Supplementary Training Modules on Good Manufacturing Practice

Water for Pharmaceutical Use

WHO Technical Report Series No 970, 2012. Annex 2

Part 2
Water purification, storage and distribution

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Water for Pharmaceutical Use

Objectives

To examine the basic technology and requirements for:

- Water purification systems
- Storage and distribution requirements
- Sanitization

5. - 6.

Water for Pharmaceutical Use

Water purification systems

- Manufacturer to select appropriate method of purification
- Appropriate sequence of purification steps
- Influenced by, e.g.
  - *Water quality specification*
  - *Feed water quality*
  - *Reliability and robustness of treatment system*
  - *Supplier support, maintenance and operation costs*

5.1.1 – 5.1.2.

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Water purification systems (2)

- Influenced by, e.g.
  - the final water quality specification
  - the quantity of water required by the user
  - the available feed-water quality and the variation over time (seasonal changes)
  - the availability of suitable support facilities for system connection (raw water, electricity, heating steam, chilled water, compressed air, sewage system, exhaust air)

5.1.1 – 5.1.2.

Water for Pharmaceutical Use

Water purification systems (3)

- Influenced by, e.g. (cont.)
  - sanitization method
  - the reliability and robustness of the water-treatment equipment in operation
  - the yield or efficiency of the purification system
  - the ability to adequately support and maintain the water purification equipment
  - the continuity of operational usage considering hours/days, days/ years and planned downtime
  - the total life-cycle costs

5.1.1 – 5.1.2.

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Water purification system considerations:

- Location of the plant room; temperatures
- Leachates and adsorptive contact materials
- Hygienic or sanitary design
- Corrosion; leakage
- Proliferation of microbiological organisms, cleaning; sanitizing
- Capacity and output requirements
- Instruments, test and sampling points

5.1.3

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Water purification system considerations (2)

Physical considerations:

- Ability to collect samples
- Space available for the installation
- Structural loadings on buildings
- Adequate access for maintenance
- Regeneration and sanitization chemicals.

5.1.4

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Pre-treatment steps

- Primary filtration and multimedia filter
- Coagulation or flocculation
- Desalination
- Softening

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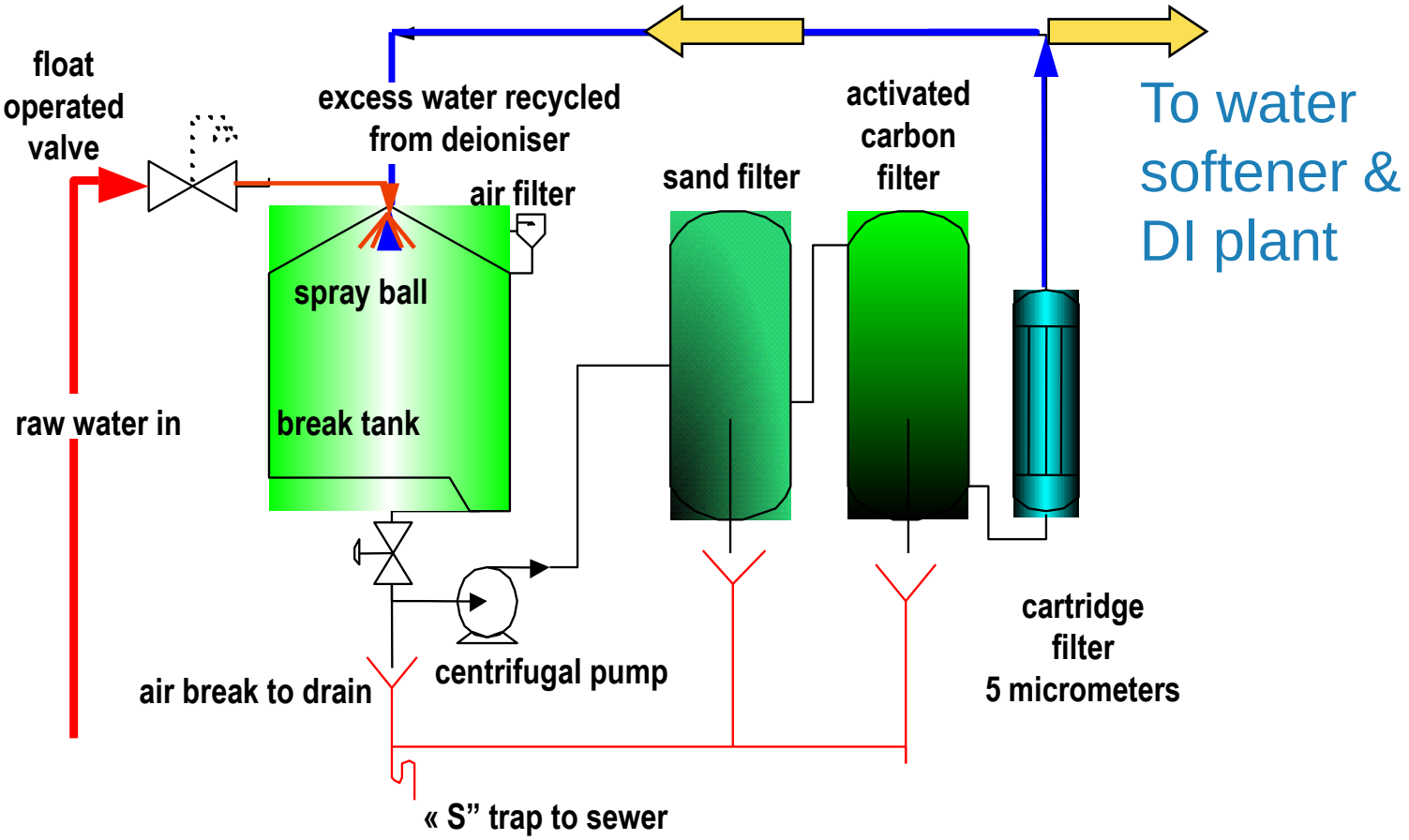
Pretreatment – schematic drawing



