires heat from an external source, and only the purified steam produced by the final effect is condensed, using an external cooling medium

VC stills can produce similar quality water using a different technique. Energy imparted to the generated steam, by a mechanical compressor, results in compressed steam with increased pressure and temperature. The higher energy steam is then discharged back into the evaporator/condenser vessel to generate more steam in a continuous cycle.

Areas of concern are carry over of impurities, evaporator flooding, stagnant water, and pump and compressor seal design. These concerns may be addressed u sing mist eliminators, high water level indicators, use of sanitary pumps and compressors, proper drainage, adequate blow down control, and conductivity sensing to divert unacceptable water to drain.

DISTILLATION APPLICATIONS AND CAPACITIES

The majority of USP WFI currently produced in the United states is produced by distillation. WFI production is shared by both ME and VC stills. SE stills are found in areas where only small quantities of WFI are required. However, where large amounts of WFI are required, economics of operation dictate the use of either ME or VC

Table below shows typical capacities and temperature of WFI produced by each process

(INSERT TABLE HERE)

Process and system description

SINGLE EFFECT DISTILLATION (SE)

se systems incorporate a single evaporator heat exchanger, separator mechanism, and a condenser.

SE systems are available in electrically or steam powered versions, although electrical units are limited to very small production rates (<30 gallons per hour)

Steam powered units typically require 30-60 psig plant steam. Cooling fluid is required for both steam and electric powered versions. When water is the coolant, the rate is apporxiametly 8-10 gallons per gallon of WFI produced, based on a supply of 4-16 degrees C, and temperature rise of 67 degrees C

SE systems typically operate at atmospheric pressure and 100 degrees C, and incorporate non-ASME code vessels.

WFI is delivered at atmospheric pressure and 80-100 degrees C, thus a distillate transfer pump is required, unless the WFI tank is at a lower elevation than the still.

MULTI EFFECT DISTILLATION (ME)

ME systems incorporate two or more evaporator heat exchangers, separator mechanisms, and a

condenser into a staged evaporation and condensation process. Typical systems have 3-8 effects. Each effect includes an evaporator and a separator (see chapter 11).

ME systems typically require plant steam at 80-120 psig, and cooling fluid at a supply temperature of 4 degrees c- 16 degrees c, based on temperature rise of 65-70 degrees c. the quantity of steam and cooling fluid required varies significantly based upon the WFI production rate and the number of effects. Capital costs increase while steam and cooling fluid consumption decrease, as the number of effects to produce a given quantity of WFI increases. ME systems operate under pressure, and typically deliver WFI at80-100 degrees C.

Normally, water used for cooling is not the same as the feed water, and does not require special pretreatment for the purpose of scale prevention. However, corrosion prevention measures, such as chloring and chloramine removal, are necessary.

Some designs deliver the water at atmospheric pressure and require a transfer pump unless the WFI storage tank is at lower elevation than the still. Other designs which may operate at 5-10 psig condenser pressure, do feature a distillate transfer pump for higher pressure deliveries

Vapor compression distillation (VC)

VC is a distillation method where water is evaporated inside, or outside, a bank of tubes arranged in a horizontal or vertical configuration. The horizontal design is normally of the forced circulation type with recirculation pump and spray nozzles, while the vertical design is of the natural circulation type.

Major system components are the evaporator, compressor, heat exchanges, deaerator, pumps, motors, valves, instruments, and controls.

The vc process operates on the same principle as the mechanical refrigeration cycle.

In a VC still, feed water is evaporated on one side of the tubes. The generated steam passes through the disengagement space, through the separator, and into the compressor.

The energy imparted by the compressor results in compressed steam with increased pressure and temperature. The higher energy steam is then discharged back into the evaporator/condenser vessel. There, the steam condenses and gives up its latent heat, which is transferred through the tube wall to the water. More water is boiled off, generating more vapor, and the process is repeated. The outgoing distillate and blow down streams preheat the incoming feed water, thus saving energy. Since the latent head is recycled there is no need for a stand-alone condenser as in the SE or ME systems.

DISTILLATION PREATREATMENT REQUIREMENTS-GENERAL

All distillation units are susceptible to scaling and corrosion, if the appropriate feed water preatreatment is not provided. VC and some SE still operate slightly above atmospheric pressure, and the removal of calcium and magnesium, by way of water softening, is normally required as a minimum. ME stills operate at a much higher pressure and temperature, and require higher quality feed water in order to prevent scaling and corrosion. Normally, ion exchange beds are employed as feed water pretreatment to a multiple effect still. RO is also used as feed water pretreatment for either the VC or multiple effect

stills. All distillation units will invariably experience some form of scale build up and must therefore include routine visual inspections plus cleaning of the still during shutdown periods when appropriate. Both types of still are susceptible to attack by chlorine. Chlorine removal is essential if damage is to be avoided. Activated carbon filters and sodium bisulfate injection are effective and common methods for chlorine removal.

From a microbiological perspective, the bacterial and endotoxin load should be consistently controlled to a level that does not overload the still.

PRETREATMENT REQUIREMENTS- SPECIFIC

PRETREATMENT FOR SINGLE EFFECT STILL (SE)

See the "pretreatment for ME still" paragraph and above for general information on distillation pretreatment

PRETREATMENT FOR MULTI EFFECT (ME)

The baseline pretreatment for ME must provide very low TDS feed water, preferably less than 10mg/l, and less than 1mg/l silica. Some manufacturers offer ME still to operate on softened water. Others allow higher levels of silica, up to 5 mg/l. the pretreatment must also remove chlorine and obnectionable volatiles, such as ammonia if present.

A BASELINE SYSTEM TO ACHIEVE VERY LOW TDS MAY BE DI OR RO

INSERT TABLE HERE BRUCE

See chapter 4 or 5 for more information on pretreatment

Pretreatment for vapor compression still (VC)

See section 6.5.4 for general information on distillation pretreatment requirements. The baseline pretreatment for VC still is softening, the removal of chlorine, and other objectionable volatiles such as ammonia, if present

INSERT TABLE HERE BRUCE

a) **ECONOMICS**
   economics of the single effect still: commercially available SE systems are inherently simple in design, configured similarly, and offered with significantly fewer options, compared to ME and VC systems. As a result, fewer factors affecting costs are applicable by comparison. Operating costs of SE systems are associated mainly with plant steam and cooling fluid. Utilities consumption rates are fairly consistent among SE manufacturers.
b) Economics of the multi effect still: although all commercially available ME systems are configured similarly and supplied with the same basic components, opportunities for cost savings exist in the areas of construction materials, surface finishes, and instrumentation.

Operating costs of ME systems are associated mainly with plant steam and cooling fluid. Utilities consumption rates vary among ME manufacturers.

c) Economic of the vapor compression still: significant opportunitites exist to reduce capital cost associated with selection of construction materials, surface finishes, and instrumentation used in the construction of VC still. Operating costs of VC systems are associated mainly with electrical power.

RECOMMEND CONSTRUCTION MATERIALS:

Materials shown table 6-2 are based on available designs by leading manufacturers. However, other materials may be utilized based on the technical application.

INSERT TABLE 6-2 HERE BRUCE

*some manufacturers may use sanitary clamps on distillate piping only

SURFACE FINISH

Mechanical polishing (MP), electropolishing (EP), and passivation processes are implemented in stainless steel distillation systems in order to improve corrosion resistance. These processes are neither necessary, nor applicable, to other alloys such as tin-coated, titanium, and Inconel, based on differences in metal chemistry.

MP and EP/passivation processes affect the microscopic amplitude and chemical composition, respectively, of the stainless surface. These processes are not considered necessary to control microbial growth due to the relatively high operating temperatures. MP is advocated for final finishing of mechanical welds and EP/passivation for all stainless steel surfaces to optimize the formation of the corrosion resistant chromium oxide barrier.

The impact of progressive mechanical polishing on the capital costs of still and other equipment is considerable, and often can account for 25% to 30% of a ME or VC still cost. MP processes, except when used to smooth out a mechanical weld or misalignment etc., may be removed from the applicable specification without fear of compromising the water quality.

INSTRUMENTATION AND CONTROLS

For WFI applications, the level of instrumentation should be sufficient to monitor parameters considered critical because they relate to ensuring proper hydraulic, thermodynamic functionality and the production of the appropriate quality of WFI. Instrumentation for critical operating parameters should be calibratable using national nation institute of standards and technology (NIST) traceable equipment.

INSERT TABLE HERE BRUCE

REVERSE OSMOSIS RO

RO employs a semi-permeable membrane and a relatively high pressure differential to force water through the membrane to achieve chemical, microbial, and endotoxin reduction, critical in USP WFI applications. The feed water is converted into two streams, permeate and reject. The permeate water flows through the membrane and is produced cold and as such does not have the temperature protection for microbial growth afforded by the alternate distillation processes. The reject stream discharges comparatively smaller volume than the permeate, and contains virtually all of the feed water contaminants.

APPLICATION

Ro systems are used as USP WFI pretreatment for distillation processes, or as final treatment for USP purified water systems. RO is also an accepted means of producing WFI, and may provide a low capital and operational cost alternative to distillation.

Membranes that are hot water santizable at 80 degrees C are now available for pretreatment and final treatment, thus eliminating the need for chemical santization and simplifying the validation process. These membranes still require periodic chemical cleaning

Membranes which may allow for continuous operation at 80 degrees C are under development. This may have a significant impact on the use of RO as a means of producing USP WFI since operation of the system at 80 degrees C may nearly eliminate biological concerns. Failure of a membrane or seal will result in permeate contamination. These problems may be controlled by:

- Pretreatment of the feed water
- Appropriate membrane material selection
- Latest technology membrane design
- Integrity challenges
- Periodic sanitization
- Monitoring of microbial levels, conductivity, total organic carbon and differential pressure

DESCRIPTION

Semi-permeable RO membranes are produced commercially for water purification in spiral wound and hollow fiber configurations. RO membranes are permeable to some substances such as water and dissolved gases, while impermeable to other substances such as salts, high molecular weight organics, acids, bases, colloids, bacteria, and endotoxins. Membranes are available in four basic materials; cellulose acetate, polyamide, thin film composite, and polysulfone. (polyamide membranes are virtually identical in performance to thin film composite membranes). All three membrane types have advantages and disadvantages (see chapter 5 for more details).

Bacteria and endotoxin removal, required for WFI applications, can be performed at ambient temperatures. This significantly reduces utility costs compared to alternative elevated temperature processes (distillation) by operating at ambient temperatures, distribution piping may not require insulation and may not need to be constructed of stainless steel.

For WFI applications, opportunities exist for enhanced control of the single pass unit, by utilizing multi-pass-product-staged or other combination designs. These configurations improve reliability and efficiency, while improving water quality and quality assurance over the single pass design.

PRETREATMENT REQUIREMNTS

RO as the final processing step, may require pretreatment using ion exchange, deionization, RO, and/or ultrafiltration to improve operability and quality attributes

Pretreatment requirements normally include gross particle filtration, scale prevention, and chlorine removal. Carbon dioxide and ammonia gas, are not removed by the Ro process, and may be removed by degasification, caustic addition, ion exchange, or electrodeionization, prior to the final RO process step. (see chapter 5 for more details)

Due to the stringent microbial and endotoxin control required for parenteral and other critical applications, the pretreatment prior to the RO should incorporate additional provisions for control and monitoring or microorganisms.

Disinfectants such as chlorine or chloramine, should be maintained when tolerable at appropriate levels throughout the pretreatment chain. Stagnant water resulting from surge tanks or dead legs should be avoided by design or by the inclusion of recirculation systems, which should include in-line microbial control devices such as uv sterilizers.

Regular and appropriate sanitization and cleaning of all unit operatuions subsequent to and associated with the disinfectant (chlorine or chloramine etc.) removal should be scheduled to maintain and complete the microorganism control of the pretreatment system (see chapter 4 for further details)

ECONOMICS

Opportunities are available to reduce capital costs associated with the selection of construction materials, surface finished, and instrumentation used in the construction of RO units without compromising the water quality. operating costs of RO system are associated mainly with replacement membranes, water concentrate discharge, electric power, cleaning and sanitizing chemicals, replacement filters, and pretreatment cost.

CONSTRUCTION MATERIALS

construction material selection for RO are driven by:

- Structural integrity, based on high operating pressure
- Structural integrity based on low pressure sections ahead and after the membranes
- Chemical compatibility with the contact fluid and its constituents
- Need to control micro-organism growth

The low operating temperature of the Ro system allows the use of non-metallic construction materials. Sanitary piping and valves are generally optional features for RO systems, based on the specific manufacturer and location of the RO in the treatment chain

For the final purification step, it may be very cost effective to utilize mill finish 304 stainless steel for the feed and concentrate waste piping for the system, maintaining 316L stainless steel or PVDF and sanitary design for the product piping only

SURFACE FINISH

MP and EP processes are not applicable to non-metallic systems

INSTRUMENTATION AND CONTROLS

RO control system usually use local control and indication, and do not typically require programmable logic controller (PLC) as a standard feature. The type and level of instrumentation is similar among manufacturers. The level of instrumentation should be sufficient to monitor parameters considered critical because they relate to ensuring proper hydraulic functionality and the consistent production of quality WFI. Instrumentation for critical operating parameters should be calibratable using NIST traceable equipment (see chapter 9 for more details)

The typically monitored operating parameters for an RO system are feed pH, feed conductivity, and product quality (TOC and conductivity) these three parameters should be measured using calibratable, NIST traceable instruments. Recording data may be accomplished manually or electronically using analog instruments and paper/paperless recording systems.

ADVANTAGES AND DISADVANATGES

Multi-pass can, in most cases, produce water quality consistent with the minimum requirements of USP WFI. In cases where the feed water quality is such that this is not possible, the use of some type of deionization (e.g. additional RO, UF, ion exchange, or electrodeionization) as a pretreatment may be required. This is to allow the final point of purification to remain RO and the system to generate consistent and reliable water within the USP WFI specifications.

Advantages associated with the design and operation of RO units used as the final treatment step for the production of WFI are:

a) Dispending on cost and complexity of pretreatment, RO systems designed for production of USP WFI may provide for significantly reduced capital costs when compared with distillation processes, while maintain the appropriate USP WFI quality
b) The utility requirements are significantly lower for the RO systems (electrically for pump horsepower) than for distillation, resulting in lower operating costs, which may be a very significant factor over the lifetime of the system.

