



GOOD PRACTICE GUIDE:

Membrane-Based Water for Injection Systems

Pharmacopeia

Reverse Osmosis

Ultrafiltration

Microbial Control

Operating Cost



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GOOD PRACTICE GUIDE:

Membrane-Based Water for Injection Systems

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Preface

With the potential impact that Water for Injection (WFI) has on product quality and patient safety, it is imperative that WFI systems are designed, operated, and maintained properly to ensure the system operates within a state of control. Failure to produce WFI consistently and reliably can result in significant business impacts and potentially even worse, harm to patients. This ISPE Good Practice Guide: Membrane-Based Water for Injection Systems provides expert guidance on the design, operation, maintenance, and quality aspects of membrane-based WFI systems. The information presented in this Guide is the combination of proven technological solutions, microbial control methods, process analytical technology, and operations and maintenance practices.

What has become clear to the authors of this Guide is that there is not a single technical solution that works in all situations, for all companies, in all locations across the globe. Each situation poses individual challenges with the source water, with the physical space available, with the utilities available and with the overall needs of the process. Every application for WFI, whether using distillation or membrane-based technology, is different and every facility/process has different needs. Developing a thorough understanding of the application and the needs of the process while also understanding the technology that is available will ensure the selection of robust and reliable solutions. Simply stating a single solution is the answer to make WFI by a membrane-based process, without going through the design process and determining the proper technical solution, can result in incorrect solutions and unreliable systems.

Improper sanitization practices and inadequate microbial control are the largest risks associated with the implementation of membrane-based WFI systems and as such an entire chapter of this Guide has been dedicated to microbial control. The increased scrutiny regarding microbial control is not debatable. Membrane-based systems lack the continuous lethal operating temperatures in distillation-based systems and rely on intermittent elevated temperature or alternative sanitization methods such as ozone for microbial control. Prior to the acceptance of alternative technologies by the European Pharmacopoeia, most companies have relied upon multi-effect and vapor compression distillation units to produce WFI. Once produced, this WFI has traditionally been stored hot before being distributed to the users as either hot or cold WFI. The benefit of hot generation and hot storage is that temperatures > 70°C are lethal to microbes which can survive in low nutrient environments such as high purity water systems.

It is not the goal of this Guide to provide a recommended combination of unit operations and design solutions that can manufacture WFI in any application. The goal of this guide is to educate end users and document all the currently available technologies which when properly combined can reliably produce WFI.

It is recognized that industry standard evolve, and this Guide reflects an understanding of them as of the publication date. It is also recognized that a draft revision (R12) of Annex 1 of the European Union GMPs was issued in February 2020; after the Annex 1 revision is finalized, respective alignment updates will be made to this Guide if necessary.

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The Guide was produced by an international Task Team, under the leadership and direction of:

Brian Pochini, CPIP	Sanofi	USA
Fritz Röder	Merck Healthcare KGaA	Germany

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Chapter Leads

The following individuals took lead roles in the preparation of this document and each managed one or more chapter teams made up of writers and contributors.

Nissan Cohen	Biopharmaceutical Water Doc	USA
Brian Cox	Eli Lilly and Company	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Nik Krpan	Cheme Engineering Inc.	Canada
Joseph Manfredi	GMP Systems, Inc.	USA
Stephan Neumann	Boehringer Ingelheim	Germany
Chris Peterson	AbbVie	USA
Stefan Raabe	Endress+Hauser (Schweiz) AG	Switzerland
Jochen Schmidt-Nawrot	CRB Group GmbH	Switzerland
Teri C. (T.C.) Soli, PhD	Soli Pharma Solutions, Inc.	USA
Anders Widov, MSc	BWT Pharma & Biotech	Sweden
Marcel Zehnder	BWT Aqua AG	Switzerland
Gary V. Zoccolante	Plymouth Rock Water Consultants	USA

Contributors

The Core Team wish to thank the following individuals for their valuable contribution during the preparation of this document.

Patrick B. Archer	BWT Pharma & Biotech	USA
Jamie Evans	Grifols Canada Therapeutics	Canada
Michelle M. Gonzalez, PE	BioPharm Engineering Consulting, Inc.	USA
Philip R. Horstmeyer	Eli Lilly and Company	USA
Ariel Kehati	Omrix Biosurgery, J&J	Israel
Kevin Kloet	Cheme Engineering Inc.	Canada
Paolo M. Leani	Stilmas S.p.A.	Italy
Rinke Nijland, MSc	MSD Biotech Oss	Netherlands
Michael Richter	Boehringer Ingelheim	Germany
Philip E. Sumner Jr, PE	Pfizer Inc.	USA
Scott H. Walker	Eli Lilly and Company	USA
John Wammes, CPIP	Water Works Inc.	USA
David Weller	GTec GmbH Wasseraufbereitung	Germany
Mike Wojcik	MECO, A Grundfos Company	USA

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

www.ISPE.org

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1 Introduction

1.1 Background

For nearly a century, production of Water for Injection (WFI) was universally accepted to be distillation based. During the latter portion of the twentieth century, as greater emphasis on costs and environmental concerns grew, pharmacopeias around the world began to focus on the quality attributes of WFI to allow for consideration of other production technologies. As a result of this enhanced focus which has occurred at different times, there are differences between pharmacopeias that have primarily resulted in pharmaceutical manufacturers defaulting to continued use of distillation and heat.

In 2017, the European Pharmacopoeia (Ph. Eur.) [1] joined the US [2], Japan [3], and many other regulatory bodies in accepting membrane-based technologies for WFI production, leaving the Chinese Pharmacopoeia (ChP) [4] as the only major pharmacopeia still requiring distillation. As a result, many companies are willing to consider membrane-based WFI, which is the driving force behind the creation of this Guide.