Water is kept circulating

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Water pre-treatment complex in a pre-treatment room

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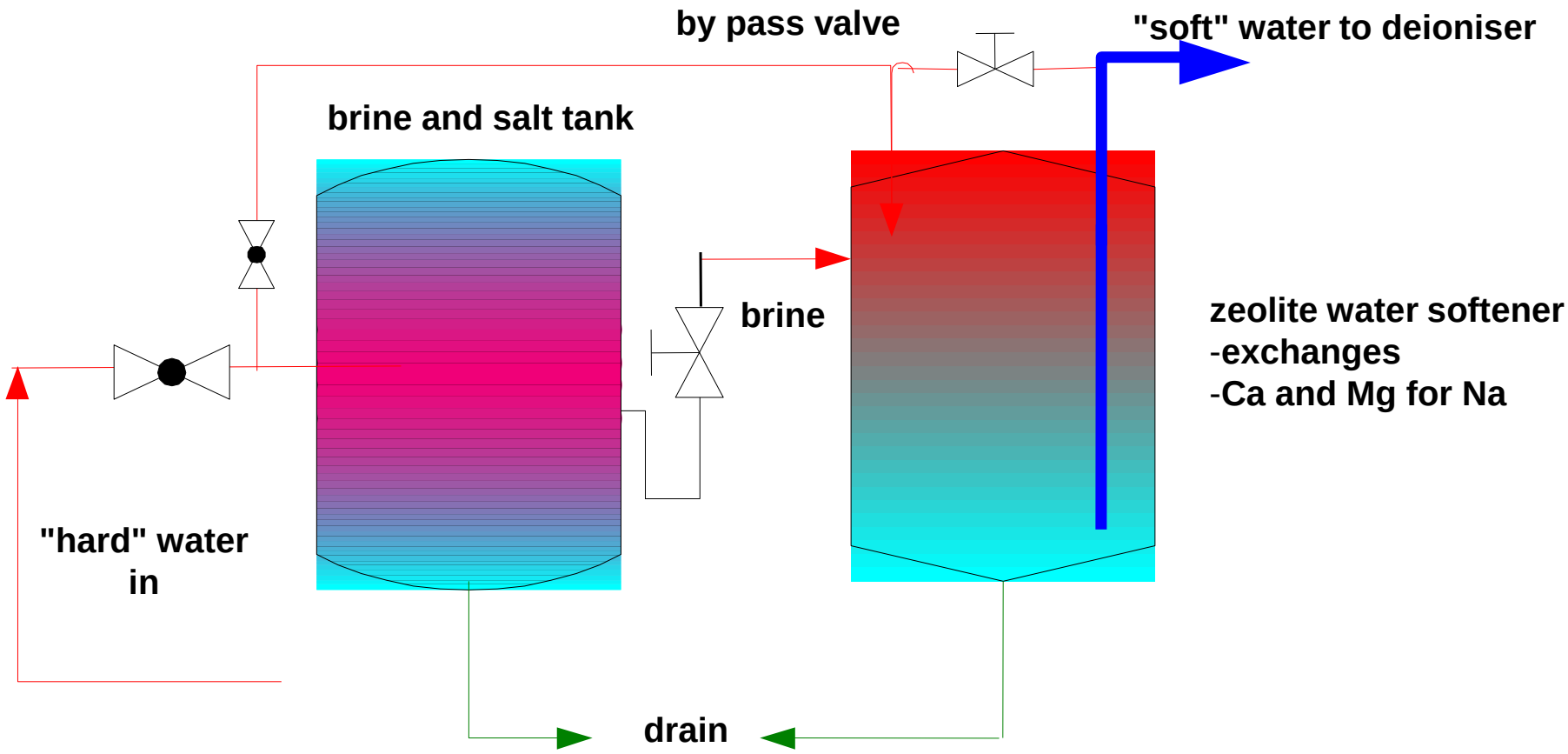
Water Softener – schematic drawing