Disadvantages associated with the design and operation of RO units used as the final treatment step for the production of WFI are

1. MEMBRANE FOULING AND INTEGRITY

- bacteria grow through
- Seal leakage or by passing
- Seal failure or damage caused by chemical attack

- Membrane damage during instillation etc
- Membrane damage due to chemical or high temperature attack

2. MEMBRANE MATERIAL SENSITIVITY TO BACTERIA AND SANITIZING AGENTS
3. INHERENT SANITIZATION LIMITATIONS

- periodic chemical or hot water sanitization may be required
- Periodic chemical cleaning may be required

4. PRETREATMENT COST MAY BE HIGH

RO systems provide a method for consistently producing ambient water in accordance with the USP WFI requirements. This not only reduces utility requirements, but also may reduce installation costs, since thermal insulation may not be required for storage and distribution.

USP-WATER INJECTION SYSTEM COMPARISON

INSERT TABLE HERE BRUCE

Ratings L=low M=medium H=high

Notes

All indicators are relative to each other within the specific category

Optimum design and operating conditions are assumed

Total water consumption dependent on pretreatment selected

RO may not meet USP TOC levels if feed water TOC is high (>3ppm)

PHARMACEUTICAL STEAM

INTRODUCTION

This chapter aims to simplify and standardize the process of selection, programming, and design of pharmaceutical steam systems. Guidelines, information, and options are provided, along with advantages and disadvantages, based on the best and most cost effective of current and proven practices and technologies.

The absence of regulations governing the use of steam in pharmaceutical processes has resulted in the proliferation of differing practices and interpretations. Most interpretations are made on the side of conservatism. Unfortunately, in addition to increasing cost without an associated increase in benefits, excessive conservatism can result in the system complexity, and possibly reduce reliability. One example is the use of clean steam (non-utility boiler produced steam) where a form of utility steam (utility boiler produced steam) would be adequate to maintain product quality. the installation of a clean steam generator when a simple steam reducing station would suffice results in added equipment and the associated impact on cost, complexity, and reliability.

In some instances, interpretations are based on inaccurate assumptions of what is important or critical. An example is the over specifying of pretreatment or using WFI as feed to solve the perceived provlem.

The chapter establishes standard definitions for terms commonly associated with pharmaceutical steam and provides information that facilitates making correct and cost effective decisions.

CGMP issues

The user has the ultimate responsibility for system design and performance, and for ensuring that the proper steam is used for a given process.

There is no FDA or USP minimum standard for clean steam. However, cGMPS for large volume parenterals (LVPS) issued in 1976 indicated that feed water for boilers supplying steam that contact components, drug products, and drug product contact surfaces shall not contain volatile additives such as amines or hydrazines.

Few regulations govern the design and construction of clean steam generators. There are also no regulations governing materials of construction, type or level of instrumentation, surface finishes, or operating temperatures.

Among US government publications, the FDA's code of federal regulations (CFR) provides culinary steam recommendations and stipulations related to heat exchanger and tank air vents design and construction. The culinary steam recommendations apply to food applications only.

US public health service/diary industry committee, 3A sanitary standards, number 609-02, adds additional limitations to culinary steam feed water additives for food applications. It should be noted

that boiler feed water additives permitted in food for human consumption may not be acceptable in drinking water or orally ingested drug products.

STEAM ATTRIBUTES

QUALITY

the term quality when referring to steam indicates the level of steam saturation. There are no FDA or USP regulations relating minimum “steam quality” or the level of non-condensable gasses present in pharmaceutical steam. (See section 7.4)

European regulators have defined specific criteria for pharmaceutical steam used for equipment sterilization. (European Standard EN-285-steam sterilizers-reference section 13.3) these cover acceptable levels of saturation or dryness, the level of superheat, and the volume of non-condensable gases present.

Purity

Purity requirements for steam in pharmaceutical manufacturing and product development are driven by the product characteristics, manufacturing process, and the intended use of the product. The product manufacturer is responsible for ensuring that steam used to process the product is appropriate.

Though steam purity requirements are product specific, it may be impractical to reliably produce special steam for each situation. Manufacturing operations typically generate and distribute only one or two steam purity grades, commonly grouped

TYPES OF STEAM

Pharmaceutical steam is classified into two (2) types based on their respective sources. These are:

1. Utility boiler produced steam, hereafter called utility steam
2. Non-utility boiler produced steam, hereafter called clean steam.

UTILITY STEAM

Utility steam is characterized with usually having:

- Chemical additives to control scale and corrosion
- Relatively high pressure with the potential of generating superheat during expansion
- Relatively high pH

Chemical additives: utility steam is produced, in most cases, using conventional fire-tube steam boilers, normally of steel construction. Such boilers are most always provided with systems that inject additives in the feed water to protect the boiler and steam distribution piping from scale and corrosion. Some of these scale and corrosion inhibitors may, and often do, include amines and other substances that may not be acceptable in steam being used in pharmaceutical processes. The user must determine what additives are used, and to verify if they are acceptable in the particular application, i.e. do not add any impurities or create a reaction in the drug product.

Utility steam can be filtered to remove particulate matter, but filtration does not remove dissolved substances and volatiles such as amines

SUPERHEAT: superheated steam is produced in water tube boilers by reheating the steam or by generating the steam at a higher pressure in a fire tube boiler and then reducing the pressure through a regulating valve. When the pressure is reduced, the energy in the higher temperature steam is dissipated to generate steam at the lower pressure and produce superheated steam above the corresponding saturation temperature. Superheat is dissipated downstream of the regulating valve due to heat loss in the line.

pH control: in order to protect carbon steel from corrosion by the steam, it is necessary to use additives to raise the pH to between 9.5-10.5.

CLEAN STEAM (CS)

Pharmaceutical clean steam is generated from treated water free of volatile additives, such as anmines, or hyrazines, and is used for thermal disinfection or sterilization processes. It is considered especially important to preclude such contamination from injectable drug product:

Clean steam is characterized as having:

- No additives
- No generated superheat except when the generates pressure is significantly higher than the use pressure of the steam (see section 7.3.1- superheat)
- Relatively low pH

There are many terms used in the pharmaceutical industry to describe clean steam. These include clean steam, pure steam, pyrogen free steam, WFI steam, and USP purified water steam. There is no standard or accepted definition for any of these terms. However, the most commonly used terms are “pure steam” and “clean steam”. In this guide, the term “clean steam” is used in lieu of all others.

The condensate of clean steam has no buffer, and may have a relatively low pH compared to that of utility steam.

BACKGROUND AND INDUSTRY PRACTICES

PURITY OF STERILIZING STEAM

when steam or the resulting condense water comes in direct or indirect contact with the drug product, the purity should be equivalent to the water purity acceptable for final rinsing of the drug contact surfaces

NOTE: a continuous supply of dry saturated steam at the point of use is considered necessary for efficient steam sterilization. Water carried by the steam in suspension may cause damp loads and superheated steam is considerably less effective than saturated steam when used for sterilization. Non-condensable gases if contained in the steam may prevent the attainment of sterilization conditions in parts of the sterilizer load.

STEAM USED FOR HUMIDIFICATION

When steam is used for indirect humidification, such as injection into HVAC air streams prior to final air filtration, the steam does not need to be purer than the air that is being mixed with. However, when humidifying process areas, the potential level of impurities, including amines and hydrazines should be evaluated in order to ascertain the impact on the final drug product. This is particularly important in areas where open processing takes place, such as aseptic filling suites and formulation areas. If the diluted water vapor is found to contribute significantly to the contamination of the drug, a purer grade of steam should be selected

COMMON PRACTICES

It is common practice to generate pharmaceutical steam from compendial waters and test the steam condensate for equivalency to the compendial standard. This practice ignores the ability of the pharmaceutical steam generator to remove impurities. This overprocessing is wasteful and unnecessary. An exception is when the steam quantity is small and the cost and maintenance of a dedicated feed water pretreatment system exceeds the cost of using compendial water. Pharmaceutical clean steam is commonly used in applications were utility steam would suffice, such as noncritical room humidification and high purity water heat exchangers.

Table lists the commonly accepted industry standards and highlights the trend in the pharmaceutical industry to provide “purer than necessary” steam and over-specified feed water.

Table 7.4.4 INDUSTRY AND BASELINE PRACTICES IN THE PRODUCTION OF STEAM

INSERT two TABLES

SYSTEM PLANNING

Pharmaceutical steam system planning, show in the figure 7-1 is a graphic representation of the system boundaries, limitations, and restrictions. Initial system planning reveals primary boundaries that establish the cornerstone for design criteria. These system boundaries are steam requirements, system design, use point criteria, and distribution system requirements.

The arrows encircling each boundary represent limitation that establish more specific operating strategies and ranges. To allow more flexibility in final planning and detailed design the designer should always indicate ranges of acceptability, rather than a specific value or position.

STEAM REQUIREMENTS

the planning process starts with the listing of all steam requirements and applications that include:

1. Company standards including QA/QC requirements and published sops
2. The categorization of usepoint by:
    - Type of application (humidification, critical or non-critical, API, and dosage for applications)
    - Purity selection (this is based primarily on the application and the endotoxin and chemical purity criteria set for the product for which the steam, or its condensate, will be in contact

with. The selection must consider underlying factors which have impacts on purity control, installed and operating cost, maintenance, and practicality
- Steam quality (dryness, non-condensable limits, and maximum superheat)

SYSTEM DESIGN

Pharmaceutical steam is generated using different methods. The most appropriate method for each application must be selected (see the pharmaceutical steam purity decision tree, section 7.6)

The process continues with an evaluation of the steam system requirements (generation) that includes: the selection of the type of generation system that would satisfy each category, which would include:

The types of generation systems available (if both pyrogen free clean steam and clean steam without endotoxin limits is required, the practicality and economy of producing only the higher grade should be raised.)

- The source of utility steam or electrical power (the plant steam requirement for clean steam as well as utility steam and the option or electric powered steam generators should be considered.)
- The type and number of systems required based on feedback from the distribution system evaluation
- The condensate sampling needs
- Safety consideration

USE POINT CRITERIA

the third step defines the specific delivery requirement ranges for clean steam at the point of use including:

- Utilization, which is determined for each overall system peak demand(S), average demand, and the relationships between peak demand time periods and their flow rates
- Pressure and flow levels
- Use periods and histogram analysis, if available
- Quality
- Purity

DISTRIBUTION SYSTEM

The fourth step includes the distribution system evaluation, which includes:

1. Condensate, non –condensable and moisture removal
2. Pipe size and insulation requirements including:
    - Materials of construction, sanitary design requirements and surface finish
    - Physical location of each use point
    - Heat and temperature losses
    - Natural drainage

NOTE: since the steam quality will decline, due to head losses, with time, the efficiency of the insulation and the length of the distribution system, the quality at the use point will not be expected to reflect the generation quality level.

RE-EVALUATION OF SYSTEM BOUNDARIES AND CONSTRAINTS

these sequential steps are repeated and re-evaluated as information in the design process iterates, and further criteria about the overall system boundaries are identified (see figure 7-3)

In operations with a requirement for only one grade of steam, the steam system is designed to meet the most stringent requirements of the most demanding product or process. With more than one purity grade of steam, products and processes are often categorized and fed by the most appropriate system. The number of types of steam generated is most often a function of the volume of steam consumed and variation of purity required.

Table 7.2 PHARMACEUTICAL STEAM PURITY DECISION TREE

INSERT TABLE HERE

PROCESS AND SYSTEM DESCRIPTION

UTILITY STEAM

Utility steam is produced in conventional plant utility boilers whose typical design and construction are well known and will not be covered in this chapter

CLEAN STEAM

Clean steam is produced in specifically designed non-fired generators or from the first effect of multi effect WFI stills, which do not use scale or corrosion inhibitor additives. The generator is fed with water pretreated for the purpose of removing elements that contribute to scaling or corrosion, and the materials of construction are resistant to corrosion inhibitors

The dedicated CS generator Is very similar in design and construction to the first effect of a multi-effect still. For information on multi-effect (ME) stills, see chapter 6

CS obtained from a ME still

When clean steam is obtained from the ME still, the first effect is usually fitted with two valves, one to isolate the remaining effects and the other to isolate the clean steam use points. Depending on the manufacturer, the still may or may not produce steam when the still is producing WFI

ADVANTAGES

- Does not require a separate generator with the associated cost, space, installation, operation, and maintenance

DISADVANTAGES

- Output is limited to the capability of the first effect of the ME still
- May not produce steam when the still is producing WFI. In an ME, the steam generated in the first effect becomes the motive (power) steam for the second effect, which in turn produces motive steam for the third effect, etc. therefore, the impact of the diverted steam is multiplied by the number of effects, and WFI production is significantly reduced.

The still manufacturer should be consulted in advance, if simultaneous production of WFI and clean steam is desired.

CS PRODUCED FROM A SANITARY CLEAN STEAM GENERATOR

CONFIGURATION OF ATPYICAL SANITARY CS GENERATOR

There are various designs of CS generators. All are evaporators.

They can be of the vertical or the horizontal type, depending on the manufacturer and the overhead space available.

The disengagement space and the separator may be housed in the same vessel as the evaporator or in the separate vessel.

Sanitary construction includes orbital tungsten insert gas (TIG) welding (see section on fabrication of distribution systems) wherever possible or mechanical welding with inner surface ground smooth after welding. All removable connections use in-line sanitary fittings. Flanges and threaded connections are not considered sanitary

Heat exchanges using utility steam as the heat source, including the evaporator should be of the doublesheet, tubular design to prevent the contamination of the clean steam by the heating medium

Most CS generators, except those with very small output are fitted with feed water heaters. In addition, a blow down cooler is used to avoid discharge of very hot and flashing water.

A feed pump may be required if the feed water supply pressure is inadequate. Depending on system design and the manufacturer, a feed pressure of approximately 8-10 psig above the maximum expected clean steam pressure is required. This allows for pressure drop in piping and valves.

A sample cooler fitted with conductivity meter and alarms is often used to monitor clean steam condensate purity. This is an optional feature whose use should be decided based on need. Conductivity of the condensate will provide information regarding the suitability and applicability of the distributed steam for its final use.

PROCESS AND OPERATING PRINCIPLE OF A TYPICAL SANITARY CS GENERATOR

Clean steam is normally generated in a shell-and-tube heat exchanger evaporator. Feed water is introduced on one side of the tubes, while the heating medium is introduce on the other side. Heating of the feed water to above the boiling temperature causes the water to evaporate, producing steam.

