Good Practice Guide:

Membrane-Based Water for Injection Systems

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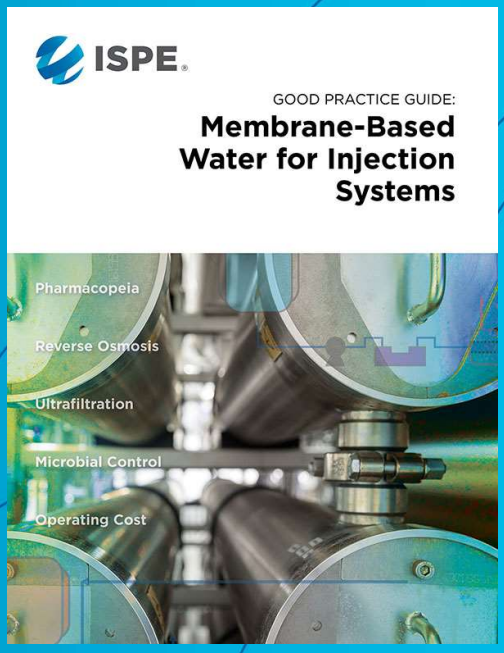

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Critical Utilities Community of Practice

- Water, Process Gases and Steam
- The Discussion Forum is the nexus of the communication with members of the CoP.
- Subject Matter Experts (SMEs) are involved in a regular, typically daily, review of the Discussion Forum.
- Topical, fundamental or basic, and debatable subjects can be placed in the Discussion Forum for all members to read or comment.
- Typically at least two to three SMEs respond to postings on the Discussion Forum - North America and Europe
- Available at no additional cost to ISPE members

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Member Quotes

"COPs provide different perspectives and real life examples."

"Topics of discussion are most of the time quite relevant to the industry and helps me keeping in touch by reading them to understand challenges."

"The community gives a broad overview of current industrial thinking."

"A valuable resource for technical hints, reference documents and shared field experience"

"CoPs are integral to the continued success of ISPE - I believe the future will need to rely more heavily on these groups and they need to become more visible and self sustaining."

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Critical Utilities Guides

- ISPE Baseline Guide: Volume 4 – Water and Steam Systems (3rd Ed)
- ISPE Good Practice Guides:
  - Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems (2nd Ed)
  - Critical Utilities GMP Compliance – How to Be Compliant and Ready to Prove It
  - Membrane-Based Water for Injection Systems
  - Ozone Sanitization of Pharmaceutical Water Systems
  - Process Gases (2nd Ed) – *COMING SOON!*
  - Sampling for Pharmaceutical Water, Steam, and Process Gases

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Why is membrane-based WFI production appealing?

Reduced carbon footprint
Reduced capital costs
Reduced operating costs
Potential for improved water quality
Reduced space requirement
Utility plant impact

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WFI Regulatory History

1820 USP 1…… “Let water be distilled….’

1942 USP XII….. WFI shall be produced by distillation

1975 USP…….WFI produced by distillation or reverse osmosis

2005 USP……”distillation or a process that is equivalent or superior to distillation in removal of chemicals and microorganisms’

2017 Ph. Eur. “distillation or reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration”

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Guide Pharmacopeial Guidance

All require CQA attainment for conductivity, TOC, micro and endotoxin
some plus additional CQA
China……distillation only
Japan…...membrane alternates allowed
International Pharmacopeia….membrane alternates allowed
India……no restrictions
Brazil…..no restrictions
Mexico…no restrictions
Russia…no restrictions if from drinking water
Korea….membrane alternates allowed

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Risk Profile

Product
Patient
Procedural controls
Personnel expertise
Incoming source water
Process design
Generation and storage/distribution

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Generation Pretreatment Process Options

Media filter
Cartridge/bag filter
Screen filter
Ultrafilter
Softener
Antiscalant
Electric scale control
Activated carbon
Chemical dechlorination/chlorination
pH adjustment

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Generation Final Treatment Process Options

Nanofiltration
Reverse osmosis
Ion exchange
Electrodeionization
Ultraviolet light
Microfiltration
Ultrafiltration
Membrane degasification

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Generation System Design

No single recommended solution

Ph. Eur. Requires reverse osmosis for compliance

No requirement for multiple membrane barriers, but recommended in guide

Most configurations include pretreatment, reverse osmosis, electrodeionization, ultrafiltration and hot water sanitization