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Chlorine removal (Activated-carbon (AC) filtration or bisulphite)

- AC removes chlorine but bacteria can then grow
- AC filtration can remove organic impurities
- Bisulphite leaves sulphate residues but is antimicrobial

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Production of drinking water

- Derived from raw water source (e.g. well, river, reservoir)
- Processes may include:
  - desalinization; filtration
  - softening; disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection)
  - iron (ferrous) removal
  - precipitation
  - reduction of concentration of specific inorganic and/or organic materials

5.2.1 – 5.1.2.

Water for Pharmaceutical Use

Drinking water (2)

- Routine monitoring of quality – cover environmental, seasonal or supply changes
- Additional testing when change in the raw water source, treatment techniques or system configuration
- Trend review
  - When quality changes significantly, but is still within specification, the direct use as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented

5.2.3. – 5.2.5.

Water for Pharmaceutical Use

Drinking water (3)

- Producing drinking water through an "in-house" system requires well documented system configuration and water quality monitoring
- Change control approved by QA
- Storage of water:
  - *no degradation, ensure turnover, routine testing*
- "indirect impact system" – qualification not needed

5.2.6. – 5.2.8.

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Drinking water (4)

- System design allows for draining and sanitization
- Closed storage tanks:
  - *With protected vents*
  - *Allows for visual inspection*
  - *Draining and sanitization possible (also pipework)*
- Control microbiological contamination of sand filters, carbon beds, water softeners. Measures include:

5.2.10. – 5.2.11.

  - *back-flushing, chemical or thermal sanitization and frequent regeneration, continuous waterflow*

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Drinking water (5)

- When supplied in bulk or by tanker – identify problems and risks
- Risk control:
  - Vendor assessment
  - Authorized certification activities
  - Acceptability of delivery vehicle
- Similar as other starting materials

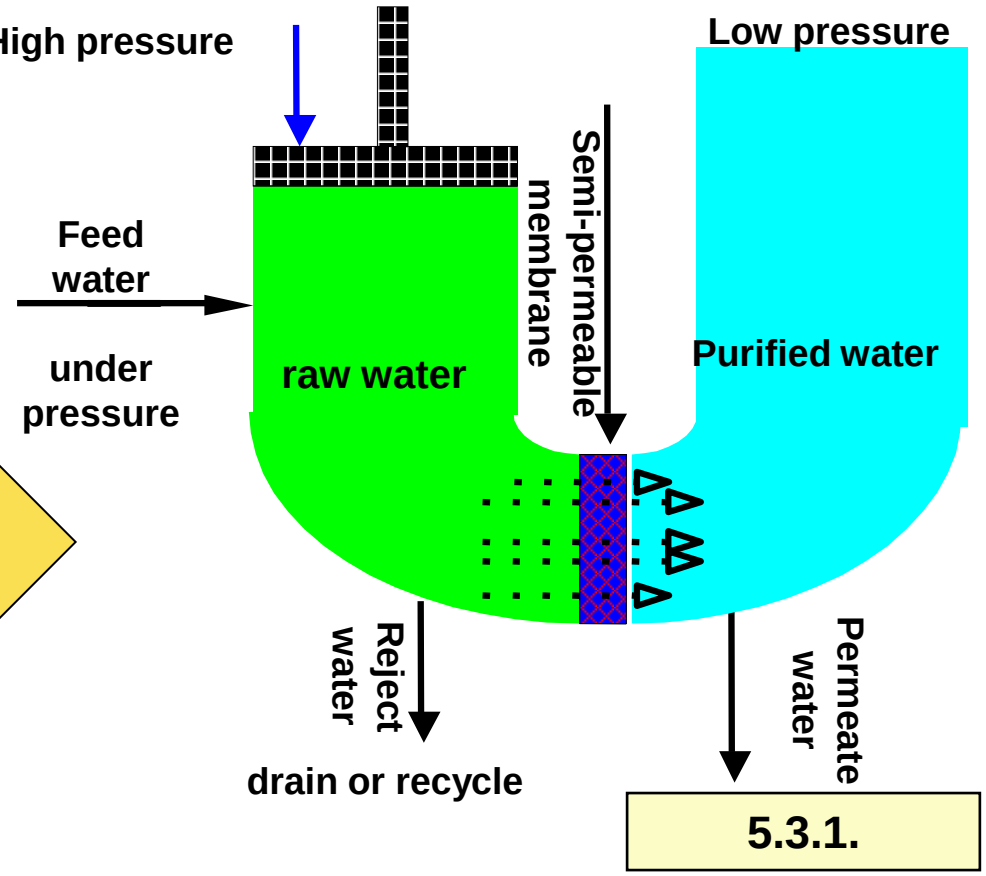
5.2.9.