The heating medium does not come in direct contact with the feed water or with the clean steam, and is normally utility steam. However, CS generators may be designed to utilize other heating mediums. The main differences in the designs are evaporator and separator.

a) OPERATION

Clean steam pressure is maintained by a feedback control loop, which modulates the supply steam control valves. The evaporator feed water is independently controlled using a level sensor and feed water pump.

b) STEAM SUPPLY

The utility steam supplied to the generator at typically 100psig to 120psig (7.0 to 8.5 ks/cm2 gauge or 7.9 to9.25 bars) must be at a higher pressure than the required clean steam pressure. In general, for a given size generator, the greater the differential between the utility steam pressure and the clean steam pressure size higher than the clean steam pressure, to optimize the production rate. Utility steam consumption will be approximately 10 to 20% greater than the quantity of clean steam produced

c) CLEAN STEAM PRESSURE

Clean steam pressure is selected by the user. Typical units are designed for pharmaceutical applications at 40-60 psig (3.75-5.1 bars).

d) Separator

Entrainment separators are normally designed to function over an optimum range of steam velocity. If the volume of steam increases substantially, carryover of endotoxins can occur. This condition can exist if the steam pressure differential significantly exceeds design conditions. Under the conditions, the velocity of the steam through the separator may be excessive. The manufacturer should be consulted regarding the output of the generator at the highest possible pressure difference. An alarm and equipment shutdown is recommended and can be incorporated into the controls to protect against such conditions.

e) FEED WATER LEVEL

The feedwater level is controlled to protect against flooding of the evaporator and carryover of the endotoxins by a high level alarm and subsequent shutdown. Evaporator level condition does not affect clean steam purity but is an indication of insufficient feed water or excessive blow down.

INSERT TABLE BRUCE

CS PRODUCED FROM A SIMPLE CLEAN STEAM GENERATOR

there are applications where pyrgoen free steam and sanitary construction features are not required, and at the same time, utility steam cannot be used. In such cases, it may be most economical to utilize a simple clean steam generator for the most economical design. Savings may be worthwhile when the elimination of the steam separator is combined with non-sanitary features such as :

- Non-sanitary pipe and fittings
- Non-sanitary instruments and valves
- No polishing
- Minimum control

The elimination of the separator alone does not provide significant cost savings. It is important to remember that the separators function is more than removal of endotoxins. It removes entrainment, which includes all types of contaminants present in the feed water, except volatiles. Without an entrainment separator, impurities from the feed water may well be entrained in the steam and the moisture content of the steam as it leaves the generator, can be much higher than in the standard entrained generator. Thus the feed water becomes a critical factor in controlling the steam purity if entrainment is not incorporated in the design.

Independent sanitary entrainment devices are available for installation at, or close to the point of use, and may be used with typical “simple CS generators” as well as to control additional moisture build up due to heat losses in the distribution system of sanitary CS Generators

STEAM CONDENSATE SAMPLING

PURITY SAMPLING

When required by the process, the steam purity shall be monitored through acceptable sampling techniques. A slipstream of the steam may be passed through a sample condenser/cooler, fitted with a sampling valve (see section 7.2.1 for information on steam attributes.)

To ensure that the steam does not contribute to drug product contamination, sampling should be included during commissioning, as good engineering practice, and/or prior to each time the steam is used.

If the sampling requirement is for endotoxin or pyrogen testing, the sample cooler, tubing and valve should be of sanitary construction.

Sample coolers can be fitted to the CS generator, or located in the distribution line, or at the use point (recommended location), or a combination thereof. It is common practice to fit sample coolers with conductivity monitors and alarms.

Endotoxin removal: the condensate sample from a clean steam generator with separator is expected to show 3-4 log10 level reduction in pyrogens compared to the level in the feed water.

STEAM QUALITY SAMPLING

Steam “quality” sampling may be employed to determine the level of saturation and non-condensable gasses. This can be determined by applying a steam calorimeter and measuring the dryness or saturation level. A steam calorimeter measures the percentage by weight of steam in a mixture of steam and entrained water.

MATERIALS OF CONSTRUCTION

MATERIALS OF CONSTRUCTION FOR SANITARY AND SIMPLE CS GENERATORS

structural integrity and chemical compatibility with the contact fluid and its constituents are two of the more practical issues that drive construction material selection for CS systems.

The inherent corrosion potential forces CS manufacturers to consider relatively inert metal including stainless steel or titanium etc. sanitary piping and valves, considered unnecessary for utility and simple CS generators, are often standard features for CS systems based on the specific manufacturer and model. The materials chosen should not contribute to contamination of the drug product.

Typical materials of construction for sanitary and simple CS generators are:

EVAPORATOR AND SEPARATOR:

shells, tubesheets, and internals: 300 series S.S

Evaporator tuves 300 series or titanium, or other suitable alloy

Heat exchangers (feed heater, blow down and sample cooler): 300 series

Piping: 300 series for water and clean steam, and carbon steel for utility steam contact

Valves: 300 series and elastomers/diaphragms for water

Skid and structural: carbon steel

MATERIALS OF CONSTRUCTION FOR UTILITY STEAM GENERATION

Chemical compatibility with the utility boiler generated steam and the carried over feed water chemicals are required for all materials used to condition the contaminated steam

Based on the particulate levels in the steam and the required steam purity, more than one filtration stage may be utilized.

Distribution of utility steam following filtration follows similar practices as CS to control condensate build up, non-condensable gases and saturation levels as required for the application

Acceptable maters must be relatively inert and may include SS or tin-coated

SURFACE FINISH

mechanical polishing (MP), electropolishing (EP), and passivation processes are implemented in some stainless CS systems. Chloring and/or chlorides will damage the generator regardless of the finish.

The operating tempertures of these systems are more than sufficient for inhibiting microbiological growth. Therefore, MP is advocated for final finishing of mechanical welds, with mill finishes and final passivation to optimize the formation of the corrosion resistant chromium oxide barrier. Electropolishing will also optimize chromium oxide barrier, and should be considered if passivation is not an option.

PRETREATMENT FOR CS (sanitary and simple) GENERATORS

the feed water pretreatment for a CS generator is born from three separate and distinct considerations:

1. Scale formation
2. Corrosion
3. Volatiles which carryover with the steam and may affect steam purity

SCALE

Scale formation is a function of generator feed water chemistry, concentration (depends on blow down rate) and temperature. It is independent of design and make, and is outside the control of the generator manufacturer or the operator.

Because scale inhibitors are not used, and because of the relatively high operating temperatures of the CS generator, the total dissolved solids (TDS) of the feed water should be very low. Silica is of particular concern. Most manufacturers stipulate a level of less than 1ppm (parts per million), some go as high as 5 ppm. In addition to having low TDS the feed water should have no measurable hardness it is therefore common to use DI or reverse osmosis as pretreatment to the CS generator. All CS generators will invariably experience some form of scale buildup and therefor must include routine visual inspections plus cleaning of the generator during shutdown periods when appropriate.

Using compendial water as feed is wasteful, unless the steam quantity is small and the cost and maintenance of a dedicated feed water pretreatment system exceeds the cost of using compendial water

Some manufacturers offer generators to operate on softened water. Usually the rate of blow down is increased in order to maintain low concentration

Note: if the TDS of the soft water is relatively high, soft scale (such as sodium scale and sludge) can form.

CORROSION

The most common cause of corrosion is free chlorine, not chlorides.

Chlorine and chlorides, at any detectable level are very detrimental to stainless steel. The higher the temperature and chlorine level, the more severe is the attack. Chlorine is known to migrate and concentrate in localized cells where the level can reach tens, or hundreds of ppm, while the concentration in the main stream is a fraction of a ppm.

Chlorine can be removed from the feed water by chemical injection of a reducing agent such as sodium bisulfate or by passing the chlorinated water through carbon cilters

VOLATILES

dissolved gasses and substances that are volatile at the operating temperature of the CS generator will carryover with the steam. If such substances are objectionable or may potentially compromise product

quality, they must be removed at the pretreatment stage. Ammonia and CO2 (carbon dioxide) are examples of volatile gases that will have an effect on the conductivity, such that a condensate sample may not meet USP requirements for purified or WFI water.

For more details on pretreatment and the advantages and disadvantages of the different processes, refer to chapters 4 and 5 of this guide.

TREATMENT OF UTILITY STEAM

when utility steam is considered, it may be necessary to filter/condition the steam. In certain applications it may also be necessary to change the steam boiler treatment and substitute additives that do not contain amines or hydrazine.

Since the type and degree of conditioning are dependent on the application, as well as on the quality of the utility steam and additives present, this guide cannot address all possible scenarios.

Prior to the elimination of amine and hydrazines, by the substitution for standard boiler pretreatment additives, the utility steam boiler manufacturer should be consulted regarding the impact on equipment warranty, performance and expected life. Some of the substitute additives are not as effective as the standard.

COST IMPLICATIONS

determining the economics of pharmaceutical steam production is complex. Costs are quite predictable but vary greatly depending on scale of operation, system design, actual usage etc. the total operating cost to produce pharmaceutical steams is obtained by adding the cost of feed water to the costs of pretreatment and final treatment (primary ion removal and polishing). The type of pharmaceutical steam system design option selected is typically based on feed water TDS, silica and hardness levels, organic and colloidal content, as well as anticipated steam system utility costs (acid, caustic, salt, power, and source water.) consideration should also be given to maintenance requirements and available resources.

STEAM “QUALITY”

Steam quality is defined as the saturation percentage of steam to water or more explicitly, the ratio of the vapor mass to the mass of the steam mixture.

Dry saturated steam within superheat is necessary for efficient steam sterilization.

Water can be generated and carried by steam within distribution systems in two ways:

In suspension as moisture when the steam is not 100% saturated

As condensate separated from the steam

Water vapor carried in suspension may be reduced by adding more heat or raising the temperature, reducing the pressure, or adding a steam entertainment separator. Water moisture and condensate may be reduced by steam traps

DISTRIBUTION

Distribution systems for clean steam follow the same good engineering practices commonly used for utility steam, with the exception that contact materials must be inert to the aggressive nature of clean steam. Corrosion-resistant 304, 316, or 316L grade stainless steel “tubing” or solid drawn “pipe”are commonly used. Surface finish is not critical due to the self sanitizing nature of the clean steam. Mill finish or 180-grit mechanically polished pipe or tubing is sufficient. TIG orbital welding and post installation passivation is considered appropriate for this application. Piping must be designed to allow for thermal expansion and to drain condensate.

Note: drains should have air breaks

Sanitary clamps or pipe flanges are most commonly used where the piping must be broken, but welded connections are used as much as possible to eliminate maintenance costs and potential for leaks. Threaded connections may be suitable for instrumentation if positioned to drain condensate and remain hot. Ball valves are commonly used for isolation because elastomeric diaphragms do not hold up well in this service. Where diaphragm valves are used, Teflon encapsulated EPDM diaphragms give the best long-term performance.

Steam quality sampling may be determined during “commissioning” and consistency ensured based on the proper location and subsequent maintenance of traps, entrainment separators, and vents. (the subject of maintenance cannot be over emphasized when these devises are involved due to the small orifices are required in the separation of gas and liquid.)

LINE SIZING

the steam distribution header should be sized for a maximum velocity of 7,200 feed per minute (120 ft/sec or 37 m/sec) to limit erosion and extended the life expectancy of the piping. Condensate line sizing should follow good engineering practices for utility condensate.

WATER MOISTURE REMOVAL

Water vapor forms in steam systems due to heat loss, causing a change in the liquid/vapor ratio or steam “quality”

Steam may be dried of moisture by reducing the generated pressure just prior to the point of use to coincide with the steam temperature of saturation at the reduced pressure.

Moisture entrained in the steam can also be removed by installing an in-line separator at the point of use, just prior to, or just after, the regulator. If the separator is located upstream of the regulator, the regulator should be protected from water damage (wire drawing) and impingement damage on the regulator diaphragms.

In-line separators are available in sizes from ½” to 6” (approx. 1cm to 15cm) and remove moisture with a series of baffles on which the suspended water droplets impinge and fall out by gravity to the drain, which must be piped to a trap. Separators have a separation efficiency of better than 99% in the removal of all liquid and solid entrainment exceeding 10 microns.

CONDENSATE REMOVAL

Condensate is the water that has separated from the liquid vapor mixture and forms in steam systems due to heat losses and natural separation effects. Lines should be designed to prevent the buildup of condensate to avoid dangerous water hammer and to eliminate potential cold spots where bacteria can grow. Any untrapped vertical length of pipe will quickly fill with condensate. If this condensate is allowed to stand for sufficient time, it can cool and become a breeding ground for bacteria. This bacteria could possibly be entrained back into the main distribution header and contaminate use points downstream. Worst case condensate removal locations should be sampled monthly for presence of bacteria. The following practices are commonly employed to minimize these concerns:

- Each line is adequately supported to avoid sagging and subsequent condensate accumulation
- Steam traps are installed at all points where condensate can collect (e.g. at least every 100 feet (30 meters) of line, upstream of control valves, at the bottom of vertical risers, etc.) steam traps used for clean steam service should be sanitary design and self-draining.
- If the main distribution header is above the use points, the branches to the users should be routed from the top of the header to avoid excessive condensate loads at the branch. Each branch should be trapped to avoid condensate buildup.
- An alternative is to run the main distribution header below the use points. Then the branches can drain back to the main distribution header, avoiding the need for additional traps.
- The requirement to trap each branch can be waived for short drops from main headers to vessels or other equipment that are in frequent use where the sterilization and water hammer is not impacted by the collected condensate. An example is a drop from a main distribution header to media storage tank, which is sterilized daily. The condensate built up in the vertical drop line has only a limited time to cool and is quickly eliminated by the trap at the bottom of the vessel when the block valve Is opened. The vertical drop is sterilized daily with the vessel, so there is little change for bacteria to grow.

NON CONDENSABLE GAS REMOVAL

Air and other non-condensable gases should be minimized from pharmaceutical steam systems. Since air acts as an insulator, incomplete sterilization can occur in the process. Air in a system offers a very effective barrier to the heat transfer which will lead to a reduced temperature at the surface of a tube, system component or process equipment.

Air can be discharged using steam traps, however excessive levels may slow down the discharge of condensate. The subcooled condensate can then lead to insufficient sterilization temperatures due to excess water.

The removal of air can be achieved by placing thermostatic pharmaceutical steam traps with the inlet in the upward position. These should be placed in positions where air is prone to collect such as the terminal points of the main and large branches of the steam header, high points in the tanks, reactors and sterilizers, etc. in the case of air and condensate discharge at the bottom of large vessels, the air and condensate should be separated by correct piping practices.

SUPERHEAT

While high pressure steam can be used to compensate for superheat, the latent heat, or killing power of the potentially superheated steam is reduced at higher pressures; leading to increased sterilization cycles.

INSERT TABLE

STORAGE AND DISTRIBUTION SYSTEMS

INTRODUCTION

this chapter provides an overview of eight common distribution configurations and a decision tree to help decide which system best suits the operating requirements. A comparison of tank versus tankless systems is addressed, as well as alternative materials of construction available, and ancillary equipment related to overall distribution systems. Common industry practices are listed as examples, to help clarify regulatory requirements.

