Pharmaceutical Water Systems

Tony Gould

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World Health Organization

Water for Pharmaceutical Use

Objective

- General information on water systems
- Design and engineering aspects of water systems
- Inspection of water systems

Water for Pharmaceutical Use

Background to water requirements and use

- Water is the most widely used substance / raw material
- Used in production, processing, formulation, cleaning, quality control
- Different grades of water quality available

1.2

Water for Pharmaceutical Use

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*
  - *Micro test results require incubation periods*

1.2

Water for Pharmaceutical Use

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

2.

Water for Pharmaceutical Use

Water system requirements (2)

- Monitoring of water sources regularly
  - *Chemical and microbiological*
  - *Endotoxin level where relevant*
- Monitoring of system performance, storage and distribution systems
- Records of results, and action taken
- Validated sanitization procedure followed on a routine basis

2.

Water for Pharmaceutical Use

Purified Water (PW)

- Prepared from potable water source
- Meet pharmacopoeia specification for chemical and microbial purity
- Protected from recontamination
- Protected from microbial proliferation

3.3.

Water for Pharmaceutical Use

Highly Purified Water (HPW)

- 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 reverse osmosis (RO), ultrafiltration (UF) and deionization (DI)

3.4.

Water for Pharmaceutical Use

Water for Injections (WFI)

- Prepared from potable water source or PW (preferred)
- WFI is not sterile
- WFI is not a final dosage form
- WFI is an intermediate bulk product
- According to *The International and European Pharmacopoeias* – final purification step should be distillation

3.5

Water for Pharmaceutical Use

General

- Water can be used directly, or stored in a storage vessel for subsequent distribution to points of use
- Design appropriately to prevent recontamination after treatment
- Combination of on-line and off-line monitoring to ensure compliance with water specification

6.1

Water for Pharmaceutical Use

WPU system contact materials (6)

- Suitable materials include:
  - *Stainless steel Grade 315 L (low carbon)*
  - *Polypropylene (PP)*
  - *Polyvinylidenedifluoride (PVDF)*
  - *Perfluoroalkoxy (PFA)*
- Unplasticized polyvinylchloride (uPVC) used for *non-hygienic* designed water treatment equipment such as ion exchangers and softeners

6.2

Micro contamination of water

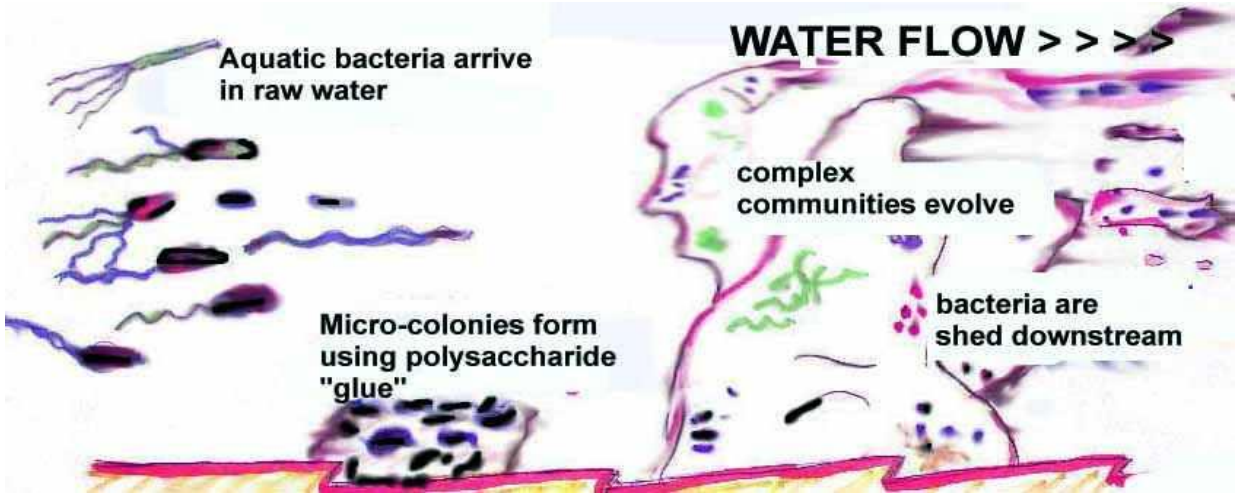
- Microorganisms – Biofilm formation
- Protozoa
  - *Cryptosporidium*
  - *Giardia*
- Bacteria
  - *Pseudomonas*
  - *Gram negative, non-fermenting bacteria*
  - *Escherichia coli and coliforms*

