Pharmaceutical Water Systems- Points to consider from the view of a microbiologist

PDA Europe

Parenterals Conference in Iran – Current Regulatory Guidelines and Pharmaceutical Technologies

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Topics of presentation

- Important References
- General information about Pharmaceutical Water Systems
- Regulatory Requirements / FDA Guidance on Highly Purity Water systems
- Design and engineering aspects of pharmaceutical water systems
- Start Up of PW (Purified Water) and WFI (Water for Injection)
- Key points in Microbiological Quality Control
- Trending and Investigations
- Biofilms
- Usage of a Rapid Microbiology Testing Method for Water (my experience over a decade)
- US FDA Warning Letter example
- Discussion and Questions

NOTE

- This presentation is based on the experience of the presenter in several companies worldwide
- It may differ with opinions and expectations of individual auditors

References

- EMEA „Note for Guidance on Quality of Water for Pharmaceutical Use“, 2002
- USP <1231> Water for Pharmaceutical Purposes, 2015
- FDA „Guide to Inspections of High Purity Water Systems“, 1993
- Fundamentals of an Environmental Monitoring Program, PDA 2014
- PDA Points to Consider fo Aseptic Processing I and II , 2015 / 2016
- Presentation of WHO „Pharmaceutical Water systems“ (T. Gould) / 2010

General information about water systems

- Water is the most widely used raw material
- Used in production, processing, compounding, cleaning & disinfection, quality control labs, …
- Different grades of water quality available

Grades of Water Quality

- Potable Water
- Process Water (for API – Active Product Ingredients) / Water for special Pharmaceutical Purposes
- Process Water (endotoxin free
- Purified Water (USP/ EP)
- Highly Purified Water (EP)
- Water For Injection (USP/ EP)

Comparison of pharmaceutical water specifications

Source: website of „Pure Water Group“

	Purified Water		Highly Purified Water		Water For Injection	
	USP	EP	USP	EP	USP	EP
Process	Distillation, reverse osmosis and any other suitable process	Distillation, ion exchange, reverse osmosis and any other suitable process	N/A	Double-pass reverse osmosis coupled with other suitable techniques such as ultrafil-tration and deionisation, for example	Distillation or reverse osmosis	Distillation
Conductivity	≤ 1,3 µS/cm @25°C	< 4,3 µS/cm @ 20ºC	N/A	≤ 1,1 µS/cm @ 20ºC	≤ 1,3 µS/cm @ 25ºC	≤ 1,1 µS/cm @ 20ºC
Bacteria	100 cfu/ml (suggested)	< 100 cfu/ml	N/A	<10 cfu/ 100 ml	< 10 cfu/ 100 ml (suggested)	< 10 cfu/ 100 ml
Endotoxin	N/A	< 0,25 IU/ml (only for bulk water for dialysis)	N/A	< 0,25 IU/ml	< 0,25 IU/ml	< 0,25 IU/ml
TOC	500 ppb	≤ 0,5 mg/l	N/A	≤ 0,5 mg/l	500 ppb	≤ 0,5 mg/l
pH	5-7	5-7	N/A	5-7	5-7	5-7
Nitrates	N/A	≤ 0,2 ppm	N/A	≤ 0,2 ppm	N/A	≤ 0,2 ppm
Heavy metals	N/A	≤ 0,1 ppm	N/A	≤ 0,1 ppm	N/A	≤ 0,1 ppm
Aluminium	N/A	≤ 10 ppb (if intended for use in the manufacture of dialysis solutions)	N/A	≤ 10 ppb (if intended for use in the manufacture of dialysis solutions)	N/A	≤ 10 ppb (if intended for use in the manufacture of dialysis solutions)

Potable Water

- **Potable Water (Drinking Water)**
- Not covered in a Pharmacopeial Monograph, but there are regulations by local authorities
- Supplied from the municipal water system (user has little control)
- Is Feed Water for Purified Water
- Often pretreated by chlorination, filtration or UV light irradiation
  - Action Level is 500 cfu/ ml (USP <1237>)
  - Absence of objectionable microorganism (Note : depends on the regulatory requirements of each country), similar to PW (see below)

Categories of Water (for the preparation of …) / EMEA 2002

Table 1: Sterile Medicinal Products

Sterile medicinal products	Minimum acceptable quality of water
Parenteral	WFI
Ophthalmic	Purified
Haemofiltration Solutions Haemodiafiltration Solutions	WFI
Peritoneal Dialysis Solutions	WFI
Irrigation Solutions	WFI
Nasal/Ear Preparations	Purified
Cutaneous Preparations	Purified

Table 2: Non-sterile Medicinal Products

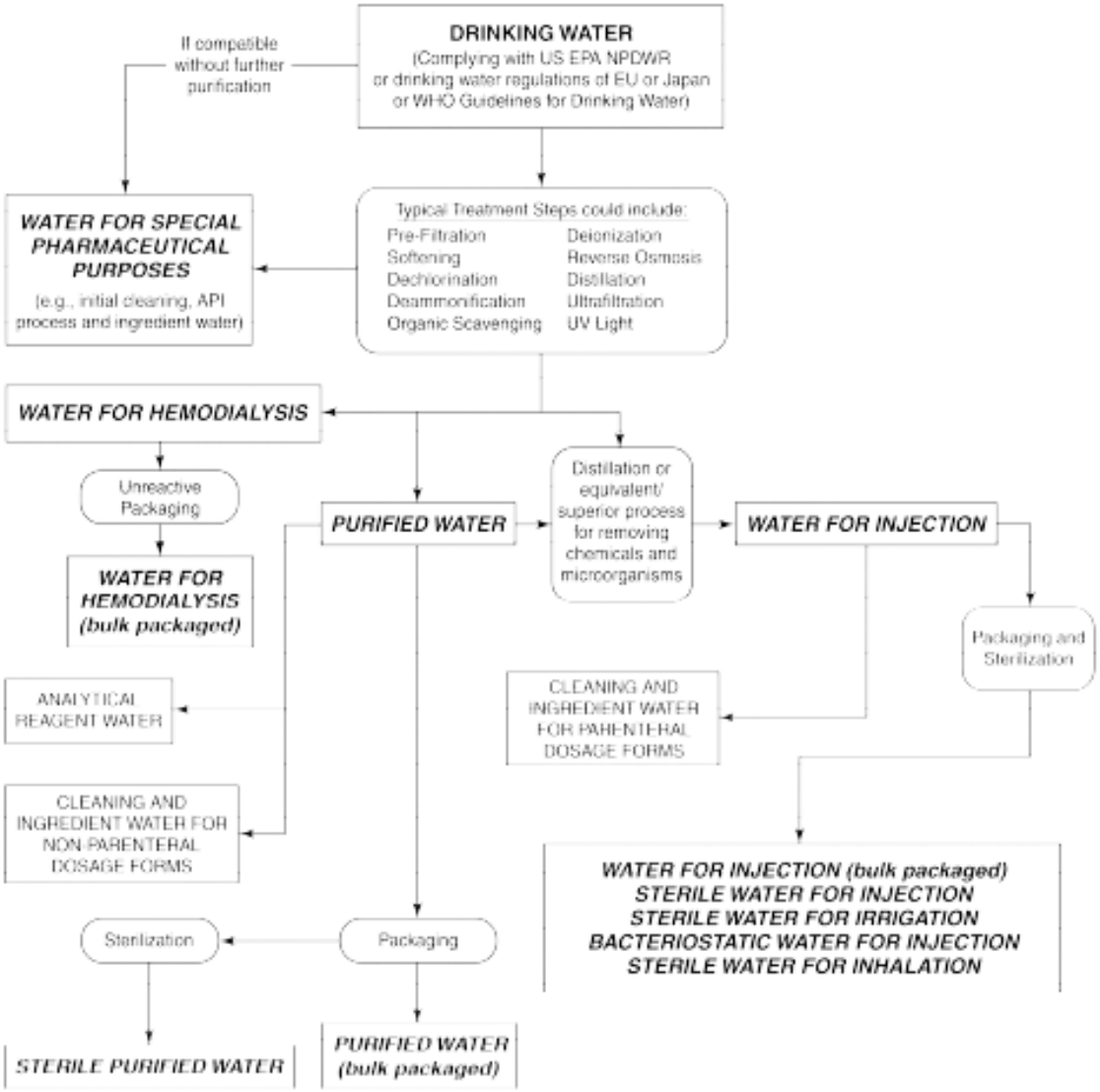
Non-sterile medicinal products	Minimum acceptable quality of water
Oral Preparations	Purified
Nebuliser Solutions	Purified*
Cutaneous Preparations	Purified **
Nasal/Ear Preparations	Purified
Rectal/Vaginal Preparations	Purified