SYSTEM DESIGN

GENERAL CONSIDERATIONS

A storage system is used to accommodate peak flow requirements against usage rates. The storage system must maintain the feed water quality to ensure the appropriate quality of the end use of product. Storage allows a smaller, less costly pretreatment system to meet peak demand. A smaller treatment system operates closer to the ideal continuous, dynamic flow. Large manufacturing sites, or systems serving different buidlings, may use storage tanks to separate one section of the loop, and others to minimize cross contamination

The main disadvantage of a storage tank is its capital cost, and the cost of associated pumps, vent filters, and instrumentation. However, this is usually less than the increased cost of pretreatment equipment sized to handle the peak use rate in the facility.

Another disadvantage of storage is that it introduces a region of slow moving water, which can promote bacterial growth.

CAPACITY

Criteria affecting storage capacity include the user's demand profile or the amount of use, duration, timing, and diversity, (in case of more than one user), balance between the supply of pre- and final-treated waters, and whether the system is recirculating or non-recirculating. Careful consideration of these criteria will affect cost and water quality

The storage tank must provide reserve to minimize cycling of the treatment equipment and to reduce pump cavitation. It should provide sufficient reserve to enable routine maintenance and orderly system shutdown in the event of an emergency, which can vary from few to many hours, depending on the size and configuration of the system and maintenance procedures.

STORAGE TANK LOCATION

It may not be cost-effective to locate storage tanks as close as possible to the point of use, within high-cost, GMP-finished areas. It may be more advantageous to locate them close to the generation and equipment, for ease of maintenance. Utility areas are acceptable for this purpose, if access is provided (and the area is kept clean).

TYPES OF STORAGE TANKS

Vertical storage tanks are common but horizontal tanks may be necessary if overhead space is limited. For recirculating systems, tank design should include an internal spray ball to ensure that all interior surfaces are welted for microbial control. Jacketing is usually provided in hot systems, to maintain water temperature over long periods without makeup, or to temper high influent temperatures, to preclude excessive rouging and pump cavitation. To avoid the absorption of carbon dioxide and its effect on conductivity, inert blanketing of the tank headspace should be considered. Storage tanks must be fitted with a sub-micron hydrophobic vent filter to reduce bio-burden and particles.

The maximum size of a single storage vessel is often limited by the space available in the facility. It may be necessary to resort to multiple tanks to obtain the desired capacity. In this case, interconnecting piping must be carefully designed to assure adequate flow through all supply and return branches

SYSTEM DISTRIBUTION DESIGN

GENERAL CONSIDERATIONS

proper design of both the water storage and distribution systems is critical to the success of a pharmaceutical water system.

The optimal design of any water storage and distribution system must accomplish three things:

1. Maintain the quality of the water within acceptable limits
2. Deliver the water to the use points at the required flow rate and temperature
3. Minimize capital and operating expenses

Although items 2 and 3 are well understood, item 1 if often misinterpreted. It is not necessary to protect the water from every form of degradation, only to maintain the quality within acceptable limits. For instance, water stored in the presence of air absorbs CO2 increasing the conductivity. This degradation can be avoided by blanketing the storage vessel with nitrogen. However, for many systems this would be wasteful expenditure if the increased conductivity were still within the required specification.

As technology has improved over the years, many design features such as storage at elevated temperature, constant circulation, use of sanitary connections, polishing tubing, orbital welding, frequent sanitization, and the use of diaphragm valves have become common place. To incorporate all of these features into each new design typically leads to ever escalating costs with little if any reduction in risk of contamination. Although each of these items provides a level of security, it is a mistake to assume that all of them need to be in every system. Many systems operate successfully with one or more of these design features omitted. In such cases, the cumulative effect of the other design features is adequate to prevent degradation of the water.

A more reasonable approach is to utilize design features that provide the greatest reduction in contamination risk at the most reasonable cost, and add the more expensive features in the design phase, only if they are required to maintain quality within acceptable limits. The systems should be designed to be robust, so features do not have to added later, affecting cost and schedule. The idea of selection design features based on “return” on invenstment where “return” is defined as reduction in contamination risk, can be very helpful in controlling system cost and in evaluating different alternatives. Ultimately, the effectiveness of each system design is determined by the quality of the water delivered to the users. The challenge for the designer engineer is to know what features to include, to achieve the required degree of protection with the lowest lifecycle cost.

EXAMPLE

A USP compendial water system is designed with a 316L SS storage and distribution system and operates normally at 80degrees C. the tubing is all sanitary, orbital welded, with minimal clamps and zero dead leg diaphragm valves at the use points. Water is kept circulating through the tubing at a minimum return velocity at 3ft/sec. in this case, use of high mechanical polish tubing (<20 Ra) with electro polishing may not be required. The risk of contamination for such a system is already low, and the impact of this upgraded surface finish is questionable. The benefits that will be achieved by further improving the quality of finish may not be justified.

However, if the same system were open to the atmosphere, consideration would be given to installing a 0.2micron vent filter on the storage vessel, as the reduction in contamination risk is quite large for a relatively small investment. Similarly, if the zero dead leg valves were replaced with less expensive valves with larger dead legs, you might consider increasing the minimal circulation velocity to help compensate.

The purpose of the following chapter sections is to provide information to help the user evaluate the advantages, disadvantages and cost effectiveness of many of the design features commonly used to protect water from degradation. A method of selection/optimizing system storage and distribution design is also presented. As a general rule, a water system is optimized as a result of the following.

1. Minimizing the time the water is held at conditions which favor growth
2. Minimizing changes to water temperature
3. Contacting all areas during sanitization

One system design can be said to be better than another, if it accomplishes these goals to the same degree, but at a reduced lifecycle cost. Examples of storage and distribution concepts commonly used today are presented in subsequent sections of this guide, to help demonstrate the idea of optima system design.

Distribution Design Concepts

The two basic concepts developed for distribution of pharmaceutical waters are referred to as the “batch” and “dynamic/continuous” distribution concepts

The batch concept utilizes at least two storage tanks. While one is being filled, the other is in service providing pharmaceutical waters to the various process users. After one tank has been filled from the water final treatment system, it is located and the water inside is tested. Only after testing is that tank put into service. The water is often drained after 24 hours, but can be validated for longer periods of time. At the completion of the draining operating, the vessel and distribution system is usually sanitized before refilling.

The dynamic/continuous concept off-sets the peak instantaneous water demand, put on the overall water system through utilization of a single water storage vessel which simultaneously receives final pretreatment system make-up, stores the water in the vessel, and ultimately supplies it to the various process users while maintaining water quality.

The advantage of the “batch” distribution concept, over the “dyniamic/continuous” distribution concept, is that the water is tested before use with tank QA/QC lots release (water used in each product batch lot is traced and is identifiable). The advantages of the “dynamic/continuous” distribution concept include lower lifecycle costs, as well as less complex piping around the storage vessel, and a much more efficient operation

One a system distribution concept has been selected, the following additional storage and distribution design considerations should be carefully evaluated:

- System configuration is including whether series or parallel loops are required, distribution loop points of use, cooling requirements (steam-able, sub-loop or multiple branched heat exchanger assemblies), reheat requirements, if any, secondary loop tanks versus tankless system considerations, etc.
- Hot (65-80 degrees C), cold (4-10 degrees C), or ambient temperatures process use point requirements
- Sanitization method (steam, hot water, ozone, or chemical)

DISTRIBUTION DECISION TREE

the decision tree in figure 8-1 is presented to aid in the analysis of distribution design. Most of the systems in use today are represented by one of these eight configurations, but other designs may also be acceptable in evaluating which configuration is optimal for a given situation, the designer needs to consider many factors, including the requirements for quality assurance release, the desired specification of water (DI, USP, WFI, etc.) hydraulic limitations, the required temperature drop, the number of use points, and the cost of energy

DECISION TREE GUIDE

1. Batched system
2. Branched/one way
3. Parallel loops, single tank
4. Hot storage hot distribution
5. Ambient storage ambient distribution

6. Hot storage, cool and reheat
7. Hot tank, selfcontained distribution
8. Point of use heat exchanger

Each configuration varies in the degree of microbial control provided and in the amount of energy required. Better microbial control is usually achieved by minimizing the amount of time water is exposed to conditions favoring microbial growth. Configurations that store water at sanitizing conditions such as hot, under ozone, or circulation at turbulent velocities, are expected to provide better microbial control than those that do not. Naturally, hot circulating systems are more forgiving that cold systems from a microbiological perspective. However, adequate microbial control may be achieved in other configurations provided they are frequently flushed or sanitized. In any case system design should prevent stagnation, which promoted formation of biofilm.

Energy usage is minimized by limiting the amount of water changing temperature. Configurations storing water hot but supplying it to the use points at lower temperature must cool the water before use. Energy requirements are minimized by cooling only that water drawn from the system. Configurations that constantly cool and reheat water utilize more energy than systems that do not.

The configurations delivering lower temperature water are shown with a single cooling exchanger for clarity. Usually the cooling medium is tower water since this is the least expensive to generate. In most parts of the world, tower water is not cold enough to allow use temperature much below 25 deggrees C. A second cooling exchanger using chilled water or glycol must be added if the required use temperature is below 25 degrees C. it is usually cost prohibitive to cool water from 80 degrees C to less than 25 degrees C using chilled water or glycol along as the chiller size becomes quite large.

INSERT TABLE

EXAMPLE SYSTEM DESCRIPTIONS

The following describes the systems, contained in the accompanying decision tree, that can be used successfully to store and distribute high purity water. Figure 8-2 through figure 8-12 present simplified schematic diagrams (not meant to be P &IDS) of each configuration

FIGURE 9-2 BATCHED TANK RECIRCULATING SYSTEM

This system is used where QA release required on the water before it goes into the process. One batch tank supplies water to the process, while the other is filled and tested for QA release (traditionally due to unreliable means of water production). This is a cumbersome system to operate and is usually limited to smaller systems. The disadvantages are the high capital and operating costs. In-line conductivity and TOC measurements can provide nearly the same degree of assurance for less money

INSERT TABLE Figure 9.2 Batched Tank Recirculating System.

Insert Figure 9.3 Branched/one-way with limited points of use

This configuration is sometimes used where capital is tight, the system is small, and microbiological quality is of lesser concern. It is also useful where frequent flushing or sanitization of the piping is possible. It is a good application where water use is continuous. It is less advantageous where water use is sporadic, as the line stays stagnant when not in use. Microbial control is more difficult to maintain. A program must be set up to flush (e.g. daily) and sanitize the loops to maintain microbial contamination within acceptable limits. More frequent sanitization may required, increasing operating costs. It is also more difficult to use on line monitoring, as indicative of the quality of the water throughout the system, in a non-recirculating system.

INSERT FIGURE 9.2 Branched One Way with Limited points of Use

INSERT FIGURE 9.4 PARALLEL LOOPS SINGLE TANK

This configuration is a combination of any of the loop distribution schemes off one storage tank. Figure 8-5 shows a hot storage tank with two separate loops; a hot distribution and a cool and reheat loop. Parallel loops are very common and are most advantageous where multiple temperatures are required, or where the area served is so large that a single loop becomes cost prohibitive or hydraulically impractical. The major concern is to balance the various loops to maintain proper pressure and flow. This is accomplished either by using pressure control valves, or by proving a separate pump for each loop. (Note: a different design is intentionally presented for each loop).

HOT STORAGE HOT DISTRIBUTION

This is the configuration of choice when all use points require hot (greater than 65 degrees C) water. Temperature is maintained in the storage tank by steam supplied to the tank jacket or alternatively by a heat exchanger on the circulation loop. Water is generally returned to the top of the tank through a spray ball to ensure that the entire top surface is wetted. This system provides excellent microbial control and is simple to operate. In addition, tank and loop sanitization is required less frequently, or not at all, if a temperature of 80 degrees C is maintained. This type of system is universally accepted by regulatory agencies.

Areas of concern include protecting workers from scalding, cavitation in the circulation pump, moisture condensation on the vent filter, and the formation of rouge. Scalding is minimized by operating at lower temperature (65 degrees C) or by proper training and personal protective gear. Cavitation is avoided by accounting for the high vapor pressure of hot water in the net positive suction head (NPSH) calculations. Condensation is prevented by position the hydrophobic vent filter for good drainage and by heating the filer with either a low pressure steam jacket or electric tracing. Avoid overheating as this can melt the filter cartridge. Rouge formation is controlled by passivation and by operating at a lower temperature. It can be eliminated by using non-metallic or lined components.

INSERT FIGURE 9.5 Hot Storage Hot Distribution

Figure 9-6 and figure 9-7 Ambient Storage, Ambient Distribution

This system is most advantageousness when the water is generated at ambient temperature, will be used only at ambient temperature, and there is adequate time for sanitization

Since the water is stored at ambient temperature with no disinfectant, microbial control is not as good as in hot storage system configurations. However, good microbial control is possible provided sanitization is conducted on a frequent basis. Frequent sanitization is usually accomplished by allowing the water level in the storage tank to drop through use, then heating the remaining contents, and circulating through the loop for a set amount of time. Reducing the water level limits the energy and time required to sanitize. Heat is provided by steam supplied to the tank jacket, or alternatively by a heat exchanger on the circulating loop. Cooling may be required to prevent temperature increases due to heat buildup from the pump, and for cool down after sanitization. Water consumption is low if the level in the storage tank is allowed to drop through use prior to sanitization and moderate if it is drained.

The capital and operating costs of this system are minimal. Another advantage is that if can provide high flow rates of ambient pharmaceutical water, without need for complex points of use heat exchanger. Its major disadvantage is the time required to sanitize, which is longer than the previously described systems, due to the need to heat and cool the contents of the storage tank

INSERT TABLE: Ambient Storage and Ambient Distribution

Many pharmaceutical water users have found that storing and distributing water at ambient temperatures with periodic sanitization, (utilizing either clean steam or heating to 80 degrees C for microbial control) to be safe and cost effective. The ambient system can also be effectively operated with an ozonated storage and a periodically ozonated loop, in lieu of hot water sanitization. Ozone needs to be completely removed from process's water prior to usage, using UV radiation. Consideration therefore must be given to verifying/assuring that ozone has been eliminated, such as the use of in-line monitors

One advantage of ozonation or chemical sanitization, is that these methods allow the use of plastics as a material of construction (popular in Europe for purified water systems)

INSERT TABLE Table 9.7 Ozonated Storage and Distribution

HOT STORAGE, COOL AND REHEAT

This system is most advantageous when the water is generated hot, tight microbial control is required, and there is little time for sanitization. It provides excellent microbial control and is easily sanitized. It requires less capital than point of use exchangers, if there are multiple low temperature use points, and then reheated in a second exchanger before returning to the storage tank. Sanitation of the loop is accomplished by turning off the cooling medium on a periodic basis. Water consumption is minimized since no flushing is required. The major disadvantage of this configuration is its high energy consumption, since it cools and reheats the circulating water regardless of whether it is drawn out of the loop.