Hygienic construction recommended

Multiple sanitization methods recommended

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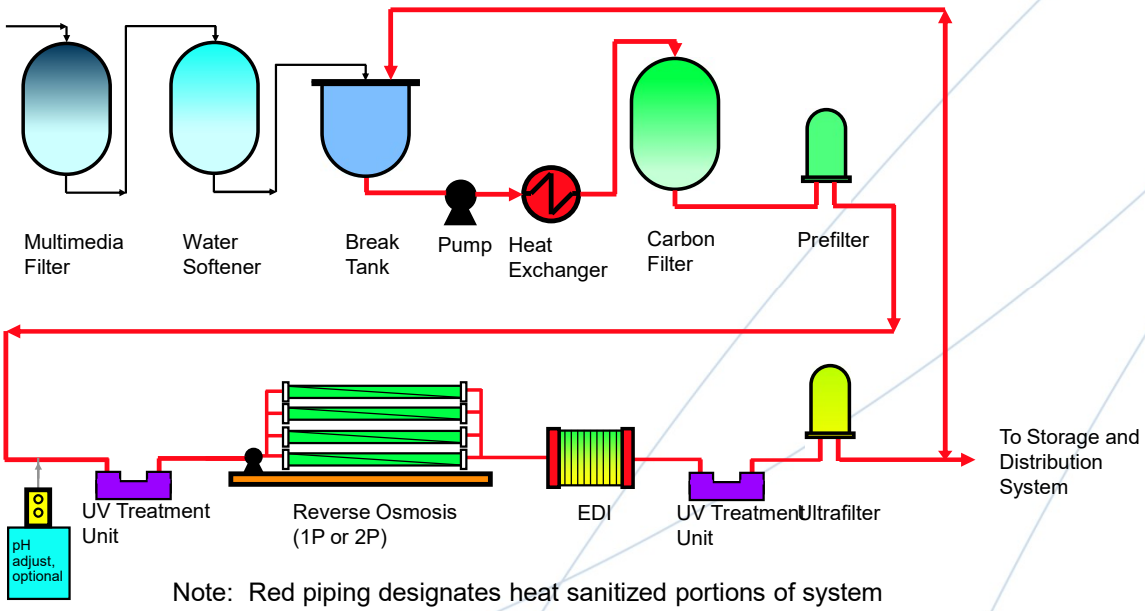
Figure 5.16: Example 1- RO/EDI/UF Membrane System



Note: Red piping designates heat sanitized portions of system

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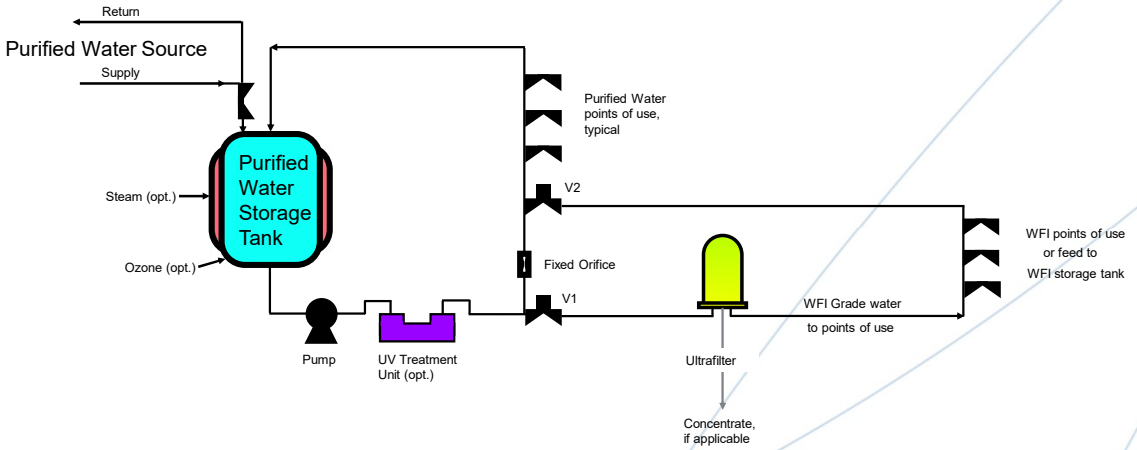
Figure 5.11