Micro contamination of water

Biofilm formation

1. Free-swimming aquatic bacteria use *polymucosaccharides* to colonize surfaces

2. Complex communities evolve which shed microcolonies and bacteria



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System sanitization and bioburden control

- Systems in place to control proliferation of microbes
- Techniques for sanitizing or sterilization
- Consideration already during design stage – then validated
- Special precautions if water not kept in the range of 70 to 80 degrees Celsius

6.3

Water for Pharmaceutical Use

Biocontamination control techniques

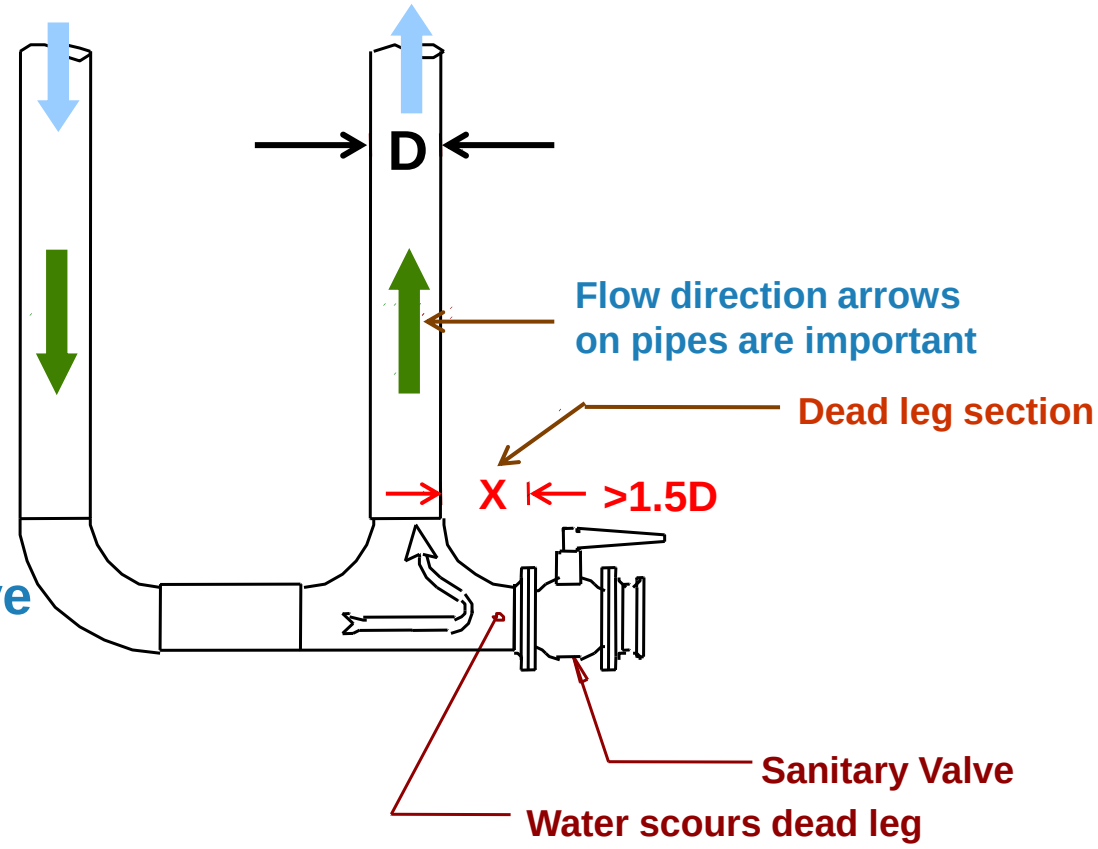
- Continuous turbulent flow circulation
  - *Specified velocity proven (qualification), and monitored*
- Avoid dead legs
- Hygienic pattern diaphragm valves
- Shortest possible length of pipe work
- Pipe work of ambient temperature systems, isolated from hot pipes