INSERT TABLE Table 8.9 Hot Storage, Cool and Reheat.

HOT STORAGE, SELF CONTAINED DISTRIBUTION

This configuration is most advantageous when water is generated hot, there are many low temperature water users, and energy consumption is critical. It provides the benefits of the cool and reheat loop without the large energy requirement. Hot water from the storage tank is cooled through the heat exchanger, circulated to the use points, and then returned to the pump suction bypassing the storage tank. The loop is sanitized on a periodic basis by turning off the cooling medium and opening up the return to the storage tank, allowing hot water to flow through the loop. An alternative is to flush the lower temperature water to drain until the loop becomes hot and then return the flow to the storage tank. The water in the storage tank is kept hto through a steam jacket or heat exchanger on an external pump around loop

When water is drawn out of a point of use valve, hot water from the storage tank flows into the loop and is cooled by the heat exchanger. The hot water flushes the short section of line between the storge tank and the circulation pump preventing a dead-leg. I most pharmaceutical installations, this happens many times per day so the line stays relatively hot. If the usage rate is low, a small amount of water can be returned to the storage tank on a continuous or timed basis, keeping this line flushed. A third alternative is to return the circulating water to just downstream of the storage tank outlet valve, so the dead-leg is negligible

INSERT TABLE 8.9 Table hot Storage, Self Contained Distribution

Hot Storage, Hot Distribution, Point of Use Heat Exchanger

This configuration is identical to figure 8-5 except that use points requiring water at lower temperature are equipped with point of use heat exchangers. Figure 8-10, figure 8-11, and figure 8-12 show three different designs for these exchangers. All three allow flushing water to drain to lower microbial counts an adjusting temperature before opening up the point of use valve. All three also allow for sanitizing the exchanger and downstream piping when water is not called for at the drop. The schemes differ in capital cost, sanitation method, and in the amount of water used for flushing. Sanitization is acoomplished using low pyrogen steam in figure 8-10. In figure 8-11 sanitization is accomplished by circulating hot water from the loop, through the point of use exchanger, back to the main loop. The operation in figure 8-11 can be facilitated by installing a block valve at the return of the main loop. The valve would be closed immediately prior to starting the sub loop, to prevent back flow from the main loop. The initial draw of point of use water would be diverted to drain. Figure 8-12 is sanitized by flushing hot water from the main loop once through to drain. Tube-in-tube or serpentine type coolers should be used, as well as double tube sheet exchangers, which are depicted.

Points of use exchangers are most advantageous when there are both hot and lower temperature water use points off the same loop, and the number of low temperature users is small. Since they maintain the water hot until it is drawn from the loop, they provide excellent microbial control, provided they are frequently flushed or sanitized when not in use. As the number of low temperature uses increases, the capital costs and space requirements become prohibitive, and one of the other configurations should be

considered. Water consumption is high due to flushing, although this is minimized by the scheme show in figure 8-11.energy consumption is moderate because only water drawn out of the loop is cooled but additional energy must be spend to make up water flushed to drain. Maintenance requirements are high due to the added exchangers and valves. Complexity is high as each exchanger must be properly flushed and sanitized. Each drop is limited in capacity by the sizing of the exchanger. The scheme shown in figure 8-11 results in added pressure drop in the main loop, which leads to a larger circulation pump.

INSERT 3 tables

STORAGE AND DISTRIBUTION COMPARISON TABLE

Table 8-1 compares several storage and distribution options currently used in the pharmaceutical industry. Comparisons are made based upon capital, energy, operating costs, maintenance, validatabilty, and other factors. Each category is rated low (L), medium (M), or high (H) for each system relative to the other systems presented. The particular storage and distribution choice for a given scenario will depend upon the specific situation being addressed, and the priority the end user gives to each of the categories, with quality being the foremost priority.

INSERT TABLE 8.1 Comparison of Storage and Distribution Options

MATERIALS OF CONSTRUCTION

Pharmaceutical equipment and piping system rely extensively on stainless steels to provide the non-reactive, corrosion-resistant construction needed in manufacturing and heat sterilization. However, thermoplastics are available that may offer improved qualities, or lower cost. Less expensive plastics such as polypropylene (PP) and polyvinyl chloride (PVC) may be acceptable for non compendial systems. Others, such as polyvinylidene fluoride (PVDF) offering greater heat resistance, may be suitable for compendial waters, although they require continuous support in hot applications. The cost of a PVDF system may be approximately 10-15 percent lower than the cost of a stainless steel system once factors such as passivation, boroscope, radiographic inspection, etc., are included. New methods of joining PVDF tubing leave a weld much smoother than possible with stainless steel. At higher temperatures, however, thermal expansion of the plastic becomes a major concern.

While certain changes to higher grade materials (higher alloys such as al6N and hastalloy) and methods of fabrication to assure compliance can yield minor improvements, others may only provide minor gain despite considerable additional expense.

Mater selection should be consistent (all 316L or all 304L etc.) throughout the distribution, storage, and processing systems, if regular passivation is planned.

For compendial water, the use of 316L stainless steel is preferred.

Insulation for stainless piping should be free of chlorides, and hangers provided with isolators to preclude galvanic corrosion.

304L and 316L stainless steel has been the industry preference in tanks for the storage of compendial waters. Jacket material in contact with the shell should be compatible, to avoid chromium depletion in

the welded affected zones. Non-compendial water storage may not require the same level of corrosion resistance or the use of low carbon nickel chromium alloys and special finishes, depending on the owners water specifications.

High purity water distribution systems, using the material and finishes specified by the design, should be joined using acceptable welding or others sanitary techniques. The distribution and storage systems should be installed in accordance with cGMPS and fabricated, manufactured, procured, and installed in strict accordance with explicit operating procedures

Orbital welding has become the preferred method for joining high purity metallic water piping systems, due to the greater control over critical weld parameters and the smooth weld bead characteristics of the process. However hand welding is still employed and may be required in certain situations.

304 and 316 stainless steel have been preferred grades for use in metallic piping systems due to their high chromium and nickel content and ease of automatic welding. Low carbon and low sulfur grades of stainless steel are preferred for compendial systems and control and inspection of the welding process is necessary to limit corrosion and crevices in the system. A maximum sulfur content of 0.04% would be ideal for welding but any mismatch in the sulfur content of the mating parts will easily cause the weld to weaken, outweighing the advantages lower sulfur levels.

Where possible, all fittings, valves, tubing, and weldable pieces of the same nominal size (diameter) should be purchased and manufactured from steel with the same specification and heat number in order to standardize the weld quality for each tubing size.

COMPARISON OF MATERIALS OF CONSTRUCTION FOR TANKS AND DISTRIBUTION SYSTEMS

Insert Table 8.2 COMPARISON OF THE RELATIVE VALUES OF KEY FACTORS IN THE DESIGN AND INSTALLATION OF WATER SYSTEMS

Legend: Y= YES N=No H=High L=low

Notes:

Based on skilled labor requirements, ease of welding, ease of visual inspection, shop fabrication requirements, etc.

The steam pressure and steam temperature control is critical to keep both below the manufacturer's ratings

WORKMANSHIP

Fabrication should be performed by certified welders in a controlled environment to preclude contamination of equipment and material surfaces. Facilities dedicated to the fabrication of stainless steel (or higher grade alloys) are preferred, to avoid contamination by carbon steel. Fabrication must follow an approved quality assurance plan. There needs to be adequate documentation in the design and construction of the system including up to date p&IDs, system isometrics, weld test reports, etc

Tubing and piping welds, whether orbital or manual, must have a smooth internal diameter countour without excessive concavity or convexity, bead wandering, misalignment, porosity, or discoloration. One hundred percent photographic or radiographic analysis, while utilized to an increasing extent, is neither cost effective nor infallible. Appropriate sampling is strongly recommended.

SYSTEM COMPONENTS

HEAT EXCHANGERS

shell and tube, tube-in-tube and plate and frame heat exchangers are employed. Although plate and frame units may offer a cost advantage, they are used less often in the distribution portion of the system in compendial service because of the perceived greater risk of contamination. However, they are common in the pretreatment side prior to final purification. In a shell and tube exchanger treated water flows through the tube bundle; the risk of contamination from cooling or heating media can be significantly reduced by means of a double tube sheet. Complete drainability of the u-tube bundle is achieved by weep holes located at the low point of each chamber in the exchanger channel. Ensuring a positive pressure differential on the “clean” side can further reduce contamination risk. Similarly, a plate and frame unit should be operated with the cleaner water side at a higher pressure than the heating or cooling medium. Conductivity meters may be used for monitoring leakage. Unit design should permit full drainage and ready access for inspection and cleaning.

VENT FILTERS

Used on storage tanks in compendial water service to reduce contamination during drawdown. U nits are constructed of hydrophobic PTFE or PVDF to prevent wetting generally rated at 0.1 to 0.2 microns. Filters should be capable of withstanding sterilization temperatures and sized for maximum fill or drawdown rates to effectively relieve the negative pressure created by high temperatures sanitization cycles. Filters in hot systems are usually jacketed to minimize condensate formation that could result in blinding vessel exhaust hydrophobic filters. Storage tanks should be rated for full vacuum, (or have vacuum protection), if steam is used for sterilization. Installation should also allow for drainage of condensate caused by high operating or sanitizing temperatures and ease of replacement. The filter cartridged need to be appropriate for the filter housing. Vent filters should be integrity tested for compendial water storage tanks, but may not need to be validated as sterile filters.

PUMPS AND MECHANICAL SEALS

centrifugal pumps are commonly employed in distribution systems. Performance curves and suction head requirements should be reviewed to preclude cavitation, which might lead to particulate contamination. The generation of pump heat over extended periods of low or no draw off should also be considered, since significant temperature rise in cold systems, or cavitation due to vapor pressure in hot systems could occur. Casing drains allow for full system drainage, where the pumps are at the low point of distribution. Although with double mechanical seals, with WFI or other compatible seal, water flushing may minimize the possibility of contamination, single mechanical seals flushed to the outside have also been used. In extremely critical applications, polished rotating elements may be warranted. The installation of dual pumps, for standby purposes, should ensure flow throughout the system

PIPING SYSTEM COMPONENTS

a) PIPING AND TUBING: extruded seamless and/or longitudinally welded tubing is commonly used in systems two inches in diameter and smaller. Recently welded steel tubing (ASTM A-270) similar to seamless in appearance has become available at significantly lower cost. PVDF has also been show to be a viable alternative
b) FITTINGS: single fittings may be manufactured from as few as one, to as many as five pieces. This can materially affect the suitability of the end product, in term of weld content, documentation, and cost.
c) VALVES: the trend in the industry has been to use diaphragm valves in high purity systems, particularly in isolation applications. For steam service, sanitary ball valves may be acceptable and require less maintenance.

The following is a summary of water system components, listing the common industry practice, and listing advantages and disadvantages

Insert Table 8.3 SYSTEM COMPONENTS COMPARISON TABLE
*if canted at the correct angle, and installed in pitched lines

COMPARISON OF WFI SYSTEMS WITH STORAGE TANK AND WIHTOUT STORAGE TANK

INSERT TABLE Figure 8.13 TANKLESS AMBIENT DISTRIBUTION
It is possible to feed sub-loops off a single main loop without the use of an intermediate storage tank (figure 813). This configuration is most advantageous when space or capital constraints are tight. The sub-loop is generally a circulating loop. Water drawn out of the main loop when a point of use valve is opened cannot return to the main since the sub-loop is at lower pressure. This provides a degree of isolation between the sub-loop and the main, or other, sub-loops. The major disadvantage is that there is no storage capacity. Usually this capacity is provided by a storage tank on the main loop.

INSERT TABLE 8.4 COMPARISON OF WFI SYSTEMS: WITH STORAGE TANK AND DWITHOUT STORAGE TANK

MICROBIAL CONTROL DESIGN CONSIDERATIONS

in any given water storage and distribution system, there are certain fundamental conditions that can always be expected to aggravate a microbial problem. Likewise, several basic measures will always tend to counteract such problems. Fundamental conditions that typically could aggravate the problem include:

- Stagnant conditions and areas of low flow rates
- Temperatures that promote microbial growth (15-55 degrees C)
- Poor quality supply water

SOME BASIC MEASURES THAT HAVE BEEN SHOW TO ALLEVITE SUCH PROBLEMS ARE:

- Maintaining ozone levels of 0.02ppm to 0.2ppm
- Continuous, turbulent flow
- Elevated temperatures
- Proper slope
- Smooth, clean surface that minimize nutrient accumulation
- Frequent draining, flushing, or sanitizing
- Air breaks in drain piping
- Ensuring no leaks in the system
- Maintaining positive system pressure

All pharmaceutical water must meet the EPA standard for microbiological quality of potable water; which means it must basically be free of specific indicator organisms. Beyond that, microbiological quality for non compendial water should be based upon its intended use and the types of products that will be formulated with it.

It is important to note that although the required microbial population acceptance level for USP compendial purified water is 100 CFU/ml, reliance on such a single parameter can be misleading. The 100 CFU/ml limit may generally be applied to the manufacture of solid oral dosage forms. Many times, however, aqueous or topical formualations require tighter controls to maintain product quality. the USP points out that these types of products have been the subject of recalls when found to be contaminated with gram negative organisms, and the typical microbiological flora of water are gram negative organisms.

A common appropriate approach to dealing with this key issue involves the use of trend analysis. Using such an approach, alter and action levels are related to the system norm. in this context, strategies for responding to the alert and action levels can, and should, be developed. Even with the most conscientious design, there may be places in which biofilm can form. Good engineering practices such as eliminating deadlegs, ensuring adequate flow velocities through out the system, and periodic sanitization help control microbial activity.

it is common practice, therefore, to store and distribute water in a circulating system under any of the following scenarios:

- At conditions which are self sanitizing such as above 65 degrees C or under ozone
- At conditions that limit microbial growth such as below 10 degrees C with periodic sanitization.
- At ambient temperatures where sanitization is determined by the validated methods that control microbial growth

REGULATORY CLARIFICATION TO COMMON INDUSTRY PRACTICES

The following are industry practices that are all good engineering practices (GEPs), and have been perceived in the past to reduce the chance of microbial growth.

If you collectively ignore all these items, you increase the likelihood of having a bio burden problem. These items include finishes, storage tank orientation, storage tank isolation, storage tank turnover, piping slop and drain ability, dead legs and velocity.