There has been greater acceptance for alternatives to distillation-based systems as the membrane-based systems and online instrumentation technologies have improved significantly. In conjunction, there has also been a parallel evolution of expertise among engineers and operators, including Subject Matter Experts (SMEs) capable of establishing design, operation, and maintenance practices that ensure these systems can reliably deliver water meeting the Critical Quality Attributes (CQAs) of WFI.

The use of membrane-based technologies for WFI production is appealing for several reasons:

- Reduced carbon footprint
- Reduced capital costs
- Reduced operating costs
- Potential for improved water quality
- Reduced space requirement (floor and height)

Despite these pharmacopeial changes and industry advancements, regulatory agencies around the world have remained understandably cautious in their acceptance of alternative technologies for WFI production because of the potential risk to patient safety.

Other industries requiring high purity water have had more latitude to investigate alternative water purification technologies for one simple reason: the impact of these changes is measured in product yield and not patient lives. However, these industries have been able to demonstrate that membrane-based technologies are capable of reliably producing water far exceeding the compendial requirements for WFI. Of particular significance is the capability of these membrane-based systems to produce water at ambient temperatures that is free from bacteria.

The authors of this Guide are confident that suitable equipment and industry expertise exist for the pharmaceutical industry to produce WFI meeting compendial requirements utilizing membrane-based systems, provided there is sufficient in-house expertise to effectively operate, monitor, and maintain these systems. Therefore, understanding the risks associated with membrane-based WFI generation and ambient storage and distribution is critical, especially since some of these technologies are relatively new to WFI production.

Additional factors that influence the reliability of a system to consistently produce WFI include the system-wide control strategy, the operation and maintenance, and the experience levels of personnel involved in the system lifecycle. Since there is no single design that works for all applications, this Guide does not attempt to describe the perfect system design. Rather, the authors of this Guide intend to provide guidance by focusing on the potential risks and the best practices to avoid the problems that can often jeopardize ongoing successful operation of membrane-based systems.

The CQA that is most concerning with membrane-based production and ambient temperature storage and distribution is microbiology. Therefore, this Guide includes detailed information regarding microbiological considerations for each unit process that may be utilized, including pretreatment, primary (and secondary) treatment, subsequent storage and distribution, and routine system sanitization. This focus is not intended to imply that other CQAs in a WFI system can be ignored, since all CQAs must be reliably met to have a system operating under a state of control.

1.2 Purpose and Scope

This Guide is intended to provide industry guidance from water systems SMEs through the challenges of uneventfully making WFI using membrane-based processes. The traditional distillation and hot distribution processes consume considerable energy and, because of that, have a large carbon footprint that needs to be reduced. The problem with using less energy-consumptive and more cost-effective processes is that it means avoiding the use of large quantities of heat that are well-known through decades of experience to be associated with the best microbial control approaches available because of its lethality and prevention of microbial growth (biofilm development) in WFI distribution systems.

This Guide provides guidance on the design, operation, maintenance, and quality aspects of membrane-based WFI systems. For anyone involved with water systems, especially WFI for the first time, the *ISPE Baseline® Guide: Volume 4 – Water and Steam Systems (Third Edition)* [5] is considered a primer for this Guide. Some recommendations in this Guide may appear inconsistent or contradictory to the *Water and Steam Baseline Guide*. These topics have been revisited in consideration of the acceptance of alternatives to distillation. This Guide reflects the expectations for membrane-based WFI generation and ambient storage and distribution systems at the time of publication.

The topic of rouging, while applicable to membrane-based WFI systems, is outside the scope of this Guide. For detailed information regarding rouging in WFI systems, refer to Chapter 10 of the *Water and Steam Baseline Guide* [5].

Computerized system lifecycle is outside the scope of this Guide. Refer to *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [6].

1.3 Sustainability

Traditional distillation-based WFI systems with hot storage and distribution systems have a large carbon footprint. As the pressure for more sustainable solutions increases, the capability to produce equal or better quality water with a smaller carbon footprint and potentially lower capital and operating costs has resulted in serious consideration for membrane-based WFI systems.

The pharmaceutical industry has a substantial impact on the environment and, as a result, there is increasing pressure to minimize any negative environmental impacts while continuing to positively impact society. The development and production of drugs and devices inherently consumes large quantities of natural, human, and economic resources, and this impact requires appropriate management.

Traditional distillation-based hot WFI systems are most often driven by non-renewable fuel sources such as gas and oil. As a result, sustainable WFI system designs most likely include membrane-based WFI generation with ambient storage and distribution. Ozonation is a proven technology for effective sanitization of loops at ambient temperature. For sanitization of the generation hardware, periodic heat sanitization remains the best option.

The carbon footprint for any system can be calculated and comparisons can be evaluated. The proper selection of technology is a balance between costs, carbon footprint, and risk. What is acceptable for one company may not be acceptable for another company. For sustainability purposes, a frequently chosen system design comprises membrane-based WFI generation with a storage and distribution system operating at ambient temperatures in combination with a constantly ozonated tank and periodic loop sanitization with ozone. The ozone is destructed *in situ* using UV lamps resulting in no environmental impact due to ozone usage. Compared to traditional vaporization systems, large ambient WFI systems can save over 1,000 tons of CO₂-equivalent and over a million kilowatt-hours (3.6 trillion joules) annually, assuming the electricity is renewable at its point of generation [7].