Water for Pharmaceutical Use

Production of Purified Water (PW) (1)

Use appropriate, qualified methods to produce PW.

Includes: Ion exchange, Reverse Osmosis, Ultrafiltration and/or EDI and distillation



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Water for Pharmaceutical Use

Factors to consider in URS for PW:

– feed-water quality (and variation over seasons) and water-quality specification;

–quantity of water required;

–sequence of purification stages and energy consumption;

– extent of pretreatment needed;

– performance optimization;

– appropriately located sampling points;

–appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

5.3.2.

Water for Pharmaceutical Use

Production of Purified Water (2)

- Ambient temperature PW systems are susceptible to microbiological contamination – especially when static and periods of low or no demand
- Evidence of effective controls
- Sanitization at different stages of purification
- If agents are used – proof of removal

5.3.3

Water for Pharmaceutical Use

Production of Purified Water (3)

Controls may include:

- Maintain minimum flow at all times
- Control temperature in the system e.g. < 25 °C
- Provide ultraviolet disinfection
- Use components that can periodically be thermally sanitized
- Chemical sanitization (e.g. ozone, hydrogen peroxide and/or peracetic acid) – and thermal sanitization at > 70 °C

5.3.4.

Water for Pharmaceutical Use

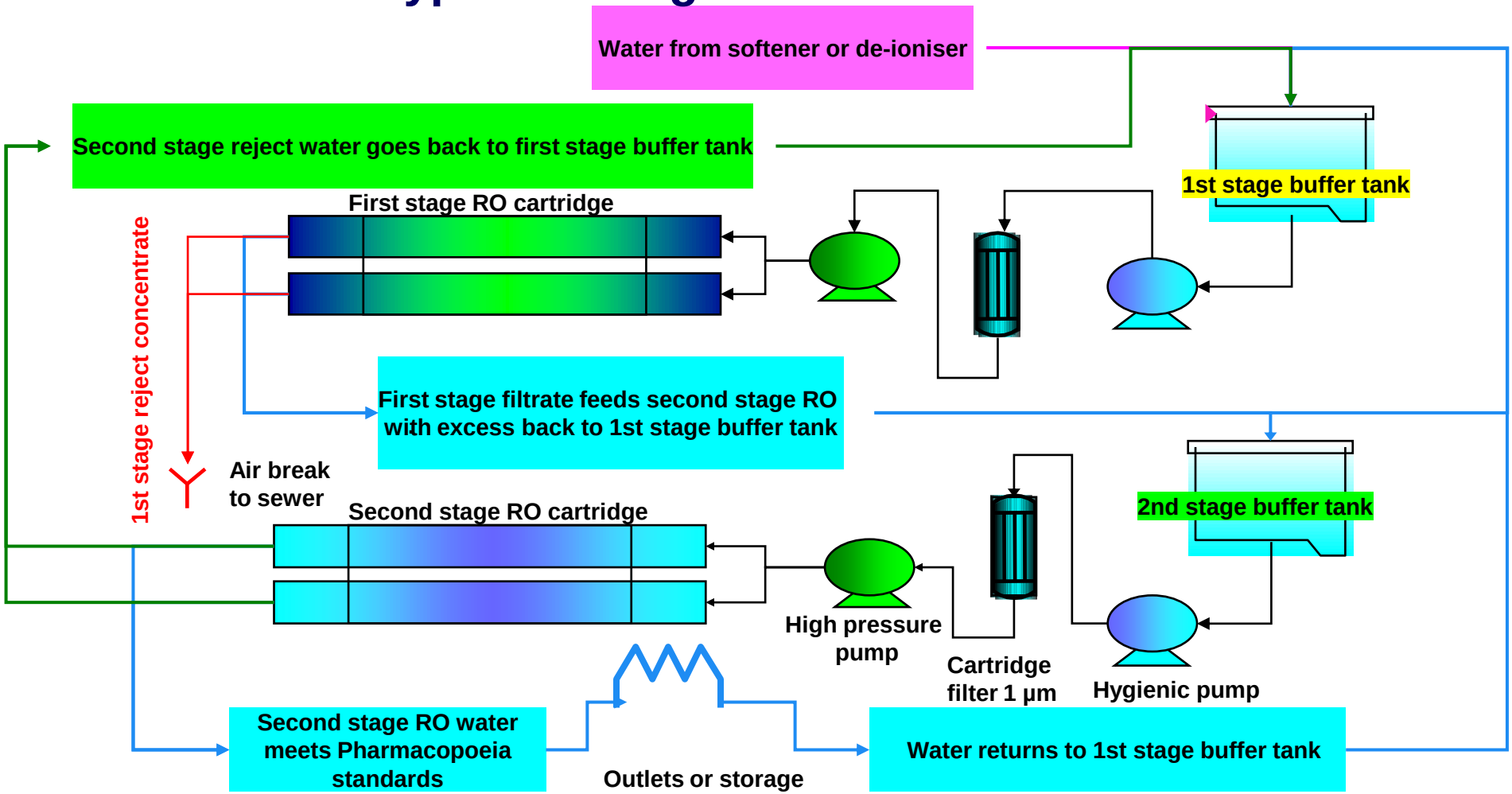
Production of Highly Purified Water (HPW)