Categories of Water (for the preparation of API and for Cleaning …) / EMEA 2002

Final isolation and purification	API is sterile and not intended for parenteral use	Purified Water
Final isolation and purification	API is not sterile, but is intended for use in a sterile, parenteral product	Purified Water with an endotoxin limit of 0.25EU/ml and control of specified organisms.
Final isolation and purification	API is sterile and apyrogenic	Water For Injections

Initial rinse** including CIP* of equipment, containers and closures, if applicable.	Sterile products	Purified Water
Final rinse***including CIP* of equipment, containers and closures, if applicable.	Sterile non-parenteral products	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Final rinse***including CIP* of equipment, containers and closures, if applicable.	Sterile parenteral products	WFI ****

USP <1231> / figure 1

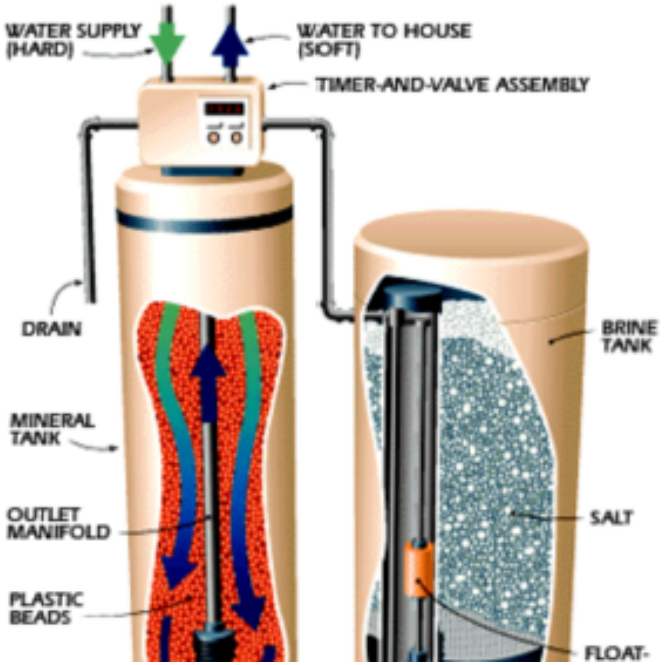


Purified Water

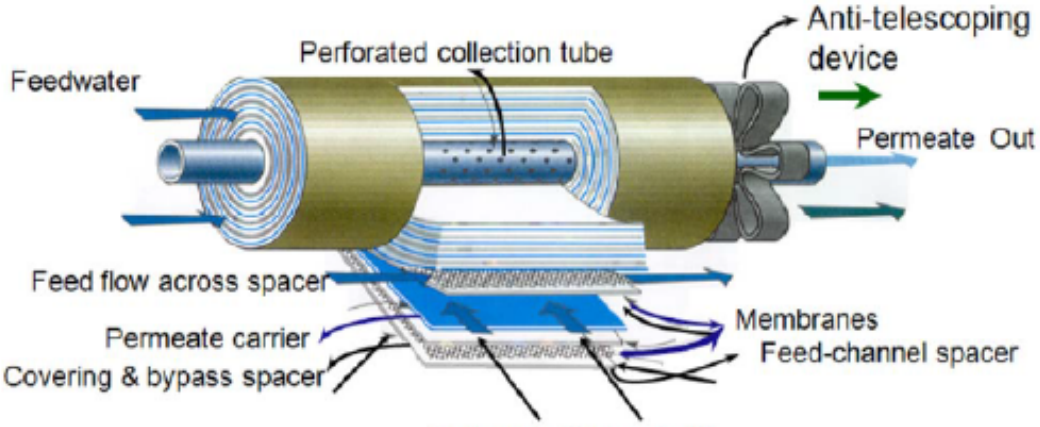
- Prepared from potable water source
- Purified Water Generation is typically performed by a combination of (electrical) Deionization, ion exchange, reverse osmosis, distillation or other suitable procedures .
- Typical modern PW preparation set-up in serial: Softener Columns unit – Reverse Osmosis unit– Membrane degassing unit– Electrical Deionization unit
- Meet pharmacopoeia specifications for chemical and microbial purity
- Protected from recontamination and microbial proliferation
- Is used as an excipient in production of non-parenteral preparations and other applications (as cleaning)
- Microbial levels: Action Levels 100 cfu/ ml and absence of objectionable microorganism (e.g. absence of E.coli/ Salmonella/ Pseudomonas aeruginosa/ Staph. aureus ...

Water Softener

Water softening is the removal of calcium and magnesium and other cations in hard water. ...usage of ion-exchange resins (* microbiological issues)



Ion Removal – Reverse Osmosis



Reverse osmosis (**RO**) is a water purification technology that uses a semipemeable membrane to remove ions, molecules, and larger particles from drinking water. In reverse osmosis, an applied pressure is used to overcome osotic pressure, a colligative property, that is driven by the chemical potential differences of the solvent, a thermodynamic parameter.

Electrodeionization

Electrodeionization is a water treatment technology that utilizes an electricity, ion exchange membranes and resin to deionize water and separate dissolved ions (impurities) from water. It differs from other water purification technologies in that it is done without the use of chemical treatments and is usually a polishing treatment to reverse osmosis (RO). There are also EDI units that are often referred to as continuous electrodeionization (CEDI) since the electric current regenerates the resin mass continuously. CEDI technique can achieve very high purity, with conductivity below 0.1 µS/cm.

