Parenteral Drug Association Pharmaceutical Water Interest Group

Non-Distillation Based USP Water for Injection Systems
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Current Water for Injection Production Method Compendial Requirements

› United States Pharmacopeia (USP) Official Monograph requirement:

“Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.”
Current Water for Injection Production Method Compendial Requirements

- European Pharmacopeia (EP) *Monograph* requirement:

  “Water for Injection in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from Purified Water by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz, or suitable metal and which is fitted with an effective device to prevent entrainment of droplets. The correct maintenance is essential. The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate collected”

EP WFI Production Method

- Distillation
  - Specifies that vapor–liquid disengaging mechanism must be employed dictating a complete water phase change from liquid to gas (steam).
  - Specifies that a proactive maintenance program is required to verify and insure proper operation of the distillation process.
  - Specifies that the first portion of distillate produced must be diverted to drain.
USP WFI Production Method

“...distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms”

- Does not specify specific water purification operations
- Does not specify a proactive maintenance program
- Does not address ambient product water issues
- Does not consider the fact that USP XIX allowed the use of reverse osmosis (RO) for WFI production over 35 years ago with very infrequent employment
- Requires an objective technical evaluations of the various unit operations that may be employed

Reverse Osmosis

- Reverse Osmosis
  - Pressure is provided by a non sanitary pump to force water through a semipermeable membrane.
  - Generally, about 75% of the pretreated, higher conductivity water is recovered as low conductivity product water (permeate). About 25% of the feed water is fed to drain as waste.
  - Generally about 97–99% rejection of ions is achieved. However, “reactive gases, principally carbon dioxide and ammonia, will pass through the RO membrane, react with product, produce ions, and increase the water conductivity.
Reverse Osmosis operates at higher feed water pressure (150–250 psig) and is capable of removing 99% or greater of all ionic material. It will not directly remove gases such as oxygen, nitrogen, carbon dioxide, and ammonia.

- RO removes organic material with a molecular weight > 100–200 Daltons, colloids, bacterial endotoxins, and bacteria.
- Complete removal of bacteria (<1 cfu/100 ml) is not achieved by a “single pass” RO unit.

Essentially all RO membranes employed for pharmaceutical applications are “spiral wound” configuration. The membrane material is high ion rejection polyamide supported over polysulfone (an ultrafiltration membrane material). The use of a thin layer of polyamide and a second layer of polysulfone is referred to as a thin–film composite (TFC) RO membrane.

The membrane “envelope” is constructed and configured in a manner depicted in the following slide.
RO Membranes are generally 4” or 8” diameter x 40” long.

“Interconnectors with O-ring seals are employed to connect multiple membranes in pressure vessels.

Pressure vessels contain one to five membranes based on system design.

“End adapters” with O-ring seals are used to direct product to a manifold.
Reverse Osmosis
Reverse Osmosis

Reverse Osmosis
Reverse Osmosis

Reverse Osmosis
Reverse Osmosis
Reverse Osmosis

- Feed Water & Waste Victaulic-Type Seals

Reverse Osmosis

- Interconnectors for Various RO Membranes
Reverse Osmosis

Scaling
- Occurs in outer layer of membranes
- More prevalent in “tail” membranes, the membranes with most concentrated impurities in feed water
- Water softening in pretreatment minimizes scaling
- “Scaling Index” employed to calculate the potential scaling tendency of feed water but seldom part of routine sampling/evaluation
- “Tapering/array” employed to maintain velocity through RO unit to minimize scaling

Fouling
- Organic fouling from Naturally Occurring Organic Material in feed water
- Microbial fouling on the RO membrane surface from feed water bacteria, bacterial endotoxins in a biofilm, and bacteria generate on the membrane surface using organic foulants as a nutrient
- Hot water sanitization can “control” microbial growth and destroy bacteria but will not remove biofilm. Chemical sanitization is required.
- Fouling potential determined by “Silt Density Index” determination/measurement
Reverse Osmosis

