New Developments in Ph. Eur. Cold WFI Production

PDA Israel

New Developments in Water Systems

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Background

- Thermal Distillation has always been the flag holder for WFI production

Background

- USP has always allowed cold production
- European Pharmacopeia (Ph. Eur.) has historically specified:
  - WFI must meet monograph specifications

    ALSO
  - Be evaporated and condensed in a thermal distillation unit
- However, distillation has always been required as few companies produce exclusively for the American market.

Background

- It has taken many years for the European Pharmacopoeia (EP) to allow use of membrane based technology, without need for final distillation.
- The process started in 1999 with an international conference which deliberated as to whether to allow reverse osmosis with/without additional technologies, e.g. continuous electrodeionization (CEDI) and/or ultrafiltration (UF) as an alternative method for production of WFI without need for a still.
- **Main concern of the regulators was the possible microbiological contamination of WFI** not undergoing a thermal process of boiling, evaporation and condensation

Background

- In 2002 the EMEA stated that membranes were **NOT** an option for WFI production.
- This was due to the potential risks associated with the membrane production method, mainly **biological** fouling of the membrane.
- In 2008, the EMEA published a reflection paper on WFI prepared by reverse osmosis (RO)

Background

- 2008, the reflection paper stated that the **major problem for production of WFI with RO is the microbiological aspect**, and the “net effect is that the RO membrane will become, in practice, a bacterial fermenter”.
- In typical pretreatment systems, the chief operating concern regarding active carbon is **microbial build up and microorganism** proliferation in softeners.

Background

- Pretreatment microbes will be fed directly to the reverse osmosis membranes and will cause surface contamination and fouling of those membranes with impact on product water.
- As these concerns were completely met by the thermal process of boiling, evaporation and condensation, thermal distillation was thought to be the only method to reliably produce WFI.

Hard data was missing

WFI production processes

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USP/ISPE Water Survey Results

Survey of Pharmaceutical Water System Users on the Use of Non-Distillation Systems for the Production of WFI

by Dr. Anthony Bevilacqua and Dr. Teri C. Soli

This article presents the results of a jointly sponsored USP/ISPE survey of the pharmaceutical industry and analyzes the potential to use alternative methods of production (other than distillation) as the final purification in the preparation of Water for Injection (WFI).

Summary

A jointly sponsored USP/ISPE survey of the pharmaceutical industry is presented and analyzed on the topic of the potential to use alternative methods of production (other than distillation) as the final purification process in the preparation of Water for Injection (WFI). The survey was prepared by USP Expert Committee members. It was reviewed, supported, and administered by the ISPE Critical Utilities Community of Practice (CU COP) leadership to the CU COP, and the results were collected and analyzed. The purpose of the survey was not only to acquire data related to the design, maintenance, and reliability of alternative non-distillation approaches for making WFI-quality water, but also to collect viable data from engineering end users so that the discussion could be removed from private unpublished anecdotes and brought to light – for better or worse – for eventual public dialogue among the industry, compendia, and regulatory groups.

Typically, past discussions centered about the topic of "distillation vs Reverse Osmosis (RO) and/or UltraFiltration (UF)" as the final step and arbiter of microbiological and endotoxin control in WFI production. The current survey asked a series of different questions. Instead of focusing on the final purification step, the entire water system design, its operation and control strategies, and testing data was studied.

Of the non-distillation systems that met all of the testing attributes of WFI, though validated as another type of water system, the analysis of the results shows a fascinating variability in the number and types of purification system designs, distribution designs, and sanitization strategies. The analysis also demonstrates that the goals of the survey were met, which were: 1. to expand the discussion to consider the entire water system and 2. achieve a meaningful dialogue based on data of real water systems.

Background

The final purification step in the production of Water for Injection, i.e., WFI, is largely relegated to distillation, and distillation is estimated to be the final step in > 99% of WFI systems for manufacturers for US, EU, and Japan markets. The motivation for the nearly exclusive use of distillation is due to pharmacopoeial standards, regulatory expectations (perceived or real), and the industry's history and inertia. Historically, distillation was the definitive purification process for removing pyrogens from the water.