6.5.3

Water for Pharmaceutical Use

Biocontamination control techniques (2)

There should be no dead legs



If D=25mm & distance X is greater than 50mm, we have a dead leg that is too long

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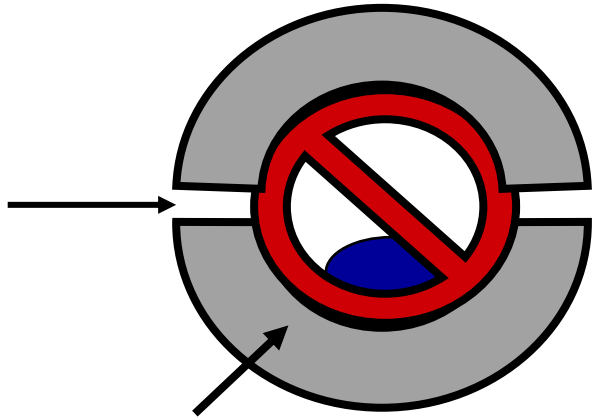
Water for Pharmaceutical Use

Biocontamination control techniques (3)

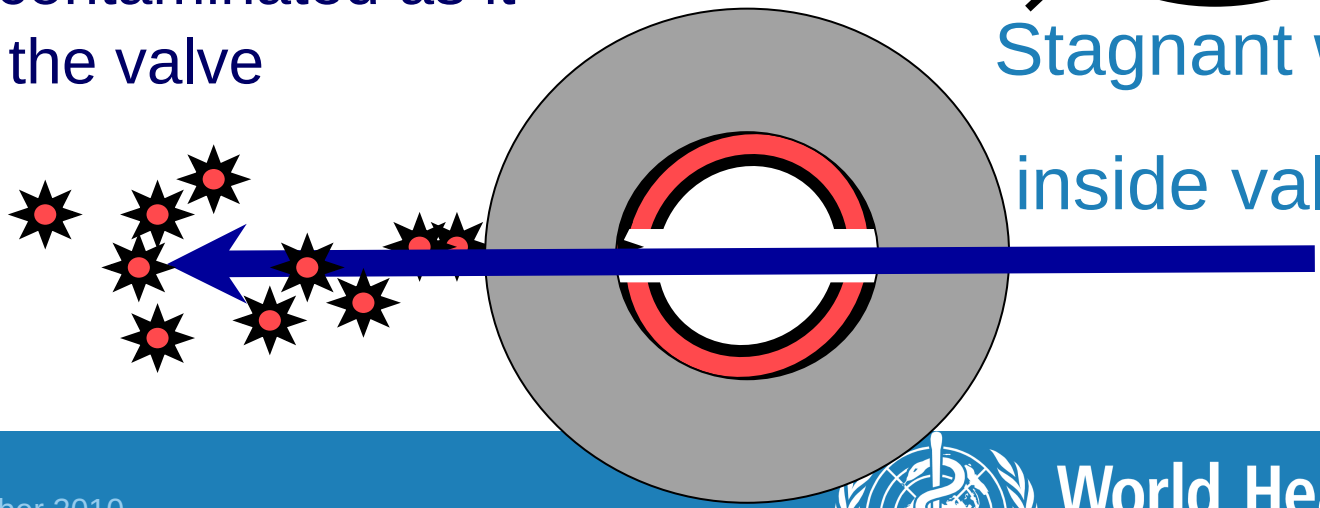
1. Ball valves are unacceptable

2. Bacteria can grow when the valve is closed



Stagnant water inside valve

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



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Biocontamination control techniques (4)