The proven technology advances coupled with greater levels of designer and operator expertise enable pharmaceutical companies to adopt membrane-based WFI generation practices. The potential negative impact of adopting these technologies is expected to continue trending downward as the technology is more widely used around the world. This Guide provides information on how to design, operate, maintain, and control membrane-based WFI systems in order to reduce the carbon footprint in global pharmaceutical operations.

1.4 Key Concepts

Sanitization of membrane-based WFI generation and ambient storage and distribution systems must be given careful consideration. Heat has traditionally been considered the “gold standard” and is most effective in applications when continuously applied. For intermittent heat sanitization, the duration between sanitizations should be validated based on risk analysis. For alternative sanitizing methods that reduce the carbon footprint even more, proper procedures and expertise are critically important as are adherence to those protocols, especially since alternative sanitization methods may not be as effective when design or operational shortcomings are present.

Ozone as a sanitizing agent has been used in pharmaceutical water systems since the 1990s. Its effectiveness and design requirements are well known. Applying this knowledge from Purified Water (PW) systems to WFI systems can result in effective microbial control.

Improper design and operation of membrane-based WFI systems can result in difficulties in achieving consistent system performance which may ultimately result in overall higher cost. The decision for a chosen process technology must be driven by a thorough risk analysis and a complete understanding of the operation and maintenance required for the unit operations selected. In addition, a suitable control strategy is needed to properly operate membrane-based WFI systems.

2 Regulatory Requirements

2.1 Introduction

The quality of WFI and the requirements for WFI production are defined in a variety of national and regional laws, ordinances, standards, norms, guidance, and guidelines. Only those documents are legally binding, as based on or referenced in the respective law or ordinance. This applies, for example, to the WFI monograph and the GMP guidelines of the country or region in which the drug is produced or marketed. In instances where a pharmacopeial monograph or a GMP guideline is not established, World Health Organization (WHO) [8] guidance may be used.

Other regulatory documents may not be legally binding (in the absence of specific legal requirements), but they are susceptible to local regulatory interpretation and use. This includes the guidelines, guidances, and questions and answers documents of the regional inspection authorities, e.g., the US Food and Drug Administration (FDA) [9] or the European Medicines Agency (EMA) [10]. EMA questions and answers documents, for example, reflect the current thinking of the EMA on certain topics, but are not legally binding in the European Union member states. They do not originate from an European Union regulation and directive and are therefore not transposed into national laws or ordinances. However, since these documents are used by the regulators/inspectors, these documents are given a high priority.

Even though the international harmonization of regulatory requirements is steadily progressing, there are still regional differences in specifications especially with respect to membrane-based WFI production. The designer of a new water system must clarify, in coordination with the quality department, which regulatory requirements are to be applied in the project-specific case. In addition to the location of production, the countries or markets in which the product is to be marketed need to be considered.

This chapter provides an overview of the regulatory documents that are most relevant to membrane-based WFI production. Since there are local pharmaceutical manufacturing requirements in most countries and regions, the following compilation is not intended to be fully comprehensive. Future International Organization of Standardization (ISO) [11] guidelines may be applicable to membrane-based non-distilled WFI generation. For example, ISO 22519 [12] is under revision and not deemed appropriate for inclusion in this Guide (at the time of publication). It is recognized that guidelines and standards evolve, and this document reflects the understanding of them as of the publication date.

2.2 Pharmacopeial Monographs on WFI Quality and Manufacturing Methods

All international pharmacopeias contain monographs for WFI that include precise quality specifications. Many pharmacopeias also specify the manufacturing methods that need to be used.

In Europe, US, and Japan [1, 2, 3], the specified quality limits for WFI are nearly harmonized. The pharmacopeias of other countries, such as China, India, Russia, and Brazil [4, 13, 14, 15], also have comparable or identical limit values for conductivity, Total Organic Carbon (TOC), and the microbiological quality of WFI. See Appendix 1 for a summary of specifications from various pharmacopeias.

Regarding the approved production methods, the 2017 revision of the WFI monograph in the Ph. Eur. [1] allowed for WFI production by membrane-based methods, leading to forward-looking harmonization. Subsequently in 2019, the Ph. Eur. deleted the monograph for Highly Purified Water (HPW) which was no longer needed with the 2017 revision. While the pharmacopeias may vary slightly in the exact specifications, most of the typical process combinations for membrane-based production of WFI available in the market meet pharmacopeial requirements. An exception is the ChP¹ which requires distillation as the only acceptable production method for WFI. The requirements for the WFI manufacturing methods in the country-specific pharmacopeias are listed in Table 2.1.

¹ The latest revision (at the time of Guide publication) of the ChP [4] was published in April 2020. The ChP is typically updated every five years.