3:2:1 Reverse Osmosis Array

Layering of Material on RO Membrane Surface
Reverse Osmosis System Concerns

- **Waste Recycle**
  - RO membrane manufacturers provide a computerized projection program for RO system design. This projection requires recycle of a portion of the RO waste, with concentrated inorganic, organic, total viable bacteria, and bacterial endotoxins back to the feed water of the RO to maintain velocity in “tail” membranes for avoiding precipitation of potential scalants. This process increases the bacteria and bacterial endotoxins in RO feed water, biofilm build-up on the RO membrane surface, and increase in RO product water total viable bacteria levels.

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**Typical Computer Generated RO “Projection” with Waste Recycle:**

```
<table>
<thead>
<tr>
<th>Stage</th>
<th>Element</th>
<th>#PV</th>
<th>#Ele</th>
<th>Feed Flow (gpm)</th>
<th>Feed Press (psig)</th>
<th>Recirc Flow (gpm)</th>
<th>Conc Flow (gpm)</th>
<th>Conc Press (psig)</th>
<th>Perm Flow (gpm)</th>
<th>Perm Press (psig)</th>
<th>Perm TDS (mg/l)</th>
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- **System Details:**
  - Feed Flow to Stage 1: 72.24 gpm
  - Raw Water Flow to System: 52.24 gpm
  - Feed Pressure: 190.92 psig
  - Flow Factor: 0.85
  - Chmn. Dose: None
  - Total Active Area: 3120.00 ft²
  - Water Classification: Surface Supply SDC < 5
  - Average Pass 1 Flux: 16.15 gfd
  - Average Pass 1 Flux: 16.15 gfd
  - Specific Energy: 3.57 kWh/gal
  - Average ND P: 163.38 psig
  - Average TDS: 7.96 psig
  - Average Temperature: 20.0 C
  - Recovery: 67.00 %
  - Concentrate: 11.91 psig
  - Feed: 4.01 psig
  - Osmotic Pressure: 35.00 gpm

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Reverse Osmosis System Concerns

- Typical Computer Generated RO “Projection” with Waste Recycle:

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<tr>
<th>Name</th>
<th>Feed</th>
<th>Initial</th>
<th>Adjusted Feed</th>
<th>Concentrate</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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</tr>
</tbody>
</table>

- Plastic end adapters and interconnectors with O-ring seal mechanism
  - Lack of PM program for replacement
  - O-ring cross section from circular to oval with higher pressure waste-to-permeate flow potential increased.
  - O-ring “roll over” potential if material such as USP Glycerin not used during RO membrane installation
  - Potential cracking of plastic interconnectors particularly with thermal cycling
  - Documentation/observation?
**Additional Reverse Osmosis System Concerns**

- **Non sanitary design**
  - Feed water pump
  - Permeate instrumentation
  - Permeate tubing/piping
  - Permeate valves

- **Permeate conductivity from single pass RO will not meet WFI conductivity specification**
  - Requires polishing
    - Canisters?
    - CEDI?

**Sanitary pressure vessels**
- Fittings
- Material of construction
- End adapters

**RO membrane selection**
- Must be “full fit” (“loose wrapped”)
- Prefer hot water sanitizable
Additional Reverse Osmosis System Concerns

- Lack of feed water microbial monitoring and control
- Lack of hot water sanitization program coupled with responsive chemical sanitization program
  - Biofilm on permeate tubing
  - Biofilm on RO membrane surface
- Lack of continuous recirculation
- Lack of proactive PM program to clean (off site preferred) RO membranes

Additional Reverse Osmosis System Concerns

- Elution of inorganic and organic impurities during hot water sanitization and “recover-to-purity” time period
  - Increase in permeate conductivity (temperature corrected).
  - Increase in permeate TOC
  - RO “recovery time” 1–2 hours maximum.
  - Greater recovery time for downstream CEDI (if employed)
Monochloramine issues:
- Municipal feed water using monochloramine as “secondary”
- Must measure “Total Chlorine” to verify complete removal
- Thin-film composite (TFC) membranes have limited tolerance although greater than stated by RO membrane manufacturers