- Pressure gauges separated from system membranes
- Pipe work laid to fall (slope) – allows drainage
- Maintain system at high temperature (above 70 degrees Celsius)
- Use UV radiation
  - *Flow rate, life-cycle of the lamp*
- Suitable construction material

6.5.3

Water for Pharmaceutical Use

Biocontamination control techniques (5)

- Periodic sanitization with hot water
- Periodic sanitization with super-heated hot water or clean steam
  - *Reliable*
  - *Monitoring temperature during cycle*
- Routine chemical sanitization using, e.g. ozone
  - *Removal of agent before use of water important*

6.5.3

Water for Pharmaceutical Use

Storage and distribution - *Storage vessels*

- Design and size important
  - *Serves as buffer between generation and use*
  - *Avoid inefficiencies and equipment stress during frequent on-off cycles*
  - *Short-term reserve in case of failure*
- Contamination control consideration
  - *Headspace (kept wet with spray ball / distributor device)*
  - *Nozzles (no dead zone design)*
  - *Vent filters (type, testing, use of heat)*
  - *Pressure relief valves and burst discs (sanitary design)*

6.4

Water for Pharmaceutical Use

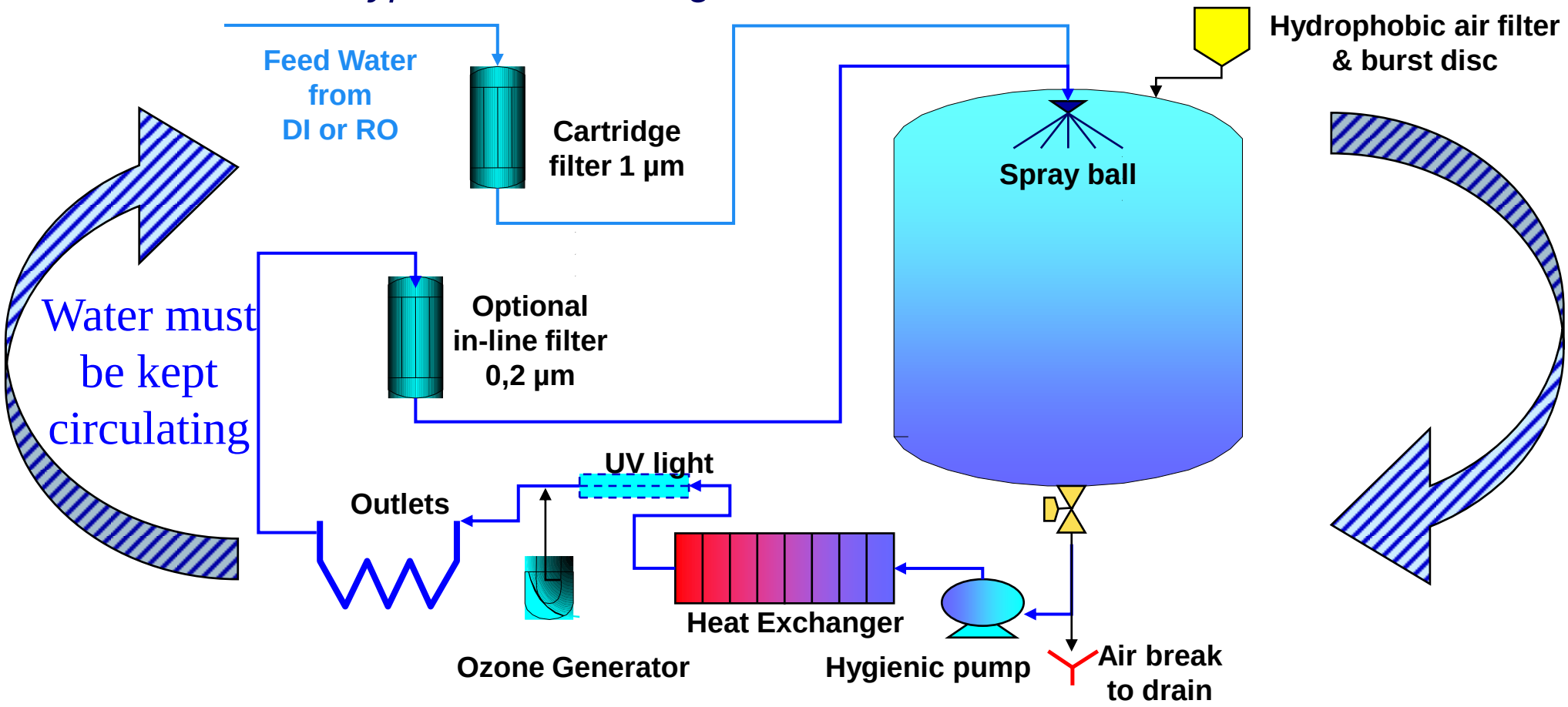
Storage and distribution – *Pipes and heat exchangers*