Table 2.1: Pharmacopoeial Requirements for WFI Production Methods

Organization/Reference	Extracted (or Translated) Text Related to Approved Production Methods for WFI	Summary
United States Pharmacopeia (USP) [2] USP–NF 2022, Issue 1 (effective May 2022)	...water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms...	No restriction with regard to the treatment technologies used.
European Pharmacopoeia (Ph. Eur.)* [1] – Monograph 0169 10th Edition 2022 – Supplement 10.7 (effective April 2022)	– by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz, or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; or – by a purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation.	In principle no restriction with regard to the treatment technologies; however, membrane-based generation of WFI may require the use of reverse osmosis. The end user should consult their supervisory authority before implementation.
Japanese Pharmacopoeia (JP) [3] JP 18th Edition (effective June 2021)	...prepared by distillation or by reverse osmosis and/or ultrafiltration ... (methods for refining water by using a reverse osmosis membrane module, an ultrafiltration membrane module capable of removing substances having molecular masses of 6,000 and above, or a module using both types of membranes)...	Membrane-based generation of WFI must include reverse osmosis and/or ultrafiltration (Molecular Weight Cut-off < 6,000).
Chinese Pharmacopoeia (ChP) [4] ChP 2020 Edition	...distilled water from purified water.	Distillation is the only approved method to produce WFI.
International Pharmacopoeia (Ph. Int.)** [16] 10th Edition (2020)	...by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz, or suitable metal and fitted with an effective device to prevent the entrainment of droplets. Other technologies proven to be equal or superior to distillation, and meeting the pharmacopoeial requirements, can be used. Details on specific points to be conserved are outlined in the guidance on Production of water for injection by means other than distillation).	No restriction with regard to the treatment technologies used provided that the requirements of the WHO guidance Production of water for injection by means other than distillation [17] are met.
Indian Pharmacopoeia (IP) [13] 8th Edition (2018) plus Addendum 2021	...prepared from Purified Water through distillation (phase separation) process or any other process that is equivalent or superior to distillation in the removal of chemicals and microorganisms such as reverse osmosis, coupled with appropriate techniques.	In principle no restriction with regard to the treatment technologies used; however, since WFI must be produced from compendial Purified Water, certain process combinations may not be permitted (e.g., softening and vapor compression).

Table 2.1: Pharmacopeial Requirements for WFI Production Methods (continued)

Organization/Reference	Extracted (or Translated) Text Related to Approved Production Methods for WFI	Summary
Brazilian Pharmacopoeia [15] 6th Edition (2019)	...obtained by distillation of the water properly treated, in equipment whose parts in contact with water are neutral glass, quartz or other appropriate material. It can also be obtained by process equivalent or higher to distillation, in the removal of chemical contaminants, microorganisms and bacterial endotoxins. The obtained process must be validated...	No restriction with regard to the treatment technologies used.
Pharmacopoeia of the United Mexican States (FEUM) [18] 12th Edition Supplement 2020	...distillation or other equivalent or higher technology demonstrating the elimination of chemical substances, microorganisms and endotoxins...	No restriction with regard to the treatment technologies used.
Russia Pharmacopoeia (Ph. RU) [14] 14th Edition (2018)	...obtained from drinking water by methods of distillation, ion exchange, reverse osmosis, a combination of these methods or by other methods, or from water purified by distillation...	In principle no restriction with regard to the treatment technologies used; however, if the source water is not of drinking water quality, WFI must be produced by distillation.
Korean Pharmacopoeia (KP) [19] 12th Edition (2019)	...prepared by distillation or ultrafiltration, either from Water after applying appropriate pretreatments such as ion exchange or reverse osmosis, or from Purified Water in Bulk...	Ultrafiltration must be used as the final treatment step to produce membrane-based WFI.
Notes: * Member States of the European Union as well as Albania, Bosnia and Herzegovina, Montenegro, North Macedonia, Norway, Republic of Moldova, Serbia, Switzerland, Turkey, Ukraine, and United Kingdom. ** The International Pharmacopoeia is issued by the WHO [8].		

2.3 Regional Guidelines – European Union

The European Directorate for the Quality of Medicines & HealthCare (EDQM) [20] is the authority that sets the quality specifications in the Ph. Eur. [1], with compliance controlled by the EMA [10]. Agreement between these two agencies is normally required to implement significant changes, such as those in the WFI monograph.

2.3.1 EMA – Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

As a follow-up to the 2017 revision of the WFI monograph in the Ph. Eur. [1], the EMA published the Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies [21]. It states the following:

“The purpose of these Questions and Answers is to provide clarification and guidance in relation to the use of reverse osmosis in the manufacture of Water for Injection (Part I) and also to provide more detailed guidance on the control of Biofilms (Part II).”

"This set of questions and answers is intended to provide preliminary guidance until such time the ongoing revision of Annex I of the GMP guide is complete."

The EMA questions and answers document [21] contains detailed guidance on the design, operation, and monitoring of membrane-based WFI generation. There are specific statements in the EMA document that warrant additional discussion, as based on the authors of this Guide and their collective experiences gained from operational and regulatory inspections. This information is intended to support readers when resolving questions they may receive from regulatory officials.

Total Organic Carbon (TOC) Monitoring

EMA Statement: *"On-line TOC instrumentation must be considered as part of the control strategy and located at various positions within the RO water system as determined through quality risk management principles. The location of on-line TOC should be based on risk assessment."* [21]

Discussion: Online TOC measurements have typically been installed in the return flow of the WFI distribution system as physicochemical parameters are equally distributed throughout a recirculating system. They have been infrequently used within the production system (at the time of Guide publication); however, some companies may choose to install as part of their risk mitigation strategy. Traditionally, the performance of a membrane-based WFI generation system has been monitored by conductivity measurements. Experience shows that when the expected/required conductivity is reached, correct functioning of the membranes is guaranteed and a TOC content in the product water of less than 50 ppb is most likely achieved. Since biofilm cannot be detected by TOC measurements, the additional gain in knowledge from additional devices within the generation system may not warrant the associated costs.

Sanitization

EMA Statement: *"Sampling must take place downstream of softeners and carbon filters, the sanitization procedure must be shown to control the microorganism level so that it doesn't proliferate above feed water levels."* [21]

Discussion: Since both activated carbon filters and softeners offer good growth conditions for bacteria, it may not be possible to prevent an increase in the bacterial count above source water levels when using these technologies without continuous or very frequent sanitization. A limited increase of the bacterial counts after these process steps can be tolerated as long as routine sanitization with hot water or chemicals ensures that the system is microbiologically under control and the downstream unit operations function properly.