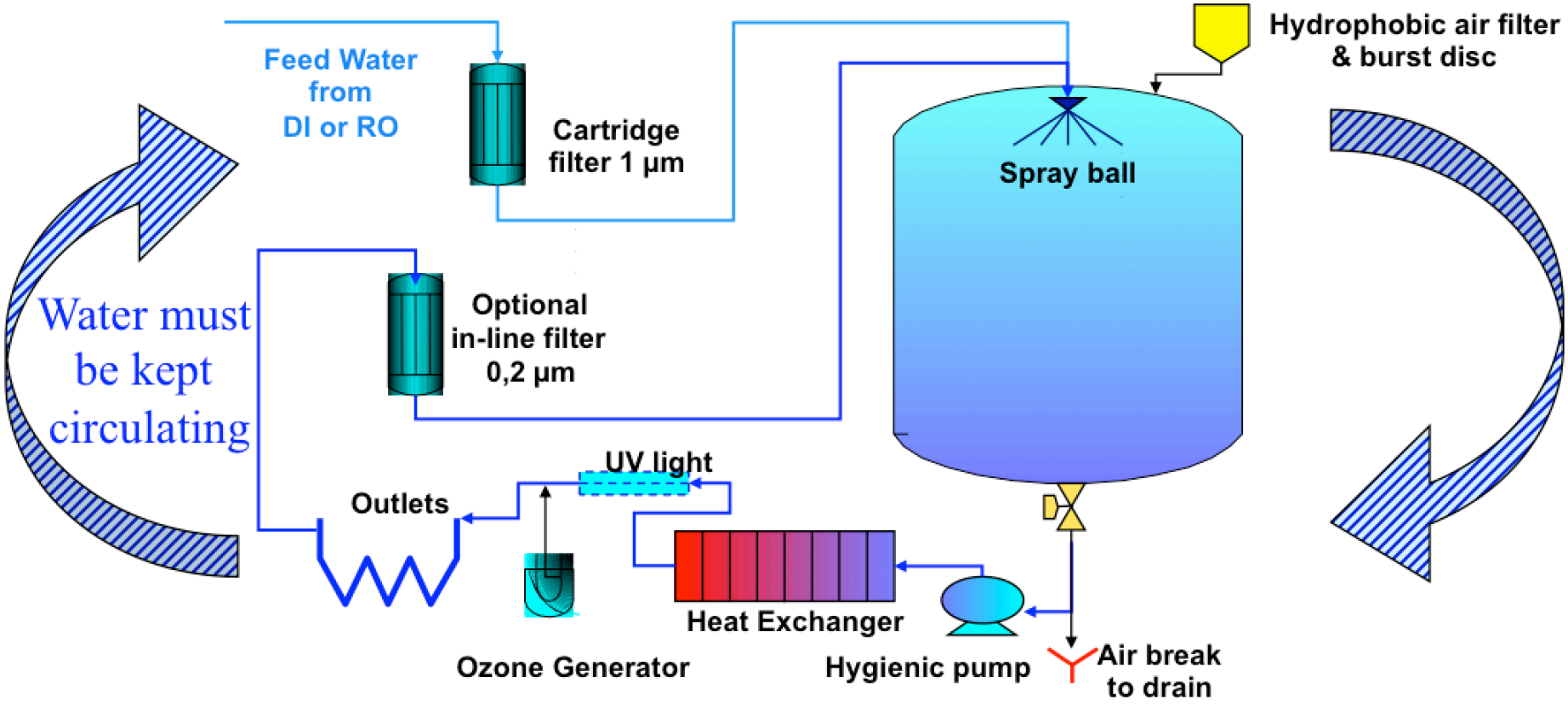
Example from Internet (randomly chosen)

OSMOTRON® – the world best-selling PW/HPW system

- Open skid pre-treatment, softening, RO, SEPTRON® EDI
- 316L SS execution
- Automatic hot water sanitization >80°C
- MULTIJOINT diaphragm bloc valve technology
- Easy modular upgrade option within the series
- 0,5 - 10m³/h single skid or >10m³/h multi skid solutions

Purified Water System example from R. Goud (from WHO presentation 2010)

Typical water storage and distribution schematic



Highly Purified Water

- Prepared from potable water source
- Specification only in the European Pharmacopoeia
- Same quality standard as WFI including limit for endotoxins, but treatment method considered less reliable than distillation
- Prepared by combination of methods including double pass reverse osmosis (RO), ultrafiltration (UF) and deionization (DI)
- Microbial levels: Action Levels 10 cfu/ 100 ml

Water for Injection

- Prepared from potable water source or Purified Water
- WFI is not sterile (but regarded as sterile)
- WFI must meet all chemical requirements of Purified Water as well as endotoxins specification
- According to *European Pharmacopoeis* – final purification step should be distillation
- Most stills are able to accomplish 3 – 4 log reduction of impurity concentrations, but a concern is carry- over of volatile organic impurities (USP <1231>)
- USP <1231> allows alternative methods such as Ultrafiltration (also as PDA PTC II/) to the distillation, but the final process must have effective endotoxin reduction capability

5 step distillation

WFI / Pure Steam Generation

Water for injection (WFI) is the most critical raw material for parenteral pharmaceutical production. As such the qualities at the point of use are regulated in the different international pharmacopeia´s such as USP, EP, JP. The EP is permitting distillation as the only method to produce WFI. Although some pharmacopeia´s allow alternative production technologies, distillation is the technology of choice and industry standard for the generation of WFI.

Pure Steam/ Clean Steam

Pure Steam (PS)
Pure steam is evaporated above 100°C and used for humidification and sterilisation of e.g. porous goods. The level of steam saturation or dryness, and the amount of non-condensable gases are to be determined by the Pure Steam application. The condensate must comply with the respective WFI requirements.

Pure Steam or condensate directly contacts product and product contact surfaces !
Saturataed steam under overpressure used for steam sterilization
Must be free of any Endotoxins (WFI quality) !
Pure Steam is distributed under pressure to user (e.g. autoclave / SIP/ ...)
Pure Steam Generators or 1st column of WFI preparation
Sampled by condensation

Background to water requirements and use

- Control quality of water
  - *Production*
  - *Storage and distribution*
- Contaminants, microbial and chemical quality
- Microbial contamination risk and concern
- Water is used on demand
  - *not subjected to testing and batch or lot release before use, therefore has to meet specification "on demand" when used (but some companies use WFI as a batch, released in their batch record)*
  - *Micro test results require incubation periods (and delayed results)*

Water system requirements

- Design, installation, commissioning, qualification / validation, operation, performance and maintenance to ensure reliable, consistent production of water of required quality
- Operate within design capacity
- Prevent unacceptable microbial, chemical and physical contamination during production, storage and distribution
- Quality Assurance involved in approval of use after installation and maintenance work

Water system requirements

- Monitoring of water sources regularly
  - *Chemical and microbiological*
  - *Endotoxin level where relevant*
  - *Particulates (WFI) – depends on process*

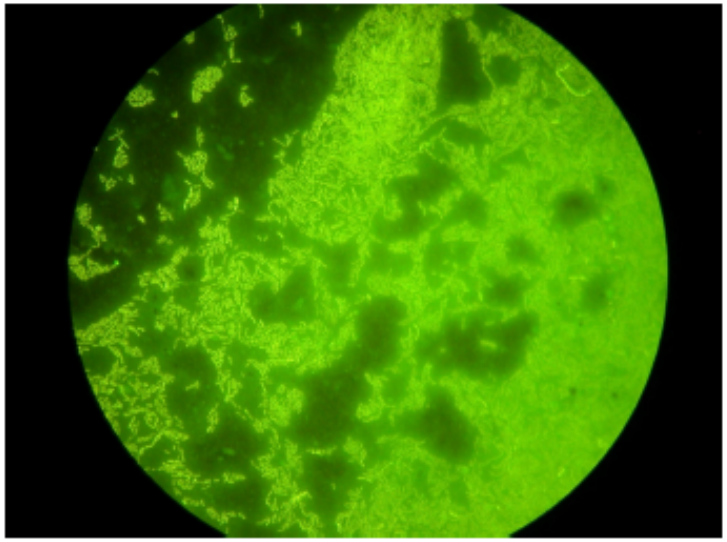
- Monitoring of system performance, storage and distribution systems
- Records of results, and action taken
- Validated sanitization procedure followed on a routine basis