- Continuous circulating loop needed
- Sanitary design with appropriate seals
- Filtration not recommended in loop and take-off point
- Heat exchangers:
  - *Double tube plate or double plate and frame type*
  - *Designed to ensure no stasis of water*
- Where water is cooled before use, done in minimum time, and validated process

6.5, 6.5.1

Water for Pharmaceutical Use

Typical water storage and distribution schematic



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On site inspection:

- Walk through the system, verifying the parts of the system as indicated in the drawing
- Review procedures and "on site" records, logs, results
- Verify components, sensors, instruments
- Start with source water supply – follow whole system "loop"

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Water treatment system inspection (1)

- Checks may include:
  - *dead legs*
  - *filters*
  - *pipes and fittings*
  - *ionic beds*
  - *storage tanks*
  - *by-pass lines*

Water for Pharmaceutical Use

Water treatment system inspection (2)

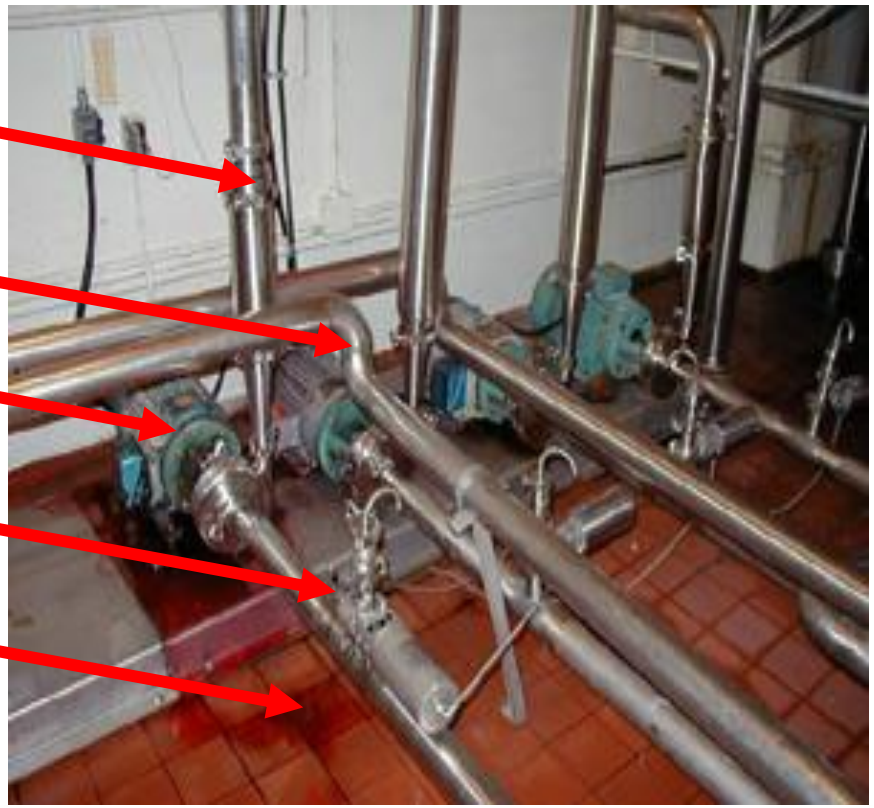
- Checks may include:
  - *pumps*
  - *UV lights*
  - *sample points*
  - *reverse osmosis*
  - *valves*
  - *heat exchangers*
  - *Instruments, controls, gauges, etc.*