EMA Statement: *"The RO membranes are currently not designed to withstand pressurised steam, but those that are capable of withstanding high temperatures are available and should be utilised in order to allow for routine high temperature flush through the system in conjunction with routine chemical sanitisation."* [21]

Discussion: While hot water sanitization is the most reliable way to kill the bacteria typically found in high purity water systems, chemical sanitization is possible. It must be properly executed to ensure proper sanitization. The limited chemical concentrations (due to low resistance of the membrane material) as well as any poorly flushed areas within the membrane modules can result in the bacteria not being completely killed, which can lead to rapid recontamination.

Additional details regarding microbial control and sanitization can be found in Chapter 8.

Reverse Osmosis Membranes

EMA Statement: *"Maximum time limits for the RO membranes usage should be established. Qualification should consider destructive analysis of RO membranes to ensure the absence of biofilm, or any surface that cannot be visually inspected regularly."* [21]

Discussion: Performance monitoring is more appropriate than time limits for assessing usable membrane life. Even if only low bacterial counts are detected in water systems, these counts result from biofilms. Since bacterial counts are normally low in the permeate of the Reverse Osmosis (RO) system, the assessment should be limited to the presence of significant biofilm on the permeate side (pure side) of the membrane. Based on the experience of the authors of this Guide, evidence of significant biofilm can be detected by clearly increasing bacteria counts first in the RO concentrate and then later in the RO permeate. Establishing non-performance-based membrane lifetime limits and performing destructive analysis of the membrane surface have limited value outside of determining the causes of membrane failures or other RO performance abnormalities.

Agents for Sanitization

EMA Statement: *“Use of thermal sanitisation where possible should also be considered. Generally temperatures above 75°C should be utilized.”* [21]

Discussion: Typical organisms present in pure water systems, such as *Pseudomonas*, are not heat resistant and experience has shown that thermal sanitizations are effective even at temperatures below 65°C. Considerations should also be made for the decreased service life of all membranes (e.g., RO, electrodeionization (EDI), ultrafiltration (UF)) with higher sanitization temperatures and increased frequency of sanitization. This Guide recommends hot water sanitization at temperatures between 65–80°C.

EMA Statement: *“An approach that utilises a minimum of a double-edged approach should be considered, e.g., thermal sanitisation in conjunction with a chemical sanitization at a set frequency based on robust risk-assessment.”* [21]

Discussion: Employing a double-edged approach is recommended, e.g., performing hot water sanitization of the entire system as well as chemical cleaning and/or disinfection (to remove thermally killed biofilm from the system). In the case of continuously sanitized WFI storage and distribution systems, which are operated either continuously with ozone or continuously at elevated temperatures, the installation of an additional sanitization option may have little added value.

It is recommended to apply the contents of the EMA questions and answers document [21] with expertise and a risk-based approach. A full and unchecked implementation of all statements contained in the document may lead to an expensive plant design and operation without added value. For example, the higher requirements of the EMA for the monitoring of membrane-based systems compared to distillation, both of the physicochemical and the microbiological quality parameters, may not be justified. TOC measurements are not suitable for monitoring of biofilms, microbiological contamination, or the integrity of individual process steps of a water treatment system.

See Chapter 8 for additional details regarding microbial control in a membrane-based WFI system.

2.3.2 EMA – Guideline on the quality of water for pharmaceutical use

With the 2017 and 2019 revision of the Ph. Eur. [1], the monograph for WFI was significantly changed and the monograph for HPW was removed. Correspondingly, the EMA published the Guideline on the quality of water for pharmaceutical use [22] in 2020. It states:

“This document is intended to provide guidance to the industry on the pharmaceutical use of different grades of water in the manufacture of active substances and medicinal products for human and veterinary use and should be considered for new marketing authorisation applications, as well as any relevant variation application to existing marketing authorisations. This guidance also applies to Advanced Therapy Medicinal Products (ATMPs).”

“This guideline complements the ‘Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies EMA/INS/GMP/443117/2017 GMP/GDP Inspectors Working Group’ which has been published following the implementation of the revised monograph for Water for Injections (0169) and it is intended that the guideline and Q&A should be read together.”

The EMA guideline [22] itself does not contain any requirements or information on the different methods for WFI production, but provides important information that can be used as the basis for selecting the appropriate water quality for the various production processes. Compared to the previous version, it contains much more specific requirements for the biotechnological production of pharmaceuticals.

2.3.3 European Union GMP Annex 1 (Draft Revision)

The measures in Eudralex Volume 4, Annex 1 – Manufacture of Sterile Medicinal Products [23] are intended to minimize the risks of contamination in sterile pharmaceuticals. It states:

“Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.”

“Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins.”

Annex 1 has been in the process of undergoing a major revision since 2017.² Annex 1 (2020 draft revision, version 12) [24] states the following regarding WFI systems including membrane-based systems:

“6.7 Water treatment plant and distribution systems should be designed, constructed and maintained to minimize the risk of particulates, microbial contamination/proliferation and pyrogens (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs), and prevent the formation of biofilms to ensure a reliable source of water of an appropriate quality. Where filters are included in the system, special attention should be given to the monitoring and maintenance of these filters. Water produced should comply with the current monograph of the relevant Pharmacopeia.

6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (for example by constant circulation at a temperature above 70°C). Where the WFI is produced by methods other than distillation, further techniques such as nanofiltration and ultra-filtration as well as electrodeionization (EDI) should be considered in conjunction with reverse osmosis (RO) membranes.”