- Will eventual result in loss of RO membrane integrity
- Can “mask” permeate bacteria
- Significant concern for RO “polishing” techniques such as CEDI

Improved product water quality
- Total viable bacteria
- Bacterial endotoxins
- TOC

Little decrease in conductivity
- Normal product conductivity about 1 μS/cm @ 25 °C
- Sodium hydroxide injection may be required but may increase conductivity associated with ammonia/ammonium ion
- Ionic polishing still required
Double Pass Reverse Osmosis

- Waste recycle from second pass entirely returned as feed to first pass
  - Total viable bacteria
  - Bacterial endotoxins

Concerns

- Similar to single pass RO
- Level of bacteria present in product water lower than single pass RO
- Requires maintenance by personnel familiar with operation and design – more complex than single pass RO.

Continuous Electrodeionization

- A RO “polishing” technique using ion exchange membranes, ion exchange resin, ion depleting “chambers”, ion concentrating “chambers” in a dense electronic field
- Capable of producing theoretical “ion-free” product water
- Continuously regenerated by “splitting” water
- Can be purchased with for hot water sanitization
- “Second generation” units appear to not only inhibit bacteria proliferation but also destroy bacteria.
**Continuous Electrodeionization Polishing Units**

- **Feed water purity**
  - Limits on specific feed water impurities
  - Must be at least single pass RO product water purity

- **Vastly superior to rechargeable mixed resin canisters**
  - Do not require replacement with off-site regenerated canisters
  - Significantly better bacteria control
  - Hot water and chemical sanitization possible

**CEDI Units – Concerns**

- **Leaching of organic material during hot water sanitization**
  - Low concentrations of organic material in RO product water may exhibit a slight negative charge. Anion resin is historically noted for “organic fouling” and chemical instability at sanitization temperature. This material appears to be eluted at low concentration during hot water sanitization. It is suggested that both inline conductivity and TOC monitoring of post RO CEDI units be considered to verify return to pre hot water sanitization levels prior to normal operation.
CEDI Units – Concerns

- Monochloramine
  - Should be removed by pretreatment but often present due to poor maintenance of RO pretreatment components
  - Unfortunately, monochloramine appears to chemical interface with ion exchange material resulting in increased pressure drop through a CEDI “Stack”. To maintain product water flow rate the RO feed water pressure must be increased. This increases several of the concerns expressed for RO units.

CEDI Concerns

- Feed and product water fittings for hot water sanitizable units
  - Fittings are made of electrically non conductive material to responsibly isolate the current in the stack from feed and product tubing, often 316L Stainless Steel
  - Fittings are generally threaded with flat gasket–type seal mechanism
  - Fittings should be replaced as part of a responsive PM program. When mated to 316L Stainless Steel sanitary ferrules, fittings demonstrate deformation at the “hinge” and “tightening” locations after several hot water sanitization cycles.
“Equivalent or Superior”

- Where are these systems currently used?
  - Distillation Feed Water
  - Pure Steam Generator Feed Water
  - Purified Water
    - “cfu/ml” TVB Action Levels
    - “cfu/100ml” Action Levels
    - Hot storage and Distribution
    - Loop TVB control
    - Ozonation
    - 184.7 nanometer high intensity UV
- From experience and technology can it be stated that process is “equivalent or superior?”

Summary

- Challenges – Are we ready?
  - Proper design
  - Proper installation
  - Operator understanding
  - Proactive preventative maintenance program
  - Proper SOPs and Maintenance Manual
  - Training program
  - Ability to identify and respond to risks
  - Ability to identify, cite, and respond to design, installation, validation, operating, and maintenance deficiencies