Microorganisms – Biofilm formation in Water – Mainly Gramnegative Bacteria

- Protozoa
  - *Cryptosporidium*
  - *Giardia*
- Bacteria
  - *Pseudomonas*
  - *Gram negative, non-fermenting bacteria*
  - *Escherichia coli and coliforms*

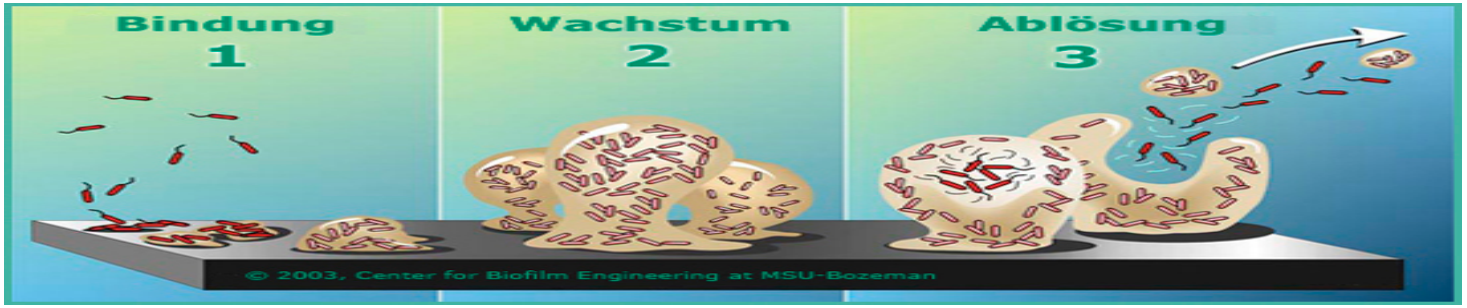
Above strains are the main isolates on water monitoring !

ENDOTOXINS !



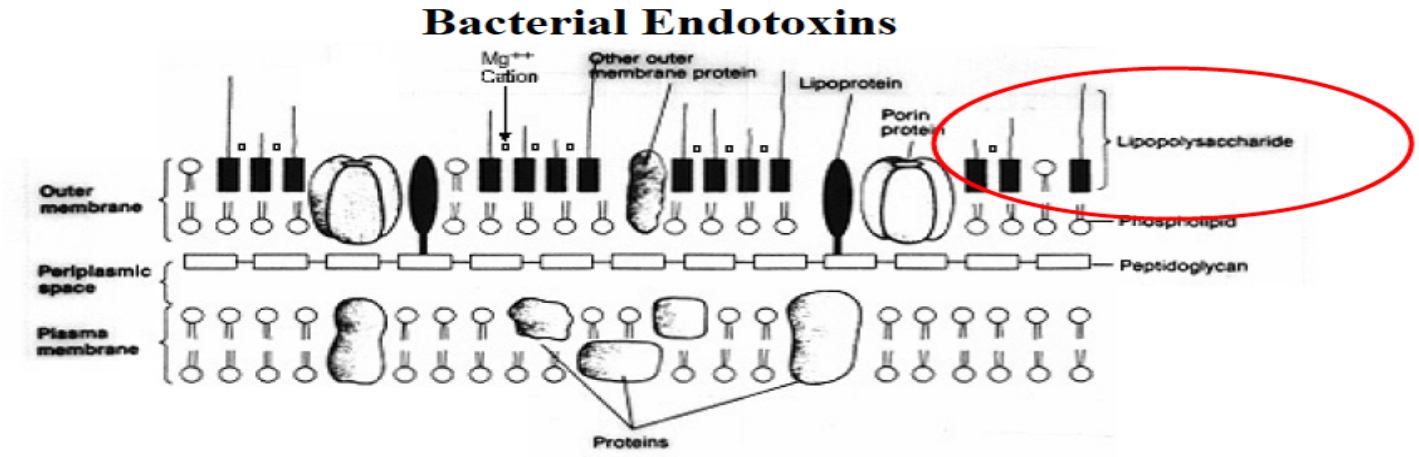
Biofilms

- Water is distributed through the pipelines and continuously circulated in a circulation loop. This helps to prevent the formation of biofilms. But there is some space between the circulation loop and the valve at the user points.



Biofilm is a thin usually resistant layer of microorganisms (as bacteria) which form on and coat various surfaces. It is a complex structure adhering to surfaces which are regularly in contact with water, consisting of colonies of bacteria that secrete a mucilaginous protective coating in which they are encased. Biofilms, which are resistant to antibiotics and disinfectants, corrode pipes and cause diseases such as lung infections, but they can be used beneficially to treat sewage, industrial waste, and contaminated soil.

Endotoxins –from gramnegative Bacteria



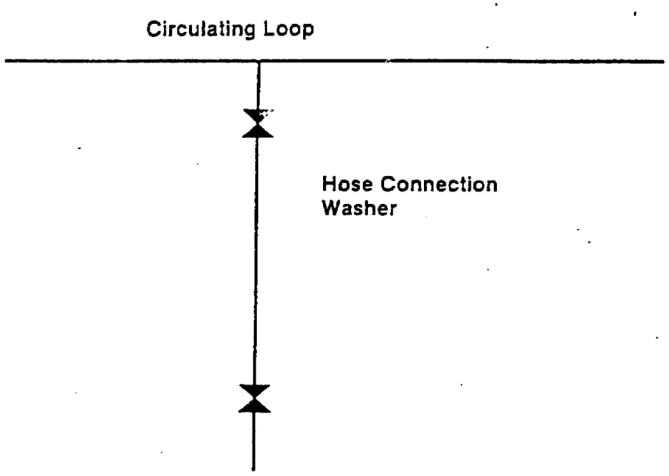
Since endotoxin is bound to the outer membrane the majority of endotoxin is released from the cell during death (lysis). The size of an endotoxin molecule allows it to pass through 0.2 micron filters once it is free of the outer membrane.

Endotoxin is heat stable and is not eliminated by autoclaving. Heat over 250ºC for an extended period is required for depyrogenation (endotoxin removal).Other methods of depyrogenation are chemical deactivation and Ion Exchange Chromatography.

Why is endotoxin so important in the cGMP environment? Endotoxin can cause severe reactions in humans including death.