- Produced by double-pass reverse osmosis coupled with ultrafiltration or by any other appropriate qualified purification technique or sequence of techniques.
- Same principles as for Purified Water

5.4.1. – 5.4.2

Water for Pharmaceutical Use

Typical 2-stage RO schematic



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Production of Water for Injections (WFI)

- Distillation is preferred technique – also in some Pharmacopoeia
- Factors to consider in design:
  - *Feed water quality*
  - *Required water quality specification and quantity of water*
  - *Optimum generator (size and variable control to prevent frequent start/stop)*
  - *Blow-down and dump functions*
  - *Cool-down venting (to avoid contamination ingress)*
- Similar principles as for PW

5.5.1. – 5.5.3

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Water storage and distribution systems

- This section applies to WPU systems for PW, BHPW and BWFI
- The water storage and distribution to work in conjunction with the purification plant to ensure delivery of water of consistent quality to the user points, and to ensure optimum operation of the water purification equipment

6

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What are the main components in a water storage and distribution system?

6.

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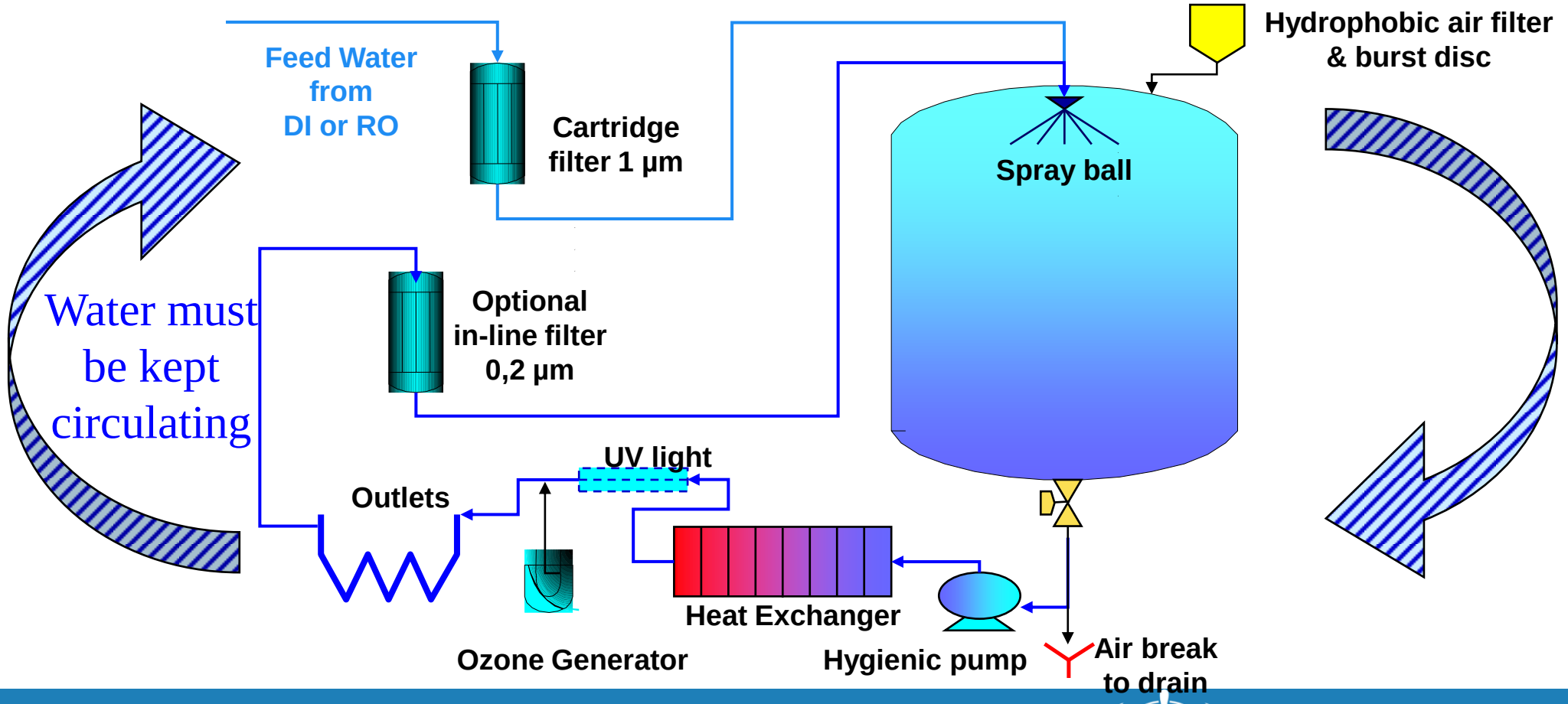
Typical water storage and distribution schematic