Standards setting bodies such as the USP, Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and European Directorate for the Quality of Medicines (EDQM) have provided some specificity regarding the production of WFI. Until 2004, USP permitted the use of distillation or Reverse Osmosis (RO) as a final purification step. Since 2004, USP has revised the allowable methods of production to "distillation or a purification technology that is equivalent or superior to distillation in the removal of chemicals and microorganisms." In Japan, the PMDA allows the use of distillation or RO and/or UF; however, recent surveys in Japan have reported that RO/UF is rarely utilized. Ph.Eur. requires the use of distillation exclusively in the

Turning point

- The change in thinking came after a large US survey of pharmaceutical water system users, the results were published in 2011.
- The survey questions were sent to users of water systems that make WFI quality water.
- The extensive survey, over 50 systems, was a turning point in the field.
- The survey asked (among other things): what are the typical microbial levels and typical endotoxin levels.
- In answers to the typical microbial count question, over 90% of the responses claimed that they were achieving WFI levels of below 10 cfu/100ml.

Why change from Distillation?

- Considerable savings of capital investment in equipment for membrane based systems vis–à–vis thermal production equipment.
- Most WFI stills are fed with water to Purified Water (PW) standards.
- In this case, the investment in distillation units is still in **addition** to the investment in membrane based production equipment.

Why change from Distillation?

- Operating costs: energy expenditure for evaporation and condensation of the feed water
- Membrane based systems drastically reduce the total life cycle costs.
- Cost of 1000 L of WFI thermal distillation: 12-30€
- Cost of 1000 L of WFI cold production: 3-10 €

Revised monograph, Water for Injections 0169

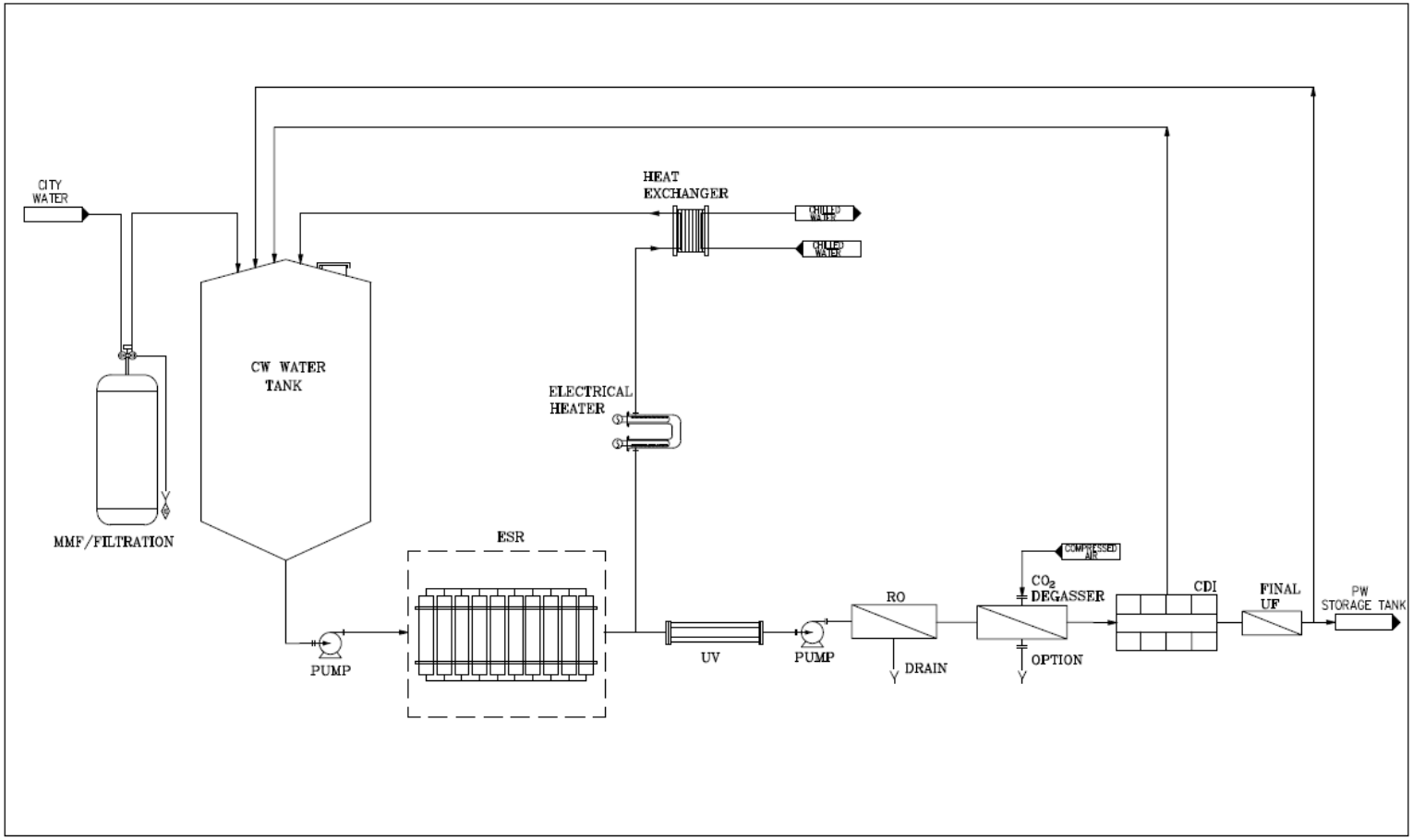
- Published in the Ph. Eur. Supplement 9.1 and became effective on 1 April 2017.
- Allows the production of WFI by a purification process equivalent to distillation.
- Based on reverse osmosis coupled with appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration.
- Highly Purified Water (HPW) has been deleted from the Ph. Eur.