FDA Guide to Inspections of Highly Purity Water systems / 1993 - Important citations :

- Distillation and Reverse Osmosis are acceptable methods listed in the USP for producing WFI
- It is recognized that hot (65- 80 °C) systems are self- sanitizing
- Water in a constant motion is less liable to have high levels of contaminant. A one-way water system is basically a “dead-leg”.
- Unused pipe of > six diameters from the axis of the pipe : dead leg.
- Problem with hoses/ valves: problem of standing water in pipes and non-sterile air in the pipings



Distillation Microbial Limits: WFI

- Important to understand: Regarding microbiological results, for Water for Injection, it is expected that they be essentially sterile. Since sampling is performed in non-sterile area and is not truly aseptic, occasional low level counts due to sampling errors may occur. Agency policies less than 10 cu/ 100 ml as an acceptable action limit. … are exceeded, the firm missed investigate the cause of the problem .
- Sample size : 100 – 300 ml (... typically 200 ml are used)
- The real concern in WFI is endotoxins. Because WFI can pass the LAL endoxin test and still fail the above microbial action limit, it is improtant to monitor WFI systems for both endotxins and microorganisms.
- My interpretation/ experience : detection of gram-negatives in WFI is not acceptable
- Problem of sampling devices
- Benefit of rapid detection methods

FDA Guide to Inspections of Highly Purity Water systems / 1993 - Important citations :

- Microbial Limits: **Purified Water**
- Not greater than 100 organism per ml
- Free of objectionable microorganism (per 100 ml)
- Definition of objectionable microorganism: depending on the drug product and application

FDA Guide to Inspections of Highly Purity Water systems / 1993 - Important citations :

- Multi effect still – most new systems
- **Heat Exchangers** : how to prevent contamination by leakage: ... to provide gauges to constantly monitor pressure differentials to ensure the higher pressure is always on the clean fluid side. The other is to utilize the double-tubesheet type of heat exchanger.
- Problems with 0,2 micro point of use filters : an mask the level of contamination !
- Sampling procedure routine: For WFI systems the samples should be taken daily from the minimum of one point of use, with all points tested weekly ... Note : all user points should be tested !
- The sampling procedre should reflect how the water is drawn , e.g. if a hose is usually attached the sample should be aken at the end of the hose.
- Further Important Notes:
  - User points – if hoses are used, use hoses
  - Same flushing points (e.g. 1 min flushing)/ TRAINING !
  - Same temperature for sampling as used in operation !
  - No residual moisture (e.g. by closing of openning) / Disinfection is risky
  - Choose and justify appropriate „worst case sample“ locations !

Important Points

- Water can be used directly from the loop, or transferred into a (mobile) storage vessel for subsequent distribution to points of use. Vessel should prevent ingress from the environment (sterilized by SIP/ pressurized/ vent- filters integrity tested)
- Problem of hoses : must be dried after sanitization or sterilization, and store properly within classified area. “Hoses” are always a hot topic in audits !
- End –point sterilizing filters: are risky, may hide a microbiolgical contamination of the water system, refer also to above citation) ; further sampling without filters is recommended

Water

Problem Statement

What methods of production for WFI should be employed?

Recommendation

WFI must meet pharmacopeial requirements for purity. Any method that has been validated to reliably yield and maintain water in compliance with the relevant pharmacopeial standard may be employed.

NOTE: Current European Pharmacopoeia only recognizes distillation as an acceptable method for the production of WFI.

Proper design, control, and monitoring should be implemented and include both the production and distribution systems to ensure continuous assurance of the quality of the output.

Levels of control and monitoring should be based upon a risk assessment of the specific WFI production process and equipment capabilities.

Rationale for Recommendation

Flexibility in selection of technologies that can provide the required quality of water will permit the adoption of the best methodologies as more advanced systems become available.

References

General Chapter <61> Microbiological Examination of Nonsterile Products: Microbial Enumerations Tests. USP 37/NF 32: U.S. Pharmacopeia: 2014. www.usp.org

Topic B: Requirements for Water For Injection

Problem Statement

What are the requirements for preventing microbial contamination of WFI?

Recommendation

Production of WFI should be via distillation or other equally effective technology. Maintenance of WFI quality may be achieved via a continuously recirculating system which operates at an elevated temperature. Hot recirculating systems operating at lower temperatures or even ambient or cold loops are acceptable, but should have a method to ensure that the bioburden of the WFI remains under control. This may also be achieved through periodic sanitization (e.g., through hot water recirculation) during periods of non-use. WFI systems should be tested according to the requirements of the applicable pharmacopeia to demonstrate control.

Rationale for Recommendation

A well-designed system can be validated to maintain acceptable quality at lower temperatures. Lower temperatures (e.g., <70°C) requires periodic sanitization with hot water (not steam – circulating water systems are usually not designed to vent steam).

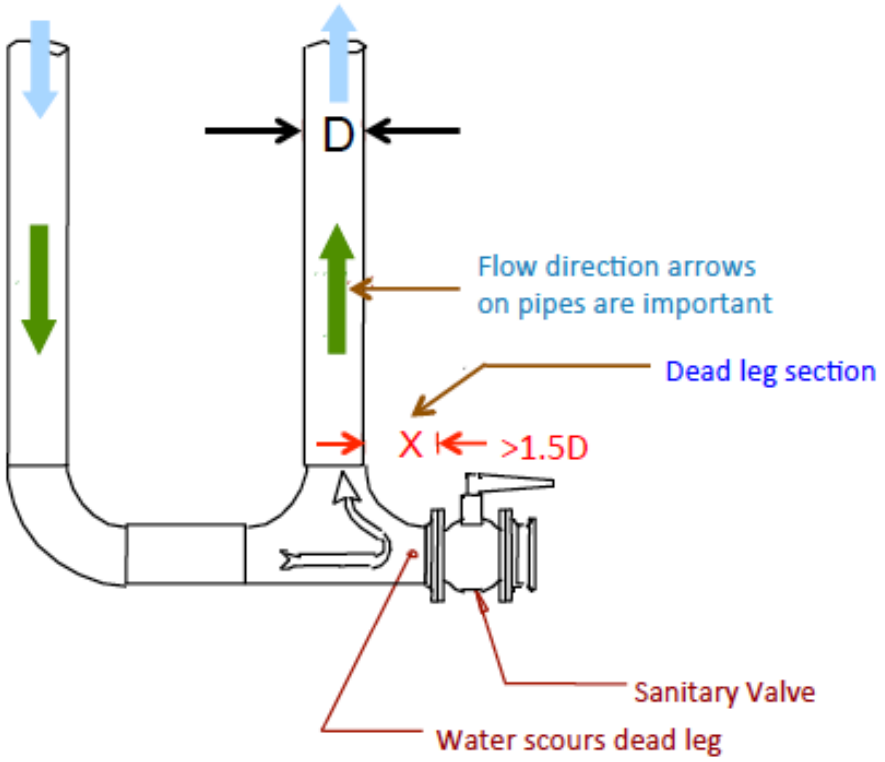
References

General Chapter <1231> Water for Pharmaceutical Purposes. USP 38/NF 33; U.S. Pharmacopeia: 2015. www.usp.org.