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General

- PW usually stored in a vessel for subsequent use
- Storage and distribution system is a key part of the whole system
- Should be appropriately designed
- Configured to prevent microbial proliferation and recontamination of the water (PW, BHPW, BWFI) after treatment
- Online and offline monitoring to ensure that the appropriate water specification is maintained

6.1.1. – 6.1.3

Water for Pharmaceutical Use

Contact materials

- Materials that come into contact with WPU should be appropriate
- Includes:
  - pipework
  - valves and fittings
  - seals
  - diaphragms and
  - Instruments

6.2.1. – 6.2.2.

Water for Pharmaceutical Use

Contact materials – Considerations (1)

- Compatibility
- Prevention of leaching
- Corrosion resistance
- Smooth internal finishing
- Jointing
- Unions and valves

6.2.2.

Water for Pharmaceutical Use

Contact materials – Considerations (2)

- Compatibility
  - Temperature and chemicals, operation, rest and sanitization
- Prevention of leaching
  - Non leaching – operation and sanitization
- Corrosion resistance
  - SS316L, cleaning and passivation
- Smooth internal finishing

6.2

Water for Pharmaceutical Use

Contact materials – Considerations (3)

- Jointing
  - Smooth. Controls (welder qualification, set-up, work session test pieces, logs, visual inspection reports

- Unions and valves
  - Sanitary design (no threads)
- Materials
  - E.g. SS316L, polypropylene, PVDF

6.2

Water for Pharmaceutical Use

System sanitization and bioburden control

- Systems in place to control proliferation of microbes
- Techniques for sanitizing or sterilization
- Consideration already during design stage – suitable materials of construction.
- Validated procedure
- Special precautions if water not kept > 65 degrees Celsius

6.3.1. -.6.3.2.

Water for Pharmaceutical Use

Storage Vessel requirements

- Design and size important
- Capacity
  - *Buffer capacity (generation and use); operate continuously, avoid inefficiencies due to frequent on and off cycles*
  - *Sufficient for 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)*

6.4.3

Water for Pharmaceutical Use

Storage Vessel Considerations and components

Water for Pharmaceutical Use

Requirements for water distribution pipework

- General considerations
- Temperature control
- Circulation pumps
- Biocontamination control techniques

6.5.

Water for Pharmaceutical Use

General considerations

- Continuous circulating loop
- Control proliferation of contaminants
- No filters in loops or at user points
- Circulation pumps – sanitary design
  - Stand by – no stagnant water

6.5.1.1. – 6.5.1.2.; 6.5.3.