Purified Water and WFI Water from a single storage tank



Storage and Distribution

Continuously sanitizing environment preferred
- ozone
- heat

Frequent sanitization if intermittent

Evaluate tank turnover, turbulence, vessel design/construction for intermittent

Minimize dead legs

Appropriate instrumentation

Figure 6.1

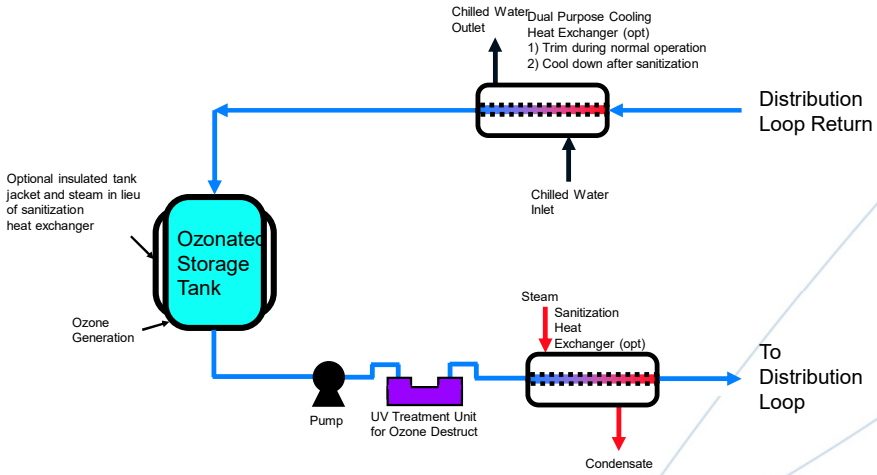


Figure 6.1 - An example showing a continuously ozonated storage tank with ambient temperature WFI distribution featuring heat sanitization capabilities as a backup sanitization method. Heat exchanger locations are for illustrative purposes and may vary.

Process Analytical Technology (PAT)

Continuous analysis and control of manufacturing processes

- real-time measurements
- rapid measurements
- continuous analysis

Measurement of CQAs and CPPs

Tighter alert and action levels to avoid OOS events

Microbial Control

Philosophies throughout guide
Chapter devoted to process design, operation and sanitization
Process Control sampling versus Quality Control sampling
Continuous bioburden analyzers
Contamination Control Strategy

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Commissioning and Qualification

User Requirement Specification
Risk Assessment
- Critical components and functions
- Critical Quality Attributes (CQAs)
- Critical Process Parameters (CPPs)
- Failure impact
- Failure likelihood
- Failure detectability

IQ
OQ
PQ

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Comparative Costs

Capital costs
- equipment
- engineering/PM
- construction and installation
- C&Q

Operating costs
- maintenance
- consumables and chemicals
- utilities
- sampling and monitoring

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Total cost of Ownership

Utilization is a key TCO factor
- standby utility costs greater factor for low utilization

Utility costs variable and significant factor

Equipment life is a significant factor due to depreciation costs

Distillate temperature (hot versus ambient) is a significant factor
- ambient distillate temperature used for VC

Water recovery is a major consideration

Sampling practice vary and can impact costs significantly

Utility plant capital costs not considered

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Additional Chapters and Appendices

Microbiological Considerations
Operation and Maintenance

Summary of Pharmacopeial Requirements
Process and Equipment Risks
Contamination Control Strategy
Ozone Flushing Sample Calculation
Cost Analysis Case Study
Ultrafilter Integrity Testing

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Process and Equipment Risks

Scale control
Oxidation
Reverse osmosis
- micro
- conductivity

Electrodeionization
- micro
- conductivity

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Process and Equipment Risks

Ultrafiltration
- fouling
- micro/endotoxin

Ozone
- micro
- product oxidation due to oxygen level
- ozone breakthrough (WFI monograph violation)
- component oxidation

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Contamination Control Strategy

Process description
WFI applications
Process drawings
Microbial monitoring points
Biofilm prevention
Sanitization procedures
Monitoring, trending and data analysis
Filters
Alarms
Maintenance
Contamination and utility interruption response

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Ozone Worker Safety

Air turnover rate
Room area
Water quantity into space
Ozone concentration
Ambient ozone monitor
SOPs

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Ultrafiltration Integrity Testing

Failure mechanisms
Intactness testing
Vendor procedures
EPA Membrane Filtration Guidance Manual
Pressure decay
Diffusive air flow
Broken fiber bubble observation

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Summary

Guide is comprehensive
Guide is well balanced - risks defined as well as advantages
No single solution
Guide has significant design information, but is not overly prescriptive

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Questions?

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