Problem of Dead Legs and stagnant water

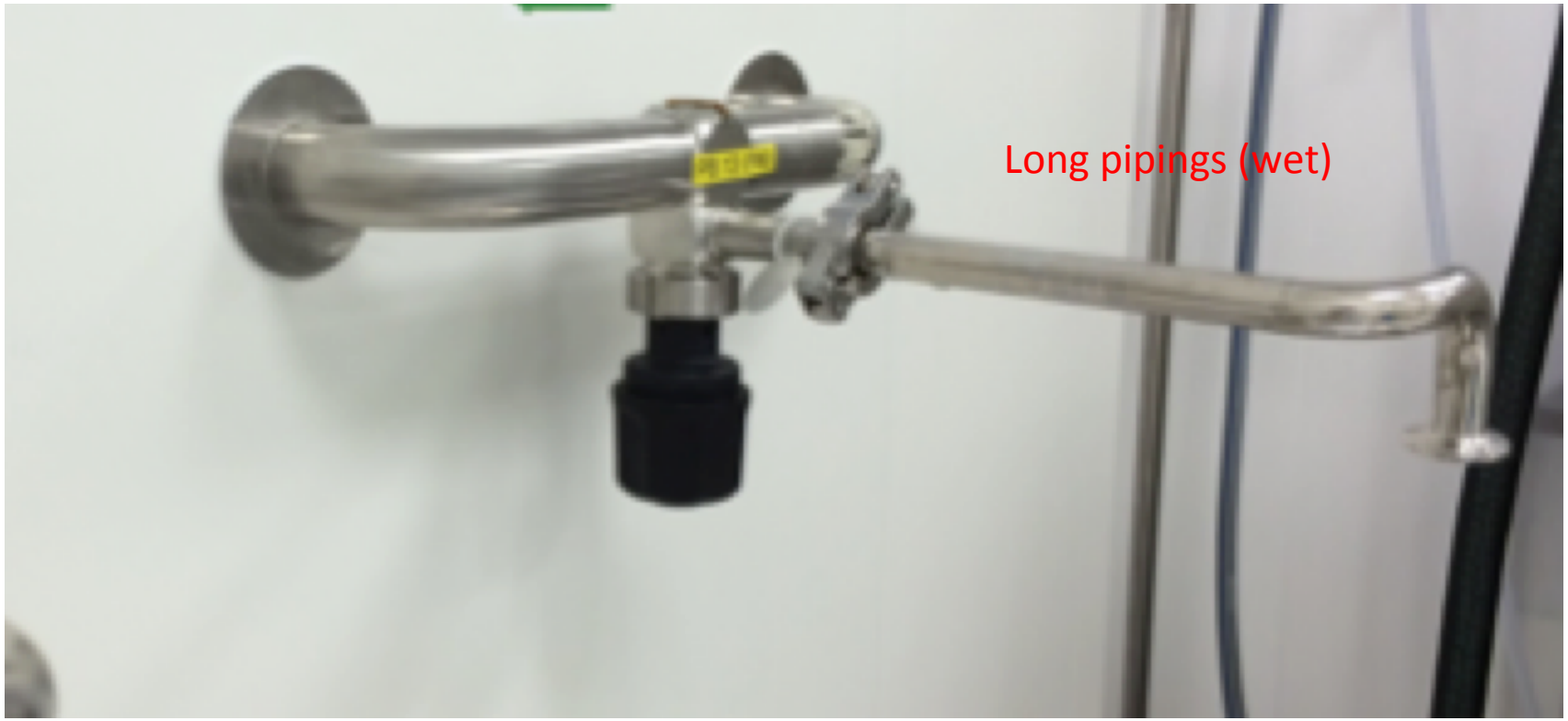
WHO/ TRS 929: dead leg should be not more than 1.5 diameter of the internal diameter of the piping. Nowadays no dead leg pipes are installed to solve the water staging problem in water systems.

Further important points for user points and sampling: same flushing time and conditions for production as for sampling !



CASE STUDIES: common problem with user points

CASE STUDIES: problem with user points



Common WFI system problems, examples and modern resolutions

- **PROBLEM**: whole Subloops are cooled down by a heatexchanger during withdrawal of WFI – Problem, that there has been no control of cooling down time period, and cold water has been standing in the rsoidual subloop (which ha sbeen closed by vaöve at the end of the subloop) , and WFI is returned later to the main loop

- Filling hot WFI into mobile holding vessel, and cooling down for usage – interity of vessel must be verified ; vessel sterilized before

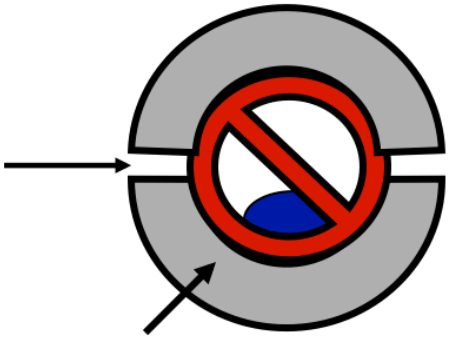
- Very common: external Heat Exchanger outside of the loop for cooling down hot WFI for the user– but may be risky, because of standing water and moisture residues; piping must be drained properly

- Modern technical solution: continuous sanitization of SST piping by steam before withdrawal and sampling ; elbow/ bow pipings connected to drainage under steam, removed before usage or samping

Biocontamination control techniques

1. Ball valves are unacceptable

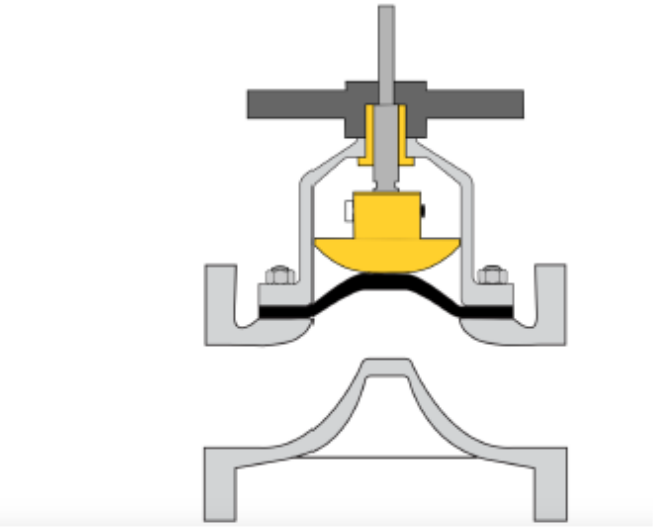
2. Bacteria can grow when the valve is closed

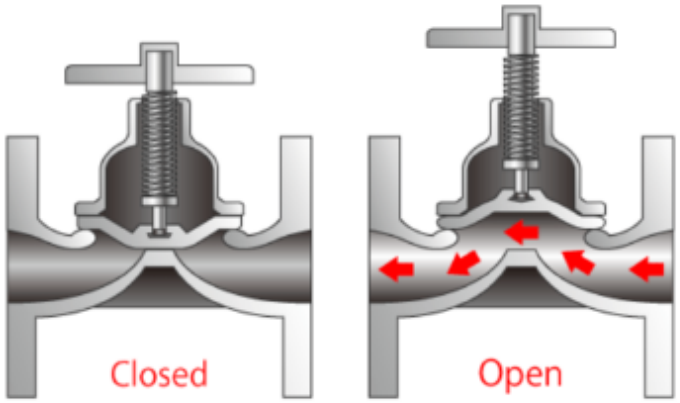


3. The water is contaminated as it passes through the valve

Source: T. Gould/ 2010

Usage Diaphragm valves (membrane valves)