Present situation

- Per Ph. Eur.: Notice is to be given to the supervisory authority of the manufacturer before implementation.

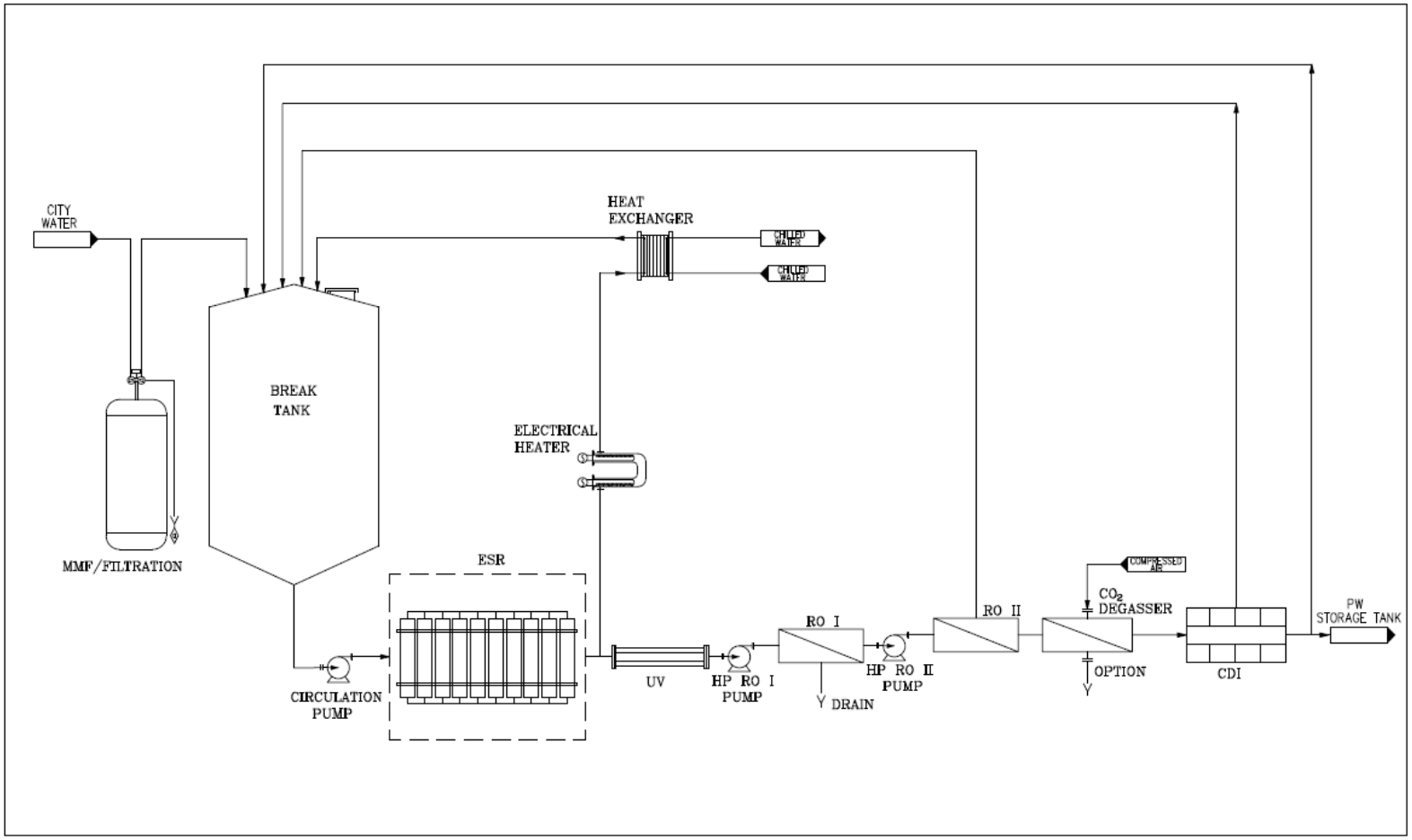
Present situation

- SPRO + UF – for WFI production



Present situation

- PFD DPRO - for WFI production



Reverse osmosis and biofilms and control strategies

- European Medicines Agency (EMA) published as a Question & Answer draft document in 2016, has now been published in its final version.
- The Q&A document clarifies and guides in relation to the use of reverse osmosis in the manufacture of Water for Injection
- This Q&A document is in **addition** to the Ph. Eur. monograph.

Reverse osmosis and biofilms and control strategies

- In the first part, questions relating to the production of WFI with membrane technologies are answered.
- The second part is about biofilms, their background and approaches for their prevention. (not dealt with in this presentation)

Reverse osmosis and biofilms and control strategies

- In order to ensure the appropriate quality of the water, validated procedures, **in-process monitoring** of the electrical conductivity, and **regular monitoring** of total organic carbon and microbial contamination are applied.
- The first portion of water obtained when the system begins to function is discarded.
- Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Q1: Who is the supervisory authority?

- GMP authority in the country of the importer

Q2: What are the main concerns around the use of reverse osmosis to manufacture WFI?

- **Microbiological** quality of the water produced