The chosen wording *“further techniques . . . should be considered in conjunction with RO”* indicates that RO is considered by the European authorities to be an essential or even mandatory part of membrane-based WFI production.

Annex 1 (draft revision) [24] does not provide more information on the production methods.

² At the time of Guide publication, the final text from the Annex 1 revision was not available.

2.4 Regional Guidelines – US

In the US, the quality criteria for WFI are defined in the US Pharmacopeia (USP) [2] and the local control authority is the FDA [9]. Since 2002, the WFI monograph of the USP has no longer specified the process technologies to be used.

2.4.1 USP <1231> Water for Pharmaceutical Purposes

USP General Chapter <1231> Water for Pharmaceutical Purposes (2021) [2] provides guidelines for WFI but does not include any mandatory specifications. The introduction to the chapter states:

“This informational chapter on pharmaceutical water topics includes some of the chemical and microbiological concerns unique to water and its preparation and uses. The chapter provides information about water quality attributes . . . and processing techniques that can be used to improve water quality.”

“This chapter is intended to be educational, and the user should also refer to existing regulations or guidelines that cover US and international . . . good manufacturing practice (GMP) issues, as well as operational and engineering guides and/or other regulatory guidance for water.”

USP <1231> [2] states the following which suggests a hot water sanitizable design of non-distillation-based WFI production systems:

“The final unit operation used to produce [WFI] is limited to distillation or other processes equivalent or superior to distillation in the removal of chemical impurities as well as microorganisms and their components, such as bacterial endotoxins. Distillation coupled with suitable pretreatment technologies has a long history of generally reliable performance (though not completely infallible) and can be validated as a unit operation for the production of [WFI]. Other combinations of purification technologies also may be suitable in the production of [WFI] if they can be shown through validation to be as effective and reliable as distillation in the removal of chemicals and microorganisms. The development of new designs and materials of construction for other technologies (e.g., reverse osmosis, electrodeionization, and ultrafiltration) that allow intermittent or continuous operation at hot bactericidal conditions show promise for a valid use in producing [WFI].”

USP <1231> [2] provides comprehensive information on the design, operation, and monitoring of compendial water systems with a focus on microbial control, which makes it a valuable document for non-distillation-based WFI generation and, in particular, systems utilizing hot water sanitization.

2.4.2 FDA Inspection Guides

The FDA provides limited but important information on the production methods for WFI. The 1993 FDA Guide to Inspections of High Purity Water Systems [25] and the 2014 Inspection Technical Guide: Water for Pharmaceutical Use [26] are reference materials for inspectors and other FDA personnel. Regarding the system design for WFI production, these documents state:

“Distillation and Reverse Osmosis (RO) filtration are the only acceptable methods listed in the USP for producing Water for Injection. However, in the bulk Pharmaceutical and Biotechnology industries and some foreign companies, Ultra Filtration (UF) is employed to minimize endotoxins in those drug substances that are administered parenterally.” [25]

“WATER PRODUCTION SOURCES

The USP defines acceptable means of producing the various types of component waters. USP WFI may be made only by distillation or reverse osmosis.” [26]

While the 1993 and 2014 FDA documents are still current (at the time of publication of this Guide) and these statements reflect the current requirements of the FDA, readers may interpret that the FDA requires the production of membrane-based WFI to contain an RO stage. However, the USP [2] clearly states in the WFI monograph:

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

2.5 Regional Guidelines – Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) [27] is responsible for both the Japanese Pharmacopoeia (JP) [3] and the GMP guidelines in Japan.

RO and UF have been allowed in Japan as alternatives to distillation for WFI production since the 1980s. In addition to the specifications in the JP, the PMDA has provided supplementary information on the three approved processes (distillation, RO, and UF) in the 2011 Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing [28] which states the following about membrane-based technologies:

“2. Reverse Osmosis (RO)

The reverse osmosis (RO) is used to improve various factors in water quality by allowing water to flow through permeable and semipermeable membranes based on osmotic pressure differentials to remove small molecular solutes similar in size to inorganic salts as well as solvent molecules, microorganisms, endotoxins, etc. depending on their respective concentrations in source water. Although RO can be treated at an ambient temperature and its performance is highly cost effective in energy-saving compared with distillation, stricter control than that of distillation is required to prevent any leaks due to pinholes into the downstream and microbial contamination. Points to consider in designing RO membrane units are shown below:

(1) As no gaseous carbon dioxide and ammonia can be removed from feed water by RO, such prior pretreatment as deaeration, neutralization, and/or ion-exchange should be required on occasional demand.

(2) Appropriate equipment for the microbiological control and monitoring should be included in place in the pretreatment system for feed water to meet the predetermined control criteria.

(3) As RO generally operated at an ambient temperature may cause some concern about downstream contamination due to leaks through pinholes developed in the membrane, the structural system composed of two ROs in series should preferentially be designed to provide enhanced reliability and better control. Additionally, UV sterilization, heat-sterilization, and other appropriate treatments in the downstream should be performed to inhibit microbial growth in the system.

3. Ultrafiltration (UF)

Ultrafiltration (UF) is a hyper-filtration method capable of removing endotoxins from feed water. Unlike RO systems, UF units can generally be operated at a far lower pressure than RO and are excellent in heat-resistance. Some UF membranes are made of materials resistant to steam sterilization, and hence the membranes can relatively allow their surfaces to be easily sterilized with high-temperature water or chemical agents. It is recommended to select high-grade UF membranes capable of removing organic substances with a molecular weight of fraction exceeding 6,000 Daltons and suitable for the intended use. Although the purification performance of UF modules is dependent on the upstream water quality and the modules' grade as that of RO, routine maintenance and control of the UF system should be made in order to exercise no ill effects on the purification performance and water quality developed by microbial growth due to the fouling of particulate matter and microorganisms.”