FINISHES

Common industry practices typically range from milled pipe to 320 grit (0.38 microns Ra) mechanical polish with electro polish. Electro polishing is a reverse plating process, which improves the surface finish of mechanically polished stainless steel piping and equipment. It reduces surface area and removes surface intrusions caused by mechanical polishing, which may cause subsequent rouging, and/or discoloration. After mechanically polishing or electro polishing the system, the polishing compounds should be confirmed to have been completely removed from the pipe, so as not to accelerate corrosion.

The benefits for electro polish or finishes smoother than 0.76 microns Ra (approx.. 180 grit or 30 micro inch) are questionable.

Systems operating at ambient temperature or with infrequent sanitization may require a smoother surface finish. The interior surfaces of stainless piping systems, in compendial water service are typically ground and/or electro polishes, at considerable cost, to achieve a smooth surface of minimal porosity (0.4 to 1.0 microns Ra), in order to reduce bacterial adhesion and enhance clean ability. A viable alternative is extruded PVDF piping, which can produce a smoother surface than most metallic systems, without recourse to polishing, although PVDF has other disadvantages (see section 8.4)

STORAGE TANK ORIENTATION

Vertical orientation is the most common because of the following advantages:

- Lower fabrication cost
- Less dead volume
- Simpler spray ball design
- Less floor space required
- Horizontal vessels are used where height is a constraint

STORAGE TANK ISOLATION

Common practice for compendial and non-compendial waters where microbial contamination is a concern is to use a 0.2 micron hydrophobic vent filter.

For hot storage vessels, the vent filter must be heated to minimize moisture condensation. An alternate practice is to blanket the tank with 0.2 micron filtered air or nitrogen. Nitrogen blanketing can be used if CO2 absorption is a concern, or if final product oxidation is a problem.

STORAGE TANK TURNOVER

Common practice is 1-5 tank turnovers per hour,

The turnover rate may be important for systems using external sanitization or polishing equipment.

The turnover rate is less important when storage is under sanitizing conditions, including hot storage or ozone. It may be less important under conditions that limit microbial growth, such as cold storage (4-10 degrees C) but this must be demonstrated by documentation

Some storage tank turnover is required to avoid dead areas

SYSTEM DRAINABILITY

System that will be steam sterilized must be fully drainable to assure complete condensate removal

Systems that will never be steam sterilized do not need to be fully drainable, as long as water is not allow to stagnate in the system

It is good engineering practice to allow for the draining of equipment and associated piping

DEADLEGS

Good engineering practice is to minimize or eliminate deadlegs where possible. Common practice is to limit deadlegs to less than 6 branch pipe diameters or less. This stems from the "6D" rule contained in the proposed CFR 212 regulations of 1976. Recently industry experts have suggested using a guideline of 3D or less. However, this new guideline causes confusion since the proponents of this standard generally are discussing the length of dead leg from the outer wall of the pipe, while the original 6D rule describes the distance from the center line of the pipe to the outer wall of the pipe is already 3D. thus, even a zero deadleg valve might not meet the 3D requirement.

To avoid confusion in the future this guide suggests that the length of the deadleg be considered from the outer wall of the pipe. We propose avoiding a hard rule of thumb for maximum allowable deadlegs.

Ultimately, the water must meet the required quality regardless of the length of the deadleg. Good engineering practice requires minimizing the length of dead legs and there are many good instrument and valve designs available to do so

It should be recognized that any one-way system can constitute a deadleg if it is not frequently flushed or sanitized.

POSITIVE PRESSURE

It is important to maintain the system under positive pressure at all times. One common concern is systems designed with insufficient return flow, which could draw a vacuum at points of use under periods of high water usage. This causes an unexpected microbial challenge to the system.

LOOP VELOCITY

Common practice is to design circulating loops for a minimum return velocity of 3 feet/second or higher, and for Reynolds numbers in the turbulent region of greater than 2,100.

Return velocitiites less than 3 feet/second are acceptable for short periods of time, or in systems that do not favor microbial growth, such as hot, chilled, or ozonated loops.

A minimum return flow is required to maintain the loop in a flooded condition under positive pressure.

CONTINOUS MICROBIAL GROWTH

Process water systems generally employ both continuous methods of microbial control, and periodic sanitizations. This section discusses continuous methods for controlling microbial growth.

"HOT" Systems

The most effective and reliable means of preventing the growth of bacteria is to operate the system at temperatures above which bacteria can survive. If the distribution system is maintained in hot conditions, santization on a routine basis can be eliminated.

Systems operating at 80 degrees C have a long history of data showing the prevention of microbial growth. More recently companies have been validation water systems at 65 degrees C. the advantages of operating at lower temperature include energy savings, lower risk of injury, and reducing the amount of rouging. Systems operating at the higher end of this range have a greater safety margin with regard to microbial contamination. The effectiveness of temperatures below 80 degrees C must be verified with test data, on a case by case basis.

Note that these temperature ranges will not destroy endotoxin. As noted in chapter 6, where endotoxin is a concern, the treatment system must be designed to remove it.

"Cold" Systems

The use of the term "cold in this case implies that a system is maintained at a low enough temperature to inhibit microbial growth. While this has been shown to be effective, the energy costs associated with it generally make this type system costly to operation. Generally, "cold" systems are operated from 4 degrees C to 10 degrees C. microbial growth rates drop off significantly below 15 degrees C, so the sanitization frequency of cold systems may be reduced compared to ambient systems. The effectiveness of a specific temperature, and the associated sanitization frequency in any particular system, must be determined by statistical analysis, on a case by case basis.

"Ambient" Systems

Circulation temperatures of any pharmaceutical water system are dictated by either the required microbial specification or the required temperature for usage. "ambient" temperature purified water systems using either ozone and/or hot water sanitizations are common throughout the industry, and normally result in lower lifecycle costs, as well as reduced energy consumption compared with either the "hot" or "cold" systems. However, without increased levels of system sanitizations, the lack of temperature control at the water storage vessel and distribution loop could result in the formation of a biofilm within the system, which could sporadically and unpredictably produce water failing microbiological specifications and necessitate non scheduled water system shutdowns.

OZONE

Ozone has been shown effective for microbial control. It is a strong oxidant, which chemically reacts with organisms and destroys them. The destruction of these organisms results in organic compounds which may be further degraded by ozone, ultimately to carbon dioxide. Ozone is twice as powerful an oxidant as chlorine and needs to be dosed continually to maintain concentration.

In any compendial water system and most other applications, water at the use points is expected to be totally free of ozone. Ozone removal is commonly affected through ultra violet radiation. 254 nanometer UV light converts ozone to oxygen. A common design is to maintain an ozone concentration between .02ppm and 0.1ppm in the storage tank, and use a UV light at the beginning of distribution loop for removal. To sanitize the loop itself, the UV light can be turned off during periods of no use, and the ozone will circulate through the loop. The UV dosage required for ozone destruction is generally 2 to 3 times that required for microbial control. Testing should be done to verify absence of ozone at the use points.

UV LIGHT

Ultraviolet lights have been shown to reduce microbial populations in storage and distribution systems. UV energy is germicidal in the wavelengths of 200 to 300 nanometers, which falls below the visible spectrum. UV light de-activates DNA leading to bacteria reduction. A UV light is not a sterilization device, as it is often referred to. The effectiveness of the light will depend on the quality of the water in which it is acting, the intensity of the light, flow rate of water, contact time, and the type of bacteria present

FILTRATION

Along with other particulate matter, bacteria and endotoxins may be removed via filtration. This filtration media can be either of the microfiltration (2-0.07 microns) or ultrafiltration (0.1-0.005 micron) scale. The integrity of these filters must be maintained.

MICROFILTRATION

Microfiltration includes the use of depth cartridge filters, pleated filters, and cross flow filtration membrane elements. These filters can remove particles ranging in size from 100 microns down to 0.1 micron. Depth and pleated filters allow water to flow through a wall of fibers perpendicular to the water direction (dead ended filters). The particles are then trapped on the outside wall of these filters, or within the filter walls (for depth filters), due to the pore size of the filter. The filter will fill up with these particles and then needs to be replaced with a new filters.

ULTRAFILTRATION

Ultrafiltration can be used to remove organics and bacteria, as well as most viruses and pyrogens from a water source. Filtration is typically from 0.1 micron down to 0.01 micron. Cross flow ultrafiltration forces the water to flow parallel to the filter media, and the particles which are too large to pass through the membrane elements are then expelled from the system in a concentrate stream to drain (typically 5-10% of the feed flow.) this allows the filters to be self-cleaning and eliminates the need to replace these

membrane elements frequently. This type of filtration can be used as a “maintenance” step downstream of the storage tank in certain situations.

In general, for any purified water system, filtration downstream of the storage tank is not recommended. This comes from concerns of “grow through” where bacteria will colonize on the upstream side of the filter, and ultimately be found on the downstream side even though the pore size of the media may theoretically be smaller than the size of the bacteria. An additional concern is the potential for accumulation of nutrients on the filter media, which may in fact increase the opportunity for microbial growth. However, filters downstream of a circulation pump are sometimes used in water systems. System designs should be predicated on obtaining the desired water quality upstream of the storage tank, using the treatment train. Filters downstream of the storage tank should not be relied on to purify the water.

CIRCULATION

Most new water systems use a circulating loop for distribution. The primary purpose of circulation is to reduce the chance of microbial growth, or microbial attatchment to the surfaces of the system. Although the mechanisms are not universally agreed upon, it is thought that the shear forces associated with turbulent water flow inhibit nutrient concentration and attachment of bacteria to surfaces. The velocity required to obtain these benefits is generally agreed to be greater than 3 feet per second, or Reynolds numbers greater than 2100. Velocity may drop off for short periuods of time during high use times without adversely affecting the system, so long as positive pressure is maintained in the system. Circulation also serves to maintain proper temperature throughout the system in hot and cold systems.

Studies have shown that the velocities required to remove biofilm are higher than practical for a water system (above 15ft/sec). however, a combination of high velocity (5ft/sec or greater) with an antimicrobial agent such as ozone or chlorine, may, over a long period of time effectively remove biofilm.

A turbulent condition may be maintained in short dead ended pipe stubs if the length of the stubs is limited. This limiting length varies with the pipe stub diameter and to a lesser degree with the main pipe diameter. A rule of thumb for the maximum deadleg is 6 b ranch pipe diameters. This “rule of thumb” may be difficult to achieve in large mains with small branches, and may result in unacceptably long dead legs in large branches. Rather than universally applying “rules of thumb”, it is important to recognize dead legs as an area of concern and take appropriate steps to prevent them in the original design or implement special provisions to address them if unavoidable. Some of the factors to consider include operating temperature, velocity in the main, and frequency of use (if the dead leg is a use points.)

PERIODIC STERILIZATION/SANITIZATION

Periodic sanitization of storage and distribution systems is generally required. Based on monitoring the microbial quality of the system, a required frequency of sanitization should be formally established. Sanitization may also be done in response to reaching an “action limit” during routine testing. Various methods of periodic sanitization are discussed below.

CHEMICAL

Various chemicals or combinations of chemicals can be used to periodically sanitize storage and distribution systems. Chlorine solutions on the order of magnitude of 100 ppm are very effective at killing organisms, but are not generally used in distribution systems because of corrosion problems associated with stainless steels. Hydrogen peroxide in concentrations on the order of 5 % is a more practical alternative. Peracetic acid can also be used, generally in concentrations of 1% or less. Many different mixtures of these and other chemicals are commercially available for the purpose of sanitization.

Verification of the removal of the sanitizing agent is critical. Commercially available indicators (test strips or sticks) are commonly used to indicate when the amount of rinse water is sufficient. A rinse water analysis is then required to verify the absence of objectionable chemicals before the system is placed into service.

OZONE

Sanitation can be done either periodically or continuously with ozone. Storage tanks are typically continuously ozonated, and then the ozone is removed prior to the distribution loop or individual use points through the use of ultraviolet radiation. The distribution system can be periodically sanitized by turning off the UV light and, if necessary, increasing the ozone concentration while allowing it to circulate through the distribution loop. Concentrations as high as 1 ppm may be needed for periodic sanitization, particularly if biofilms must be removed

HEAT

It has been found that periodic sanitization by heating of the process water system is highly reliable and effective. The frequency at which sanitization must occur will vary depending on many factors

- System design
- Size of distribution system
- Components of system
- Volume of process water in the system
- Frequency of use of the process water (turnover volume)
- Temperature of the circulating process water

Each distribution system must develop its own microbial profile, and the sanitization cycle and frequency will have to be developed to fit that system.

The most straightforward method of sanitization is to heat the circulating process water in the distribution system to 80 degrees C ±3 degrees C and hold it at the temperature for a validated period of time. The use of this heat sanitization has been proven to be very effective and if designed properly can also be economical controls needed to perform this cycle of sanitization can be either manual or automatic.

Because of the types of bacteria found in purified water systems, the use of steam is not required for effective microbial kill. Steam sterilization of distribution piping may require additional valving for rents

and drains, and may require a higher pressure rating than otherwise needed. Storage tanks are by their nature more easily steam sterilized and this practice is common, although not required.

Hot systems inherently are continuously sanitized. Thus, the need for sanitization should be based on microbial testing results, or when the system is off line for an extended period of time and the temperature of the loop drops to below the validated temperature range.

Depending on the process water specification, a conservative initial sanitization frequency should be assigned for “cold” systems. After the operating characteristics of the system are determined through microbial testing, the routine sanitization frequency can be determined.

INITIAL SANITIZATION (ambient system)

Steam sanitization has a successful history, and is probably the most reliable method for sanitization. However, there is no requirement for steam sanitization in purified water or WFI systems. The following procedure is suggested as one option for hot water sanitization of an ambient system.

Immediately after passivation (for a SS system), the system should be flushed with process water at a high temperature (80 degrees C ± 5 degrees C) and all valves opened and points of use flushed. Normally two (2) times the volume of the system (after conductivity readings), or rinse water tests indicate that no passivation chemicals are detected, is required. This is the initial sanitization of the system.

Once it has been determined that the chemical charachteristics for the quality of the process water have been achieved by USP chemical testing, then microbial samples should be taken after each component, the points of use, and the storage tank. This initial sampling should show that the distribution system at any sampling point has no viable bacterial contamination. Once this is achieved, the system should be brought down to its operating temperature and allowed to stabilize.

SYSTEM DESIGN FOR STERILIZATION/SANITIZATION

The following sections highlight particular aspects of storage and distribution system design, which are relevant to sanitization.

MATERIALS OF CONSTRUCTION

The sanitization methods used must be compatible with the materials in the system. By far the most widely used material for storage tanks and piping is 300 series stainless steel (generally 316L). this choice provides the most flexibility with regard to sanitization options. Sanitization with heat, UV, or ozone can be used in stainless steel systems practically without restriction. Chemical sanitization must be carefully managed with regard to concentration, pH, and temperature to avoid corrosive effects on stainless distribution systems.