- Control mechanisms in place to minimize the risks associated with **microbiological** proliferation
- Formation of a **biofilm** in a RO system

Q2: What are the main concerns around the use of reverse osmosis to manufacture WFI?

- Removal of b**iofilms** as they are notoriously difficult to remove, because they protect flora contained within against the action of shear forces and disinfection chemicals.
- Incompletely removed **biofilms** lead to a rapid regrowth and proliferation as well as increasing the likelihood of microbiological by-products throughout a system.

Q3: What are the main elements that should be considered in the design of such a system?

- Control Strategy: Based on risk assessment for identification of issues
- Materials of construction: must not be reactive, additive or absorptive (**not PVC**), only SS, PVDF or PP.
- Pre-treatment: Ensure adequate removal of organic particles, matter and **microbiological** impurities
- RO Membranes: routine high temperature sanitization =SS
- **Total Organic Carbon** (TOC): consideration of online TOC based on risk assessment.

Q3: What are the main elements that should be considered in the design of such a system?

- Conductivity: should be considered as part of the control strategy and be installed at various locations within the RO system as determined based on quality risk management principles.
- Sanitisation: **Sampling** must take place downstream of softeners and carbon filters

  The sanitisation procedure must be shown to control the microorganism level so that it doesn't proliferate above feed water levels

Q4: What approach should be considered for the qualification of such a system?