2.6 International Organizations

2.6.1 World Health Organization (WHO)

The WHO [8] Technical Report Series (TRS) is described as follows:

“The WHO Technical Report Series (TRS) makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. It includes the reports of the annual meetings of the WHO Expert Committee on Biological Standardization . . . The development of norms, standards, and guidelines to promote quality assurance and quality control is an integral part of WHO’s Constitution and a unique responsibility. . . WHO inspections of the manufacturing sites of active pharmaceutical ingredients and finished pharmaceutical products, undertaken as a component of evaluation for WHO prequalification, are based on WHO GMP.”

2.6.1.1 TRS 1033 Annex 3 – Good manufacturing practices: water for pharmaceutical use

Annex 3, Good manufacturing practices: water for pharmaceutical use [29] in the WHO TRS 1033 (2021) states:

“This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for the management of the quality of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.”

The following sections of TRS 1033 Annex 3 [29] contain important statements on the subject of non-distillation-based WFI:

“2.3 To reduce the risks associated with the production, storage and distribution of water, and considering the properties and use, it is essential:

- to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage, and distribution systems;*
- to continuously or periodically perform sanitization;*
- to take the appropriate measures in order to minimize chemical and microbial contamination; and*
- to minimize microbial proliferation and endotoxin formation, where applicable.”*

“3.2 The capacity of these [pharmaceutical water production, storage and distribution] systems should be enough to meet both the minimum and peak demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.”

“4.4.4 [Bulk WFI] may be prepared, for example, by distillation as the final purification step. Alternatively, [bulk WFI] may be produced by means other than distillation. Techniques such as deionisation, electro deionization, nanofiltration, ultrafiltration, water-softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see Production of water for injection by means other than distillation as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 (6).”

2.6.1.2 TRS 1025 Annex 3 – Production of water for injection by means other than distillation

In response to the revision of the Ph. Eur. [1], the WHO published a guideline for the production of WFI by means other than distillation, Annex 3 [17] in the WHO TRS 1025 (2020). It is important to note that this document is specifically referenced in the International Pharmacopoeia (Ph. Int.) [16] monograph for WFI:

“Details on specific points to be conserved are outlined in the guidance on Production of water for injection by means other than distillation (WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report, WHO Technical Report Series, No. 1025, 2020, Annex 3).”

However, TRS 1025 Annex 3 [17] primarily covers information on the lifecycle approach, risk assessment, and control strategy. It does not contain specific information on preferred production, operating, and sanitization methods. Instead, it states the following general statements:

“6.6 Techniques such as deionization, electro-deionization, nanofiltration, ultrafiltration, water softening, descaling, prefiltration, degasification, and ultraviolet treatment, along with other techniques, may be considered in conjunction with a single- or double-pass reverse osmosis system.”

6.7 These [techniques] should allow for sanitization (thermal or chemical, or a combination thereof) when required. The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals, in accordance with a documented procedure.”

“7.5 A combination of online and offline monitoring of WFI should be done, to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with online instruments. Use of rapid microbiological methods is encouraged for timely monitoring, and aids with rapid responses to prevent deterioration of the system.”

In the section titled “Monographs”, it merely states that the drug manufacturer should have appropriate specifications for WFI and that the quality of the WFI produced should meet the requirements of the pharmacopeias [17].

2.6.2 Pharmaceutical Inspection Co-Operation Scheme (PIC/S)

The PIC/S [30] is a “non-binding, informal co-operative arrangement between Regulatory Authorities in the field of [GMP]. It is open to any Authority having a comparable GMP inspection system.” Since 1997, the EMA [10] and PIC/S [30] have developed their GMP guidelines in parallel. Whenever a change has been made to one, the other has been amended so that both guidelines are practically identical.

2.6.3 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

The ICH [31] has contributed significantly to the harmonization of requirements in the pharmacopeial monographs and created ICH guidelines adopted by a growing number of regulatory authorities. As of the publication date of this Guide, ICH has not developed a guideline that addresses the quality or the methods for the production of WFI.

3 Risk Considerations

3.1 Introduction

The use of membrane-based technology for WFI generation and storage and distribution at ambient temperatures carries a greater risk compared to distillation methods if the systems are not properly designed, installed, operated, and maintained. A higher degree of rigor is required in the system design and in the operational, maintenance, sampling, and sanitization practices to ensure the water meets WFI quality requirements.

This chapter focuses on the increased risk of microbial contamination with respect to membrane-based technology due to operation at ambient temperatures and the use of numerous seals in the system. An entire chapter in this Guide has been devoted to microbial control in membrane-based WFI systems. See Chapter 8.