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Temperature control

- Heat exchangers should not be source of contamination
  - Double tube plate or double plate and frame or tube and shell configuration preferred
  - arranged in continually circulating loops or sub-loops to avoid static water
  - Where cooling is done – for minimum periods of time

6.5.2.1. – 6.5.2.3., 6.5.3

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Biocontamination control techniques

Sanitization (chemical or thermal) - production and distribution – and include:

- Continuous turbulent flow circulation
- Shortest possible length of pipework
- Isolated from adjacent hot pipes

6.5.4..2

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Biocontamination control techniques (2)

- Minimized deadlegs (NMT 3D)
- Pressure gauges separated by membranes
- Use of diaphragm valves
- Sloped and fully drainable

6.5.4.2

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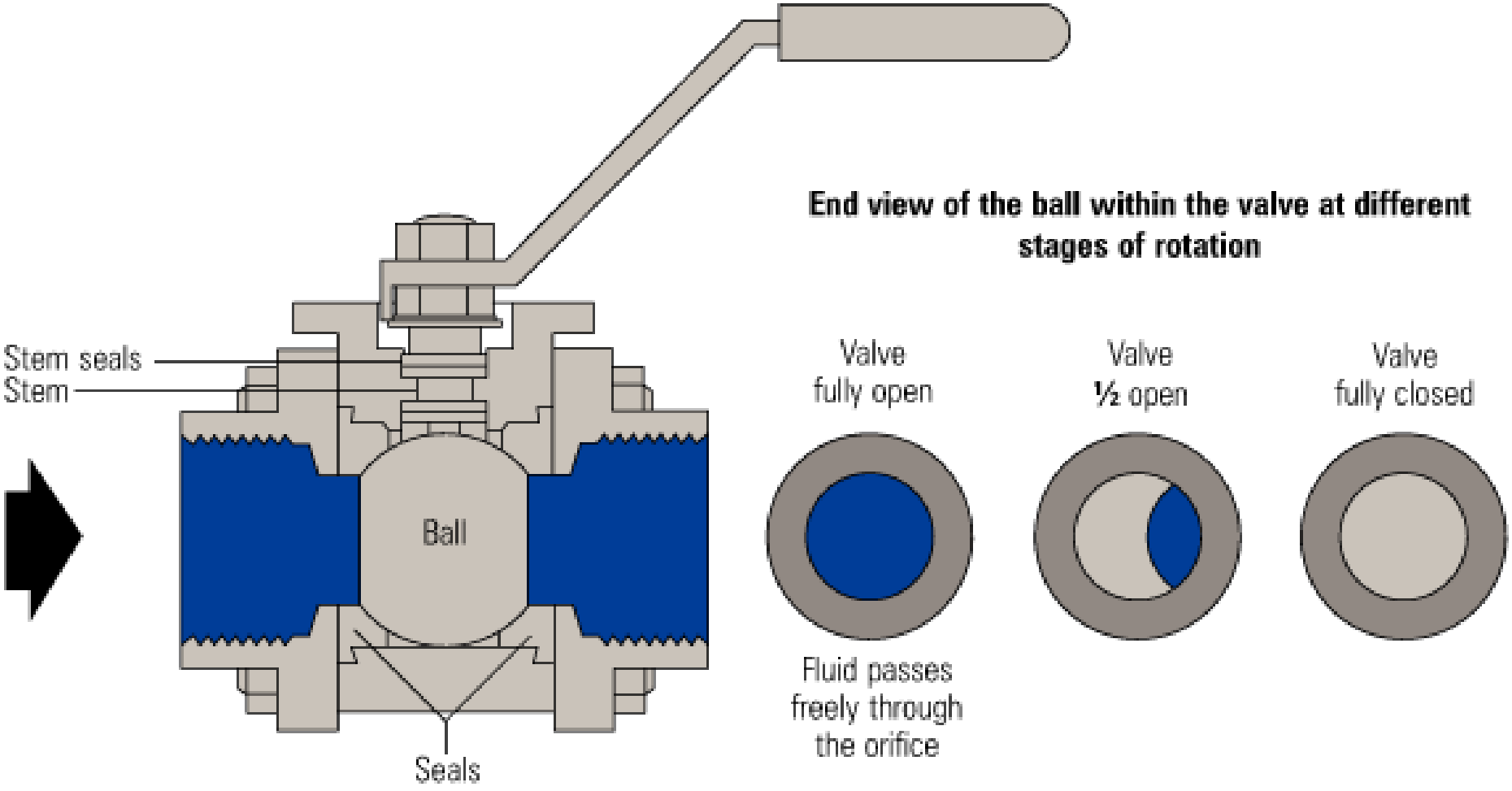

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What type of valves are these?