- Per good engineering practice (GEP).
- Provide the necessary evidence that the **design** of the water system is in line with that intended in order to assure the quality of the water produced during routine operation.
- Performance of the system must be proven over an extended period of time
- Robust sampling program
- Maximum time limits for the RO membranes usage should be stablished. Consider destructive analysis of RO membranes to ensure the absence of biofilm.

Q4: What approach should be considered for the qualification of such a system?

- The initial validation period of the water system where testing is carried out on all points should demonstrate that the system is operating as designed.
- Similarly, subsequent phases of system validation should be robust and capture significant data to verify ongoing capability of the system.

Q5: What type of sampling regime should be employed during qualification and during operation?

- Sample locations to consider include:
  - Feed/raw water source.
  - Stages of pre-treatment.
  - Pre and post RO membrane.
  - Post final purification phase.
  - Storage tank.
  - All user points.
  - Return loop post final user point.

=Sample Pretreatment

Q5: What type of sampling regime should be employed during qualification and during operation?

- Typically during initial phase, qualification testing of all of the above points should be sampled and tested daily for a specified period of time in order to assure the correct installation and operation of the system. =PQ Stage 1
- The sampling frequency should be designed in a manner to assure satisfactory performance of the system over a year to take account of seasonal variations associated with feed

=PQ Stage 2-3

Q6: What testing should be employed during initial qualification and routine operation sampling?

- Testing should be conducted in line with Ph.Eur. Monograph 169 ‘Water for Injections’.

Q6: What testing should be employed during initial qualification and routine operation sampling?

- Methods to be considered should include:
  - Rapid microbiological methods
  - Quantitative microbiological test methods*
  - Rapid Endotoxin testing
  - Conductivity.
  - TOC.

* in line with Ph. Eur. 5.1.6 monograph ‘Alternative Methods for control of Microbiological Quality’

Q6: What testing should be employed during initial qualification and routine operation sampling?

- Appropriate alert levels should be established based on statistical analysis of data.
- Trend data should be reviewed routinely and any adverse trend should be appropriately investigated.
- The review of trend data should not only take account the % alert and % actions occurring but also review of the quantitative and qualitative (identifications) raw data.

Q6: What testing should be employed during initial qualification and routine operation sampling?

- Alerts should be reassessed routinely to enable, where possible, a tightening of those control limits.
- Increasing of such limits is not good practice and may mask a failing system.

Q7: What are the expectations for preventative maintenance on RO systems used for the production of WFI?

- A robust system for preventative maintenance of such systems should be designed as part of a control strategy in order to minimize the risks associated with **microbiological** and/or by-product proliferation.

Q7: What are the expectations for preventative maintenance on RO systems used for the production of WFI?

- The planned maintenance system should incorporate routine regeneration of pre-treatment systems, replenishment of resin beds (as required), change out of filters, gaskets, seals and RO membranes at a defined frequency or following adverse indicators as well as routine thermal and/or chemical sanitisation of such systems.

Keep it Clean!

Q7: What are the expectations for preventative maintenance on RO systems used for the production of WFI?

- Detailed inspection checks should be incorporated into the routine planned maintenance to take account of the potential for the formation of **biofilm** within the system: e.g. Inspection for leaks within the system, inspection of the condition of gaskets and seals.
- Performance of the RO membranes should also be assessed including pressures and flow rates in order to maintain the quality of water produced to the appropriate standard.

Production of WFI per Ph. Eur. WFI

- Single pass RO with EDI and UF
- Double pass RO with EDI
- Distillation unit (ME, VC)

Q&A Document Summary

- Inform the GMP authority of cold production of WFI
- Main concern of authorities is **microbiological** proliferation
- Materials of construction: SS, PVDF, PP
- RO Membranes: routine high temperature sanitization
- Sampling from **all** parts of pretreatment and product systems
- Testing to include Rapid microbiological methods Rapid endotoxin, conductivity, TOC
- Plot trends in both raw data and %
- Maintenance to minimize microbiological growth

Q&A Document Summary

- Keep Micro in-system levels less than feed water

Stay in control of micro

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