System sanitization and bioburden control of PW and WFI systems

- Systems in place to control proliferation of microbes and biofilm formation
- Periodic sanitizing (UV light/ Ozone/ heat up) – for cold systems , or sterilization
- Continuous overpressure of the system ! (to prevent ingress from outside)
- Consideration already during design stage – include sanitization into validation
- Special precautions if water is cooled down – define maximum cool down time !
- Continuous turbulent flow circulation
  - *Specified velocity proven (qualification), and monitored*
- Hygienic pattern diaphragm valves
- Use the shortest possible length of pipe work
- Pipe work should have slope for drainage
- Possibility to sanitize the piping with steam prior to use and sampling (NOTE: disinfection of pipe opening is risky !
- No moisture or droplets left in the openings

Important Points

- URS / DQ/ IQ / OQ
- Define suitable, representative sampling points (examples see next slide) – by “On Site Inspection” in a team !
- PQ :
  - PQ 1: 2 weeks all sampling locations/ reduced usage of water
  - PQ 2: 2 weeks all sampling locations/ water used for production
  - PQ 3: 11 months: to include seasonal influences , already reduced sampling
  - Afterwards: routine sampling according a justified sampling plan and SOP

Washing machine (inside)

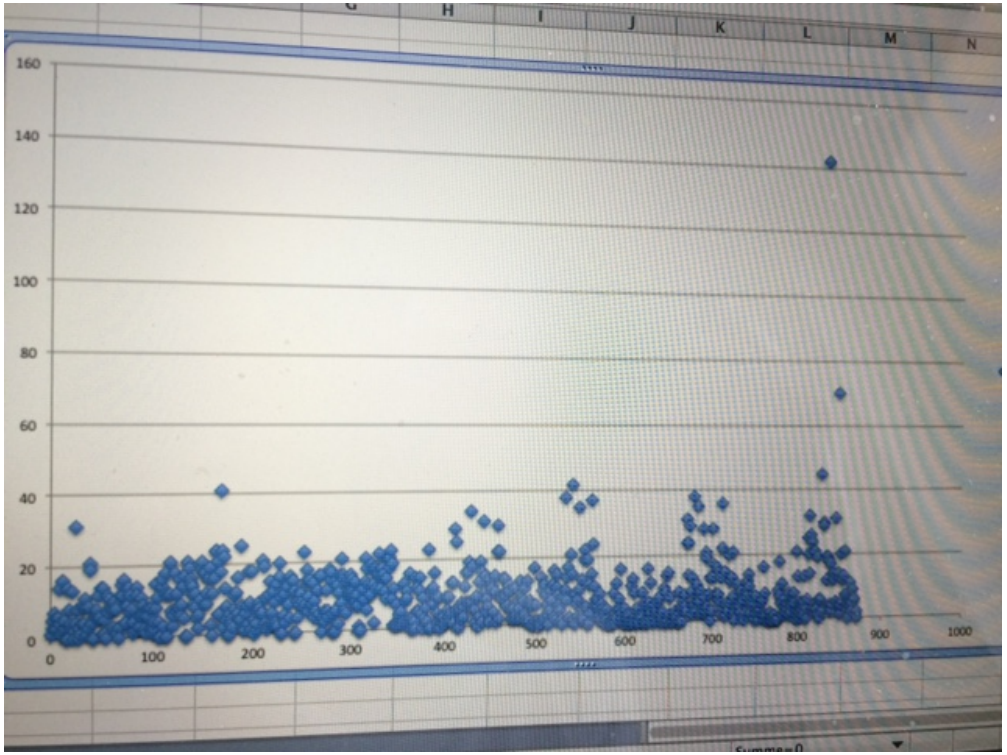
Sink with sterilized hose (e.g. with rinsing)

Requires several careful walk through with QA , before preparation of a PQ protocol !

Key points to condiser for QC Microbiology labs

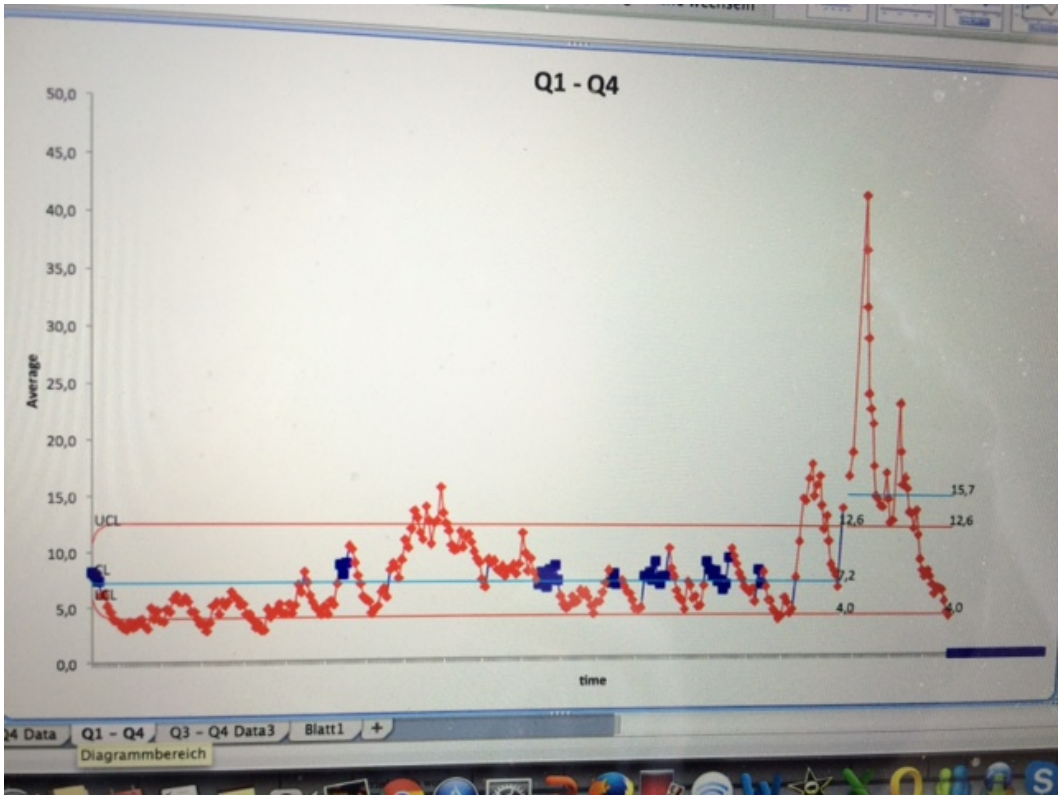
- Lab technicians must be (re)qualified for their specific task (Microbial count testing/ LAL testing)
- All Methods must be validated
- For MCT: use low nutrient agar (R2A/ PCA) and not TSA
- Prevent contamination during sampling and testing
- Have a validated, defined maximum storage times fro samples (e.g. 12 h at lower temperatures as recommended in USP <1231>
- Have adequate Action Limits defined, and historically based Alert Levels.
- Have qualified identification methods (Action Level exceeded; WFI is commended to identify all different colonies; compare profiles for a potential biofilm problem)
- Have a well defined OOS procedure according to cGMP (Note: retesting will not be possible, resampling may provide limited information)
- Perform good Trending reports (e.g. quarterly) and Trend analysis

Trending



- There are better way to do – Statistical based control charts to assess changes in trends !

Trending



- Statistical Control Charts may provide more information !