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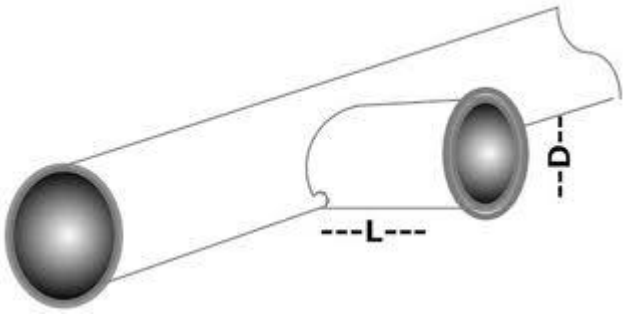
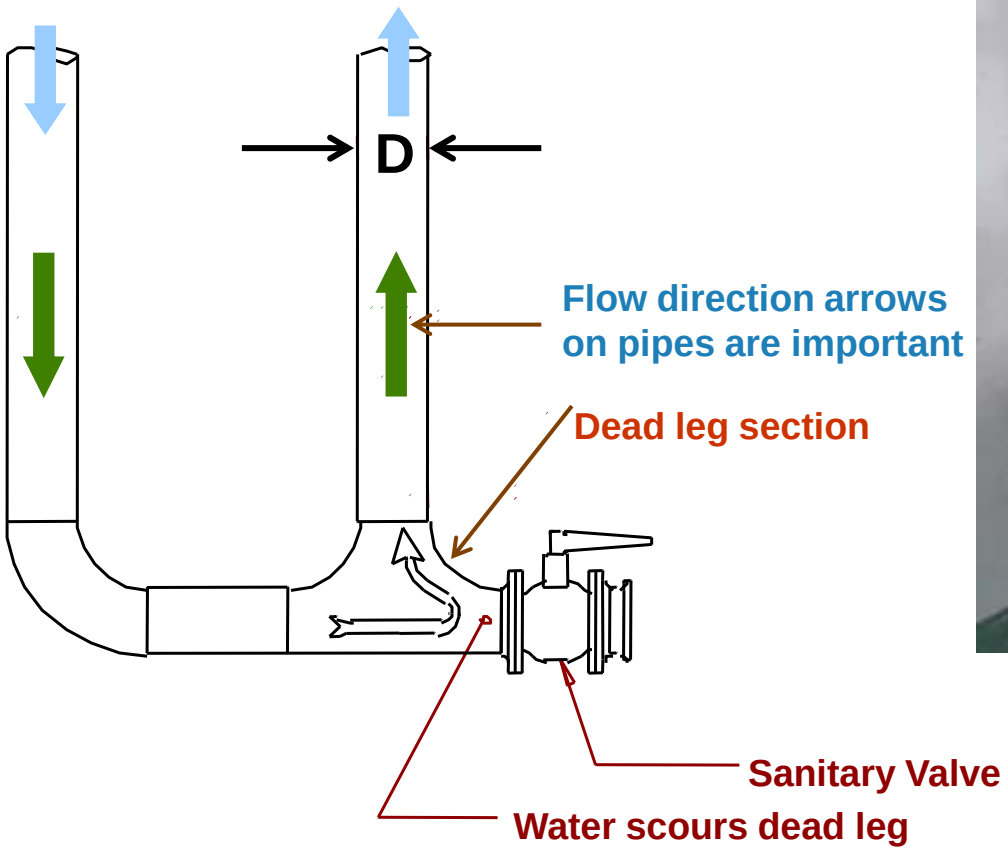
Biocontamination control techniques (2)



There should be no dead legs



Dead leg:
Measured from the ID pipe wall to centre line of the point-of-use valve where significant stagnation potential exists

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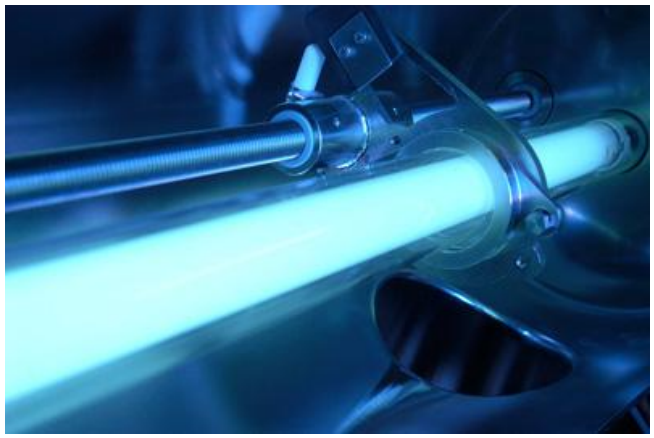
The growth of microorganisms can be inhibited by:



- UV radiation
- Maintain system <25°C or > 65°C
- Periodic and routine sanitizing of the system e.g. with:
  - water > 70 °C)
  - superheated hot water or clean steam
  - chemicals e.g. ozone

6.5.4.2.