Other material used for distribution piping is PVDF. PVDF is susceptible to degradation by UV light. It is common to use stainless piping immediately adjacent to the UV light in a PVDF system to compensate for this problem. The temperature limitation of PVDF is approximately 140 degrees C, which is high enough to allow heat sanitization or sterilization.

In stainless systems, the gaskets used must be reviewed for compatibility with the sanitization method. A widely used gasket mater is PTFE or EPDM, both of which have good thermal memory and excellent resistance to temperature ozone and chemical sanitizers. Other gasket materials must be carefully reviewed for compatibility with the sanitization methods, and to ensure that they will not leach substances into water.

The key is to recognize that the materials of construction "shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (21 CFR 211.65) the sanitization procedures must be considered when selecting materials to comply with this requirements.

STORAGE TANK DESIGN

Storage tanks are an are in the system that could be considered at high risk for microbial contamination because of the large surface are, low velocities, the need for venting, and potential for "cold spots" in the head space.

Tank size is generally based on economic considerations in combination with the pretreatment train sizing. From a bacterial standpoint, smaller tanks are preferred because they have higher turnover rates, which reduce the likelihood of bacterial growth. They also reduce surface areas and make it easier for ozone to permeate the water, if the tank is ozonated

Spray balls may be used on the return loop to wet the head space of storage tanks. The use of a spray ball serves to keep the top of the tank at the same temperature as the water, in heated systems, and avoids alternately wet and dry surfaces, which could promote corrosive action with stainless steel and allow microbial growth. Connections on the top head (relief devices, instrument connections, etc) should be kept as close to the head as possible to simplify the spray ball design and get the benefit of the sptray action. An expception is the vent filter, which should be removed far enough from the storage tank to avoid direct contact from the water spray, which could blind the filter. If dip tubes or instruments project down from the head, multiple spray balls may needed to avoid a "shadow" being created in the spray pattern.

The tanks must be vented to allow filling, and a filter should be used at the vent to avoid airbone particulate and microbial contamination. To avoid the problem of condensation in the filter and the resultant potential for colonization and grow through, hydrophobic vent filters are used and/or the filters are maintained at a temperature above the tank temperature with steam jacketing or electric tracing.

To help avoid microbial growth, and avoid the change in conductivity resulting from absorption of atmospheric gasses into the water, nitrogen blanketing on the head space may be used. This eliminates outside air passing into the tank through the vent filter. Note that gasses added to storage tanks should be appropriately filtered to avoid objectionable contamination.

INSERT TABLE 8.5 Comparison of Alternate Designs for Microbial Control in Storage and Distribution

Note 1: all systems are circulating

Note 2: operating costs and effectiveness will increase with frequency and sanitization

INSTRUMENTATION AND CONTROL

INTRODUCTION

Instrumentation and controls are often used within pharmaceutical water systems to:

- Control the operation of equipment and components
- Monitor and document the performance of critical equipment
- Monitor and document pharmaceutical water quality

The concepts and regulatory philosophy of defining critical versus non-critical parameters is discussed as it related to instrumentation and controls. This definition could be summarized as:

“all instruments and control systems should be commissioned following good engineering practices. Critical instruments and control systems should be commissioned and qualified.”

There is no regulatory requirement that requires the use of On-line instrumentation. A monitoring program may include a combination of on-line instrumentation, manual documentation, and laboratory analysis.

If on-line instrumentation is used to measure or record a critical parameter, action and alert limits may be established. The methods of addressing “spikes” are also discussed.

Automatic can have a significant impact on the cost and performance of a pharmaceutical water system. There is no single optimum level of instrumentation and control for all systems. The optimum level for a given system balances the benefits of improved process control, improved documentation, and lower labor costs against the procuring, installing, validating, and maintaining the instruments and control systems. In many cases, the level of automation for a pharmaceutical water system should be consistent with that utilized for the manufacturing process it supports.

PRINCIPLES

a) To achieve GMP compliance, the manufacturer must demonstrate, through documented evidence, that the pharmaceutical water system is in control and consistently produces and delivers water of acceptable quality.
b) Although many quality attributes can be continuously monitored using on-line instrumentation, there is no compendial or regulatory requirement for on-line monitoring of pharmaceutical water quality. a monitoring program typically includes a combination of on-line instrumentation, manual documentation of operation parameters, and laboratory analysis of water samples.
c) Instruments and control system are critical and must be qualified when they are used to measure, monitor, control, or record a critical process parameter. A critical parameter is a processing parameter that affects the final water quality. For example the temperature of the final water product may be considered critical from microbial control. In this case, temperature controls (e.g. sensors and alarms) would be considered critical. However, it is

not necessary to consider the temperature of the heating media (e.g., steam) as a critical parameter. Documentation should clearly indicate which instruments are critical and which are not. It is also advisable to identify non-critical instruments as such on the field device

d) All instruments and control systems should be designed, installed, calibrated, and maintained appropriately according to good engineering practice. All critical instruments and controls require qualification.

e) Items that should be recorded in the system documentation include maintenance procedures and maintenance work performed, procedures for sampling and analysis, reporting the results, and trend analysis of the laboratory data. The monitoring program during start-up typically defines maintenance frequency and alert and action levels for the process variables.

GENERAL INSTRUMENATION REQUIREMENT

INSTRUMENT SELECTION AND INSTALLATION

a) Instruments should be selected for accuracy and reliability over the entire process range.

b) Instruments should be selected and installed in a way that reduces the potential for contamination
   - Water contact surfaces should be constructed of materials that are compatible with the water they contact. Materials of construction and surface finishes (see chapter 8) are commonly specified for instruments installed in distribution systems
   - Sensors in direct contact with waters with strict microbial limits should be of sanitary design. Non sanitary instrumentation is commonly used in feed water and pretreatment systems
   - Instruments may be installed directly in the water system or in a side stream that may, or may not, be returned to the main system
   - Deadlegs should be avoided

c) When possible, instruments should be installed such that exposure to harsh process conditions, such as pH and temperature extremes, is avoided. For example, in-line sensors used to monitor effluent from a deionizer should be positioned such that exposure to regeneration chemicals is avoided. Instruments that are not compatible with passivation agents, sanitization agents, or sanitization temperatures should be installed so that they may be easily removed or bypassed. Such devices may need to be sanitized off line.

d) Instruments should be installed in accordance with manufacturers' requirements to ensure proper operation. For example, flow meters should be installed in the proper orientation and with the correct upstream and downstream straight run of pipe. The impact of process and ambient conditions on an instruments accuracy and reliability should be addressed.

e) Conductivity cells are especially sensitive to the presence of air or steam bubbles which can be present where there is turbulence, cavitation, or flashing. Such locations should be avoided

f) Accessibility for maintenance should be considered, but improving control response is usually more critical. Poor response time may be consequences of the poor placement of a device and, in most cases, can be improved by installing the device closer to the point of measurement.

INSTRUMENT CALIBRATION

a) The calibration of critical instruments should follow a regular program, which provides evidence of consistently acceptable performance. Non-critical instruments may be calibrated on a frequency deemed appropriate for the service.
b) Calibration should follow approved procedures and the results should be documented. Each component in a control loop should be calibrated individually or the loop may be calibrated in its entirety. All calibrations should be traceable to certified standards (e.g., NIST)
c) Vendor supplied calibration certificates should reference the applicable instrument serial numbers. The impact of shipment and installation on the vendors calibration should be addressed

TYPES OF INSTRUMENTATION

CONDUCTIVITY

a) Although non-ion specific, conductivity is a valuable tool for measuring the total ionic quality of water and is a critical parameter for many high purity water systems. Conductivity limits for purified water and WFI are specified in the USP.
b) On-line conductivity instrumentation is frequently used to monitor and control the performance of many types of purification equipment and to continuously monitor the quality of pharmaceutical waters. On-line conductivity instrumentation may also be used for final quality assurance testing, thus eliminating the need for periodic laboratory analysis of water samples.
c) Temperature has a profound impact upon conductivity measurement. To eliminate this temperature dependence, most instruments include a temperature sensor in the conductivity probe and one ore more algorithms to correct the actual measurement to a standard temperature. However, due to the inaccuracy inherent in temperature compensation algorithms, compensated conductivity measurements are not suitable for critical quality assurance testing of USP purified water and WFI. When in-line conductivity measurements are used for final quality assurance testing of USP purified water and WFI, a non-compensated conductivity value and the water temperature must be measured as required by the USP. Compensated conductivity values strictly for process control and monitoring are not subject to USP requirements.
d) To operate properly, conductivity sensors must be installed such that there is continuous water flow through the sensor and air bubbles or solids cannot become trapped inside the electrodes. Air bubbles will result in lower-than-expected conductivity readings while solids can impact the conductivity in either direction. Clean steam must be condensed prior to conductivity measurement.
e) Conductivity meters may be used throughout a pharmaceutical water system to monitor and control purification processes or to monitor pharmaceutical water quality. some examples are:
    - Feed water monitoring can detect seasonal or unanticipated quality changes that could impact pretreatment equipment operation

- RO influent and effluent monitoring allows calculation and trending of percentage rejection. Changes in percentage rejection may be a sign of membrane failure, scaling or fouling, seal failure, improper pH, inadequate feed pressure, or too high a recovery rate.
- Deioniozer effluent or in-bed monitoring detects, or predicts, resin exhaustion and allows automatic initiation of regeneration cycles.
- The conductivity of pharmaceutical water many be monitored after the final treatment step to verify acceptable quality prior to delivery to a storage tank. In addition, conductivity meters are often installed in the return piping of distribution loops downstream of the final point of use. Many systems include provisions for automatic diversion to drain or recirculation back through purification equipment when water quality entering the tank is outside the acceptable range

a) **TOTAL ORGANIC CARBON (TOC)**
total organic carbon (TOC) is a measure of the carbon dissolved in water in the form of organic compounds. It is a valuable tool for measuring the aggregate level of organic impurities in pharmaceutical water systems. A TOC test with a nominal limit of 500ppb for USP purified water and WFI Is a required test in the USP

b) TOC meters are relatively sophisticated analytical instruments. The USP provides guidance on how to qualify an instrument and how to interpret the instrument results.

c) In addition to “continuous” monitoring of equipment performance and pharmaceutical water quality, on-line TOC meters may be used for final quality assurance testing, thus eliminating the need for periodic laboratory analysis. When used for critical assurance testing of USP purified water and WFI, instrument precision, system suitability, test methodology and calibration procedures must meet USP requirements. Instruments used strictly for process control and monitoring are not subject to USP requirements

d) TOC is often monitored at several locations in a pharmaceutical water system some examples are
   - Feed water monitoring can detect seasonal or unanticipated quality changes that could impact pretreatment equipment operation or the potential for resin or membrane fouling.
   - Monitoring TOC downstream of carbon filters, organic scavengers, RO units, and UV lights can verify proper equipment operation and provide advance warning of bed exhaustion, compromised membranes, or the need for lamp replacement.
   - TOC levels of pharmaceutical water may be monitored after the final treatment step to verify acceptable quality prior to delivery to a storage tank. In addition, TOC meters are often installed in the return piping of distribution loops downstream of the final point of use. Many systems include provisions for automatic diversion to drain or recirculation back through purification equipment when water quality is outside the acceptable range

e) There has been much interest in the possible use of TOC analyzers to indicate endotoxin contamination. While this type of contamination will lead to higher TOC levels, there is no quantitative correlation to TOC levels. TOC results cannot substitute for microbial or endotoxin testing.

PH

a) PH measurement is relatively straightforward for high conductivity water. Reliable results can generally be obtained using pH indicators or laboratory field, or on-line pH meters
b) Accurate pH measurement is difficult in many pharmaceutical waters due to the low conductivity. Low conductivity water is susceptible to pH swings due to contaminants introduced from the air, sample containers, and test equipment, as well as instrument difficulties associated with measuring low ionic strength solutions
c) Common locations for on-line pH measurement and control include:
    - upstream of cellulose acetate RO membranes, where acid is injected to minimize membrane hydrolysis
    - Upstream of degasifier, where acid is injected to increase Co2 removal
d) While pH limits for purified water and WFI are no longer specified in the USP, on-line pH meters are rarely used for process control or for final quality assurance testing of pharmaceutical waters for several reasons
    - Conductivity is a more sensitive measurement of overall ionic quality since changed in pH reflect logarithmic changes in water quality
    - A ph Sensors reference electrode contains a buffer solution that may leak through the reference electrode into the water being measured. To prevent contamination of the pharmaceutical water system, a pH sensor is installed in a side stream that flows to drain. The water flow rate through the meter must be controlled and held constant to achieve repeatable results
    - pH meters require frequent (daily in some cases) calibration with standard buffer solutions

OZONE

a) Dissolved ozone levels should be monitored in storage and distribution systems that utilize ozone for microbial control. Ozone levels can be determined periodically in the laboratory using several we chemistry methods, or continuously using an on-line analyzer. On-line analyzers are relatively inexpensive and easy to maintain, but they should periodically be calibrated against laboratory methods.
b) For effective and safe system operation, ozone levels should be monitored at the following locations
    - At the storage tank discharge to control operation of the ozone generator
    - Downstream of the UV light to ensure ozone destruction prior to water use
    - In loop return piping to ensure proper ozone levels are maintained during sanitization
c) Since oxidation reduction potential (ORP) analyzers are nonspecific and unable to differentiate ozone from other oxidants, ORP analyzers should not be used for controlling ozone levels in pharmaceutical water systems

FLOW

A wide variety of flow meters may be used in the feed water and pretreatment portion of a pharmaceutical water system including magnetic flow meters, mass flow meters, vortex shedding

meters, and ultrasonic meters. All meters should be installed according to the manufacturer's instructions, to ensure proper operation

Water flow rate (or velocity) may help to reduce microbial growth and maintain temperature within hot or cold systems. It is commonly verified upon startup, but not continuously monitored. Flow rate may vary, it may be monitored for information only.

TEMPERATURE

temperature is often monitored and/or controlled at various locations to ensure optimum equipment operation and/or for microbial control. Temperature interlocks may be used to prevent damage to membranes, resins, or equipment if water temperatures drift outside allowable ranges

In distribution systems where temperature is controlled or where heat sanitization is used, temperature is considered critical to ensure proper system operation or effective sanitization.

PRESSURE

Pressure may be monitored and controlled throughout the purification process to ensure optimum equipment operation. Monitoring differential pressure across filters indicates when backwashing or element replacement is needed. Differential pressure measurement across resin beds is useful in detecting resin fouling and poor flow distribution. Monitoring RO feed, interstage, permeate, and concentrate pressures provide early warning of membrane fouling and scaling. Back pressure control in distribution systems may be critical, if minimum pressures are required at points of use.