Modern Rapid Method: Scan RDI (Chemscan)

- Method: Scan RDI from AES- Chemunex
  - Direct cell counting method: growth is not required
  - Viability based technology via fluorescent labelling of all viable micro-organisms including spores
- Advantages
  - Results within 2 hours
  - Higher sensitivity: beneficial for investigations to find root cause, f.e. biofilm detection in WFI water systems
  - „VBNC“ detection (viable but not cultivable)
- Disadavantages
  - Identification of detected cells is not possible
  - Higher risk for „false positives“ versus classical sterility testing
- Publication: Guenther Gapp, Syvlie Guyomard, Pascale Nabet, Jean Scouvart: *Evaluation of the applications of a system for real- time microbial analysis of pharmaceutical water systems*; Europ. Journal of Parenteral Sciences, Vol 4, 131 – 136, 2000

RAPID Micro Testing Experience : CHEMUNEX Scan RDI/ Chemscan

BIOMÉRIEUX INDUSTRY

ABOUT US | MICROBIOLOGY HUB | FOOD | BIOPHARMA | VETERINARY DIAGNOSTICS | COSMETI

Home › Biopharma › Rapid microbial detection & sterility testing › ScanRDI®

ScanRDI®

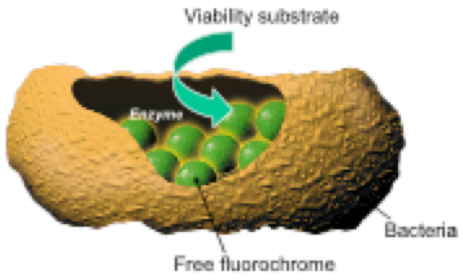
Automated real-time microbial detection and enumeration method

- Extreme sensitivity
- Extreme speed
- Simple process

Fluorassure® Viability Markers

Criteria of Viability :

- Enzyme activity
- Membrane integrity



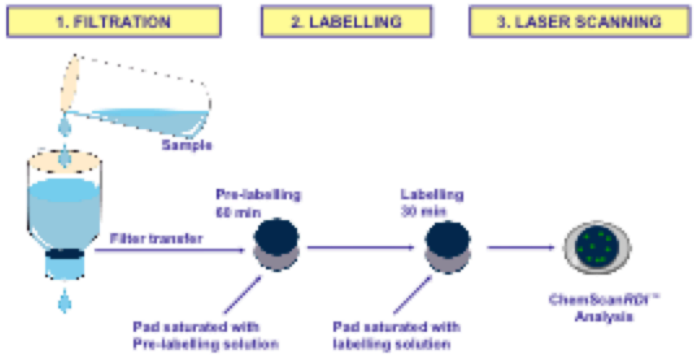
ChemScan Analysis : A Simple Three Step Procedure

1. Membrane Filtration

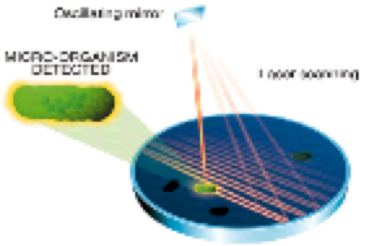
2. Cell Labelling

3. Laser scanning

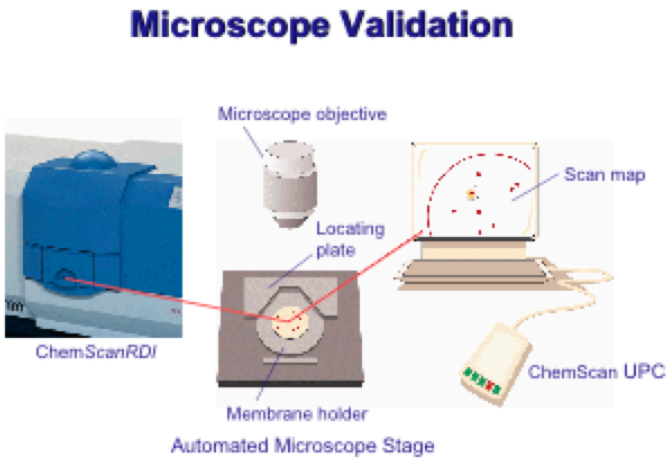
Analysis Protocol - TVC

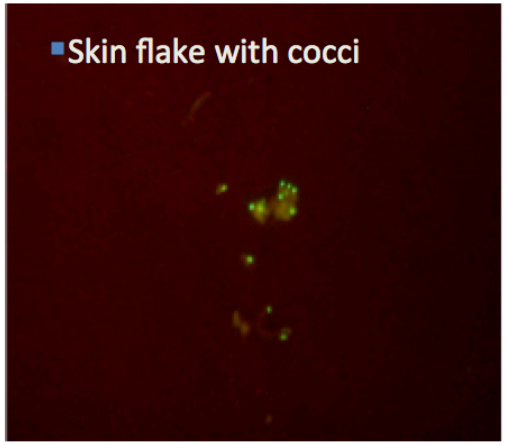


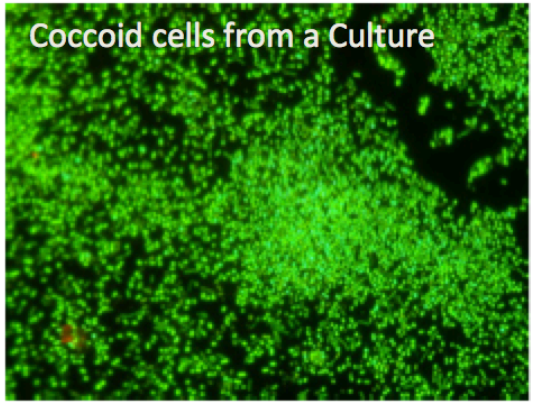
Laser Scanning



RAPID Testing Experience : CHEMUNEX Scan RDI/ Chemscan has been validated for WFI monitoring







US FDA Warning Letter

1. Failure to validate that your water system is capable of consistently producing purified water suitable for its intended use.

Your API, **(b)(4)**, is used in the manufacture of sterile drug (medicinal) products. Your firm failed to validate the performance of the purified water system that provides water for the **(b)(4)**. It is essential that this water system consistently produces water that meets an appropriate endotoxin limit, in order to prevent contamination of the **(b)(4)** API. Your firm began to use the purified water system in November 2004 but did not perform a validation of the system until January 2010. The 2010 validation conducted was retrospective and included very limited sampling data. Significantly, this 2010 study included data from only one point of use per month over a period of eleven months. The validation failed to include a thorough assessment of elements critical to the performance of the system such as an evaluation of the quality of the water at each step in the **(b)(4)** process, a thorough evaluation at all points of use, and a complete microbial and endotoxin analysis.

1. Failure to validate and monitor the water purification system to ensure that water is of appropriate quality.

Your firm uses water in the final purification step of Fluorescein USP, an API intended for use in sterile drug products. However, your firm failed to demonstrate that your purified water system can consistently produce water that is suitable for use in the manufacture of this API.

This is a repeat observation from the July 21-August 8, 2010 inspection. In your response to observations made at the 2010 inspection, your firm promised actions it would take to assure reliable water quality. However, those changes were inadequate, as you continued to get periodic out-of-specification (OOS) endotoxin and total organic carbon (TOC) test results.

Many Thanks !