Water for Pharmaceutical Use

Other checks

Pipes and pumps

- *hygienic couplings*
- *welded pipes*
- *hygienic pumps*
- *hygienic sampling points*
- *acceptable floor*
- *no leaks*



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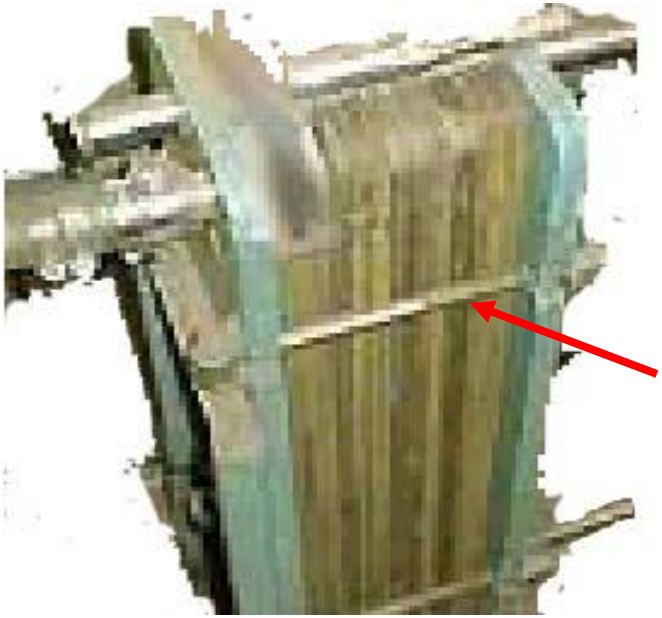
Other checks

Check condition of equipment



Staining on water storage tanks

Corrosion on plates of heat exchangers indicates possible contamination

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Other checks

Maintenance records, maintenance of pump seals and O rings

Water for Pharmaceutical Use

Other checks

Air filters

- Integrity testing, sterilization and replacement frequency
- Check burst discs

Water for Pharmaceutical Use

Other checks

- UV light – monitoring performance and lamp life and intensity
- Validating ozone dosage
- Specifications for acids, alkalis for DI and sodium chloride for water softener

Water for Pharmaceutical Use

Additional documentation to review:

- Qualification protocols and reports
- Change control request (where applicable)
- Requalification (where applicable)
- QC and microbiology laboratory:
- SOP for sampling
- Procedures and records

Water for Pharmaceutical Use

Sampling

- There must be a sampling procedure
- Sample integrity must be assured
- Sampler training
- Sample point
- Sample size

Water for Pharmaceutical Use

Testing

- Review method verification
- Chemical testing
- Microbiological testing
  - *test method*
  - *types of media used*
  - *incubation time and temperature*
  - *objectionable and indicator organisms*
  - *manufacturer must set specifications*

Water for Pharmaceutical Use

Suggested bacterial limits *(CFU /mL)*

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
Points of Use	1	10	100

Thank you for listening!