Pressure is not normally considered a critical parameter, however, the system should maintain positive pressure at all times. It may typically be monitored for information only.

LEVEL

Various types of level measurement are used in the feed water and pretreatment portion of a pharmaceutical water system, including simple float switches, ultrasonic sensors, capacitance sensors, and differential pressure transmitters. The stub from the tank must be kept as short as possible to minimize deadleags. Calibration of this type of transmitter is time consuming, since it requires filling the tank to verify proper operation. Tank nozzles with integral valves minimize deadlegs and allow calibration while the tank is in service.

Tank level may be monitored to control the supply of water into a tank and for control and protection of downstream pumps

In some instances level may not normally be considered a critical parameter and may be monitored for information only. In these cases, it is usually not validated.

DESIGN CONDITIONS VERSUS OPERATING RANGE

The control system may recognize the distinction between design conditions and operating ranges, and the impact this distinction has upon validation and facility operation. These criteria are defined as:

- Design condition: the specified range, or accuracy, of a controlled variable used by the designer as a basis to determine the performance requirements for an engineered system
- Allowable operating range: the range of validated critical parameters within which acceptable water product can be produced
- Normal operating range: a range that may be selected as the desired acceptable values for parameter during normal operations. This range must be within the allowable operating range

a) While it is desirable that a facility should meet all stated design conditions, the acceptability of the water system for operating from a cGMP standpoint depends on operating within the allowable operating ranges
b) Normal operating ranges cannot exceed the allowable operating range for the product water. Deisgn condition selection should reflect good engineering practice.
c) It may be desirable to apply the concept of alert and action points along with normal operating range. Alert levels are based on normal operating experience and are used to initiate investigations or corrective measures, before reaching an action level. Action level are defined as the level at which some corrective action must be taken to avoid jeopardizing water quality.

INSTRUMENTATION SPIKES

"spikes" may be experienced in the measurement of some parameters. These excursions may be result of the measurement technique or sensor and may not be representative of the actual parameter value. If a spike occurs in a system with a significant physical lag or mass, the rapid changes in a parameter as evidenced by spikes may be physically impossible and consequently can be treated as instrumentation spikes. In other cases, it may be decided to treat these spikes as alert level deviations based upon their frequency and duration even though their magnitude may exceed the action level.

A procedure for defining and handling spikes should be developed in conjunction with quality assurance based on the specific water system.

CONTROL SYSTEMS

LEVEL OF AUTOMATION

Selection of a control strategy for a pharmaceutical water system should consider feed water quality and reliability, the complexity for the purification and/or distribution system, labor costs, personnel skills levels and capabilities, and documentation and reporting requirements. Options for control include:

a) Local instrumentation with manual control: in this option, a combination of instrumentation, periodic samples, and visual examination is used to monitor critical process parameters. Data is collected and recorded manually, and analysis and trending capabilities are limited. Excursions of critical parameters outside acceptable ranges typically trigger local alarms to reduce the risk of unacceptable water quality. satisfactory manual operation requires significant human intervention. This requires detailed operating procedures and conscientious documentation of critical quality parameters. This option has the lowest installed cost, but is very labor intensive and may be subject to human error.

b) Semi-automatic control: these systems use local operator control panels, relay logic control, local chart recorders and printers, and some manual data collection to monitor and control the water system. These systems are less labor intensive over the manual systems, but are still labor intensive due to the manual data collection and monitoring required to control the process.
c) Automatic control: automated systems use a computer (PLC or DCS), or computers, to control the pharmaceutical water system. The computer system utilized appropriate process monitoring instrumentation (conductivity probes, flow meters etc.) to gather data and make appropriate adjustments to the system automatically. As water generating system become more sophisticated, relying on human intervention to control and monitor the water system becomes more difficult and labor intensive. An automated system requires less operator involvement, but requires a more highly trained maintenance and engineering support staff.
d) Fully integrated systems: these systems include a fully automated system and a wide area network connected to other computer systems in the building or site. These systems allow for central site monitoring, automatic electronic data collection, centralized alarm monitoring with automatic recording, response, and report generation

Additional information on control system design is available in the good automated manufacturing practice (GAMP) guide and in various guidelines by the instrument society of America (ISA). Whichever level of automation is selected, the validation effort should verify operation of the complete system, including vendor-supplied sub-systems.

CONTROL SYSTEM SOFTWARE

The software/control system may be used to measure , monitor, control, or record critical process parameters. Programming and design standards, especially concern operating interface, control techniques, alarm handling, and interlock processing should be applied during the development, validation and maintenance phases of the project. The control system software consists of:

a) FIRMWARE, OPERATING SYSTEM, AND APPLICATION SOFTWARE: this software permanently loaded into memory that may or may not be accessible to the user. While the functions performed by the control system may be divided between critical and non-critical functions, it is impossible to divide or isolate the firmware, operating system, application software, and associated hardware functions. Therefore, if some of the functions of a control system are considered critical, all of the above software is considered critical and should be validated.
b) USER CONFIGURABLE SOFTWARE the functions of the user configurable software may be defined as critical or non-critical. The critical functions or modules require enhanced documentation, including validation. In some cases, it may be impossible to divide or isolate software adequately. In such cases, if some of the functions are critical, it may be necessary to validate all the software.

The type of process control required is often the determining factor in the type of software needed, and software requirements often define the type of system selected. Major considerations are:

- Number of 1/0 points

- Mathematical or statistical functions required
- Reporting features required (particularly if the control system is to be further integrated in to higher systems)
- Whether or not advanced control techniques are required (e.g. neutral nets, fuzzy logic controllers; adaptive gain; dead-time compensation

CONTROL HARDWARE AND OPERATION INTERFACE

a) Critical software requires enhanced documentation and should be designed and tested in accordance with the lifecycle methodology
b) The water system, field instruments and control requirements all affect control hardware selection. Plant standards or a large installed base of a particular system may drive the selection.

COMMISIONING AND QUALIFICATION

INTRODUCTION

Commissioning and qualification comprise the validation process by which a system is put into service and demonstrated to consistently produce water of a specified quality, under various conditions, while operated under set procedures. Although commissioning and qualification are typically separated within a project schedule, they are in essence, one continuous process.

The specific activities and processes during commissioning and qualification will not be discussed in this guide. These are considered by a separate ISPE baseline guide on commissioning and qualification, and pharmaceutical water systems are used as examples throughout. A summary of key concepts are listed below

a) Due to the interdependence between activities and those involved, excellent communication, planning and coordination between operations, engineering, commissioning, and validation personnel will enable timely and cost-effective project completion
b) Each component of the system should be built in accordance with plans and specification and should be inspected, tested, and documented by qualified individuals. These activities, and the production of supporting documentation, are defined as good engineering practice (GEP).
c) GEP recommends a minimum level of documentation for all systems and equipment. This encompasses design, fabrication, vendor testing, construction, field inspection, and commissioning. If these documents are appropriately planned, organized, and authorized, they may become an integral part of qualification support documentation, thus avoiding redundancy and saving time and money.
d) Design criteria and documentation requirements should be clearly defined early in the design phased, to ensure clear expectations and appropriate planning, and facilitate timely commissioning and validation. Engineering firms, vendors, and contractors should be required, per the system specification, to provide the necessary documentation, to avoid unnecessary costs and delays associated with obtaining or creating these documents.
e) During construction, timely review of documentation and periodic “walk-throughs” can ensure that installation qualification requirements are met
f) Commissioning takes the system from a state of substantial completion to a state of operation. It is the phase of a project that includes mechanical completion, start-up, and turnover. Commissioning incorporates a systematic method of testing and documenting the system at the conclusion of construction, and prior to the completion of validation activities.
g) Commissioning documents should not be created and executed for the purpose of regulatory compliance. However, commissioning tests and documentation will typically satisfy manly installation and operational qualification requirements.

SYSTEM QUALIFICATION DOCUMENTATION

Good engineering practice dictates that documentation be developed to provide evidence of the design, and that the water system operates in accordance with the design. This documentation encompasses

engineering, installation, inspection, and testing. Such documentation is common to all system commissioning activities and is partially summarized below:

- A system description stating design intent
- A schematic drawing of the system (P&ID)
- Written system specifications
- Detailed design drawings
- Vendor manuals and drawings
- Field inspection and test reports
- System qualification test results

Because of their critical impact on pharmaceutical production, water systems require additional emphasis on certain sections of this documentation. Specific design requirements for water and steam systems are contained within the body of this guide. When compiling documentation related to water systems, particular attention should be paid to the following:

a) Schematic documentation may be enhanced by the inclusion of a system isometric diagram (or diagrams) indicating location and numbering of welds, relative elevations, slope of lines, and points of drainage
b) The system specification should indicate performance criteria, as well as design parameters
c) Field inspection and test reports should include cleaning and passivation procedure and record, weld parameter documentation and inspection reports, slop verification, and verification of the absence of “dead-legs”
d) System qualification tests may or may not be subject to a pre-approved protocol addressing qualification test requirements. In either case, test results should be reported in direct comparison to acceptance criteria derived from system design and operating specifications.
e) System qualification tests should include verification of all automated functions, specified temperature control, distribution system velocity, and initial water quality determination.

Addition details regarding water system qualification may be found in the associated “ISPE BASELINE GUIDE ON COMMISIONING AND QUALIFICATION.”

SYSTEM QUALIFICATION SAMPLING PROGRAM

the qualification of water systems is unique in that performance must be proven over an extended period of time, and is subject to variations in use rate and initial feed water quality. therefore, the sampling program associated with pharmaceutical water systems validation is unique and specialized.

Extensive sampling is required to establish and confirm that the entire system will operate within specified operating ranges, to develop and evaluate the system of operation and maintenance procedures and to verify that the water produced and delivered to the points of use consistently meets the required quality specifications and acceptance criteria. This portion of the program is sometimes termed performance qualification.

Because of the critical impact that water has upon pharmaceutical quality, the sampling program and evaluation of results is usually subject to a pre-approved plan or protocol, with clearly defined acceptance criteria. Also included should be procedures to deal with deviations from specified parameters and analytical results. The sampling program consists of three successive phases, each with a specific purpose and sampling scheme, as outline below. The initial phase of the sampling program typically begins after the water system is shown to be fully operational, as demonstrated through integrated system testing in operational qualification.

The water generated during the various phases may be used for manufacturing as long as analytical results are acceptable. The intended applications and impact of water quality should be considered in determining how much data is required before use.

INSERT TABLE 10.1 Sampling Program

PHASE 1

The purpose of this phase is to establish appropriate operating ranges and provide data for the development of cleaning and sanitization procedures and frequencies. Sampling should be performed after each step in the treatment process and from each point of use. In addition, the incoming feed water to the water system should be tested and verified to comply with the relevant “drinking water” regulations. The FDA guide to inspections of high purity water suggests daily sampling for two to four weeks, but recognizes that other sampling programs may be acceptable.

In devising the sampling scheme, consideration should be given to the system configuration, maintenance cycles, how the water is drawn for use, and the expected or potential variation in chemistry and microbiological testing between each component is important to determine the microbial load and the components ability to manage the load.

At the end of this phase, the SOPs for system operation and maintenance should be developed and approved for continue interim use during the next phase. System logs, documentations for critical parameters (e.g. conductivity and TOC data, sanitization data, etc.) and responses to critical alarms or action levels should be reviewed, to verify the appropriate procedures are in place. In addition, the process that will be followed to investigate a confirmed test failure should be developed at this time. The intent of this process is to assess whether a failure is localized (i.e. isolated to a specific port) or systematic, and to define how different types of failures will be handles.

PHASE 2

The second phase is intended to demonstrate that the system consistently operates within pre-determined operating ranges and delivers water of the required quality when operated in accordance with the SOPs. The FDA guide suggests that the sampling scheme and duration should be the same as for phase one. During phases 1 and 2, multiple samples should be taken from each point of use. Sampling methodology should be representative of the way water will be used. For example, sampling should not involve a lengthy preliminary purge if water usage will be direct and immediate. If water is used through an attached hose, then the sample should be taken from the hose.

It is recommended that each point be sampled at least once per week as minimum. In this manner, localized contamination may be discovered. (Note that too frequent sampling of little used points may mask incipient localized microbial growth by artificial purging.) Phase 2 allows the gathering of sufficient data to establish microbial alert and action limits (see section 10.4)

PHASE 3

The third phase is intended to demonstrate that, when operated for an extended time period (typically one year), the system produces and delivers water of the required quality, despite possible seasonal variations of the feed water. Sample locations, frequencies, and test requirements are based on the established procedures. For WFI systems, the FDA guide recommends sampling daily from a minimum of one points of use, with all points of use tested weekly. At the end of this phase (i.e., after a fully year of testing), the validation is considered completed. In most cases, ongoing monitoring will establish a continuing record of water quality.

ACCEPTANCE CRITERIA

acceptance criteria for water are dependent upon its use. For both purified water and WFI, the chemical acceptance criteria are clearly described in the US pharmacopoeia (USP). It is expected that a well-designed water system, operating within specified design parameters will consistently be able to meet these criteria. Therefore, failures in chemical analysis during phases 1 and 2 must be investigated, the reason for failure corrected, and (except where errors in sampling or laboratory error and clearly indicated) the sampling phase extended to re-establish consistency of performance.

Microbial quality is not specified by the USP, but is established by the user based upon water use. The USP does recommended action limits for the different waters in its general information chapter. These are 10 CFU/ 100ml for WFI and 100 CFU/ml for purified water. These may be employed as initial acceptance criteria for system qualification, although some flexibility is allowable, depending upon system design and use. It is permissible that single excursion, followed by acceptable re-sampling would not constitute a failure. In addition, because of the inherently bacteriostatic nature of WFI production and distribution systems, it should be expected that the large majority of samples should be well below the initial acceptance criterion. Therefore, for WFI it is prudent to establish a sample average acceptance criterion, which will be below the limit for a single sample. Failure investigation would be handles similarly to chemical analysis failure.

During phases 1 and 2, normal system microbial limits may be established. Acceptance criteria may then be converted to alert and action limits for use during phase 3 and beyond. These would take into account repeated excursions from the norm as well as step increases in micro count.

QUALIFICATION REPORTS

qualification data should be compiled and conclusions written into a summary report. This is to be reviewed and approved by those responsible for operation and quality assurance of the water system. An interim report should be written and approved at such time during the qualification sampling program, as it is desired to use water in production activities. A summary report should be prepared at

the conclusion of phase 2, periodic updates provided throughout phase 3 and a major update issued as the conclusion of phase 3.

CHANGE CONTROL AND REQUALIFICATION

changes to the system must be assessed with regard to potential impact of the change on the entire system. Required action would be determined based on that assessment. It may involve extensive re-qualification, localized increase in sampling frequency, or inclusion in the routine monitoring program.