Microbial risks are mitigated primarily through the application of carefully planned and implemented:

- Overall system design
- Robust Contamination Control Strategy (CCS)
- Routine system operation
- Sanitization methodology and frequency
- Monitoring and maintenance

Enhancements taken in these areas for a membrane-based WFI system as compared to a similar system designed to produce PW can reduce the overall risk by the following means:

1. Reduction of the probability of the risk materializing
2. Earlier detection of the risk, enabling mitigating actions to minimize or eliminate the risk
3. Reduction of the severity of the risk

It is strongly recommended that users develop a thorough understanding of pharmaceutical grade water systems prior to designing, installing, and operating membrane-based WFI systems. There are numerous other potential issues related to system operation which are outside the scope of this Guide and discussed at length in the following publications:

- *ISPE Baseline Guide: Volume 4 – Water and Steam Systems* (Third Edition) [5]
- *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems* [32]
- *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [33]

3.2 Regulatory Concerns

The generation of WFI using membrane-based technologies has been accepted by the US and Japan for some time. For example, USP XIX (1975) recognized RO for the production of WFI [2]. In addition, from 2002 to 2019, the Ph. Eur. [1] included an HPW monograph that allowed for production of WFI quality water by alternatives to distillation. During this time period, the use of HPW was restricted to applications with reduced risk per the EMA Note for guidance on quality of water for pharmaceutical use, which was replaced by the EMA Guideline on the quality of water for pharmaceutical use [22] in 2020. With fifteen years of successful experience, the Ph. Eur. was updated in 2017 to allow membrane-based technology to produce WFI for all applications. Without the built-in safety factor of heat and the phase change that exists with distillation, there is the potential for additional risk with membrane-based technology. Therefore, regulators may expect more robust controls, testing, and risk assessments for membrane-based WFI generation systems as well as ambient storage and distribution systems.

With this historical background, there are several specific regulatory concerns to be aware of, including:

- The Chemistry, Manufacturing and Controls (CMC) is an integral part of any pharmaceutical product application to a regulatory authority. In this section, the ingredients used in manufacturing are listed, including WFI. In some instances, there may be a brief description of the WFI generation system. This description must match the actual WFI system. If there is a change, the product application/registration must be changed, which may be a lengthy process, before the product may be sold or distributed.
- Drug manufacturing must comply with the pharmacopeia where it is to be sold or used. At the time of this Guide publication, the ChP does not allow for membrane-based technologies for WFI generation. Therefore, any product made with WFI via membrane-based systems may not be sold in China.
- The Ph. Eur.³ states a requirement about giving notice to the supervisory authority, but does not provide clear guidance on how this notification process is to take place or specifically who to notify. Therefore, each proposed membrane-based WFI system project must address this requirement on a case-by-case basis.
- At the time of Guide publication, the European Union Annex 1 [23] is in the process of undergoing a major revision. This revision may include additional requirements for WFI via membrane-based technology, but the 2020 draft revision (version 12) [24] indicates otherwise. Refer to the EMA Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies [21] which describes control strategies and risks. See Section 2.3.1 of this Guide.

Additional details on regulatory requirements are in Chapter 2.

3.3 Quality Risk Management

Quality Risk Management (QRM) as outlined in ICH Q9 [34] is a systematic process that provides a consistent framework for assessing risk in the pharmaceutical product lifecycle. The ICH Q9 model is not the only possible method, however, it provides the basic principles for risk management. The process as shown in ICH Q9 involves the assessment of risk, the implementation of control measures, the communication of the risk, and the overall review of the risk.

ICH Q9 identifies the two primary principles of QRM—how these are applied to membrane-based WFI systems are of critical importance:

- *“The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient”*

³ Ph. Eur. [1] states: “A purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionization, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation per Ph. Eur. requirement.”

- WFI generated by any method has a potential impact on the patient
- *“The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk”*
- As previously stated, this second principle is where the use of WFI comes into play. The risk associated with WFI must be evaluated and documented based on scientific knowledge. The level of evaluation and documentation is dependent on the level of risk.

A variety of formal risk assessment tools are available, however effective risk management requires the participation of an appropriate cross-functional team of SMEs. The most commonly utilized risk assessment tools include:

- Failure Mode and Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis Critical Control Point (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Cause and effect diagram (Fishbone diagram)
- Bow-tie method
- Layer of Protection Analysis (LOPA)

For more comprehensive details regarding QRM and the overall risk management process, refer to ICH Q9 [34].

3.4 Risk Profile

ICH Q9 [34] defines risk as *“the combination of the probability of occurrence of harm and the severity of that harm.”* When evaluating the severity of risk, one consideration is the application for which the WFI is used. There is some disagreement on whether this should be a consideration, with one argument being that WFI is WFI and that there has been no change to the chemical and microbial requirements, only the allowable production methods. The other argument is that not all applications are equal. The following examples illustrate the severity of impact to the product and the patient and how this may impact technology selection:

1. An injectable terminally sterilized product made with WFI
2. A suspension-based aseptically processed product (this product is neither terminally sterilized, nor is it subjected to a final sterilizing filtration step)

A microbial control failure with the WFI system used for the second example will clearly have a higher degree of impact to the product and the patient than for the first example. This factor may be directly considered in the risk assessment, or it may be considered by management in the overall technology selection decision-making process.

The risk profile of using the selected membrane-based technology to produce WFI should compare favorably to the risk profile of distillation-based technology as determined by risk assessment. Some regulations specifically cite this equivalency, as summarized in Table 2.1.

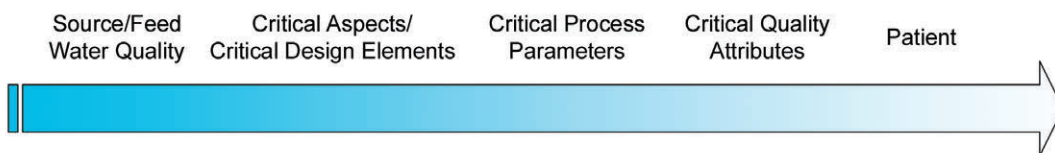
USP <1231> [2] provides some guidance as to the level of performance one should expect from membrane-based WFI systems. USP <1231> Section 5.11 states:

“In spite of general perceptions, even the best distillation process does not ensure absolute removal of contaminating ions, organics and endotoxins. Most stills are recognized as being able to accomplish at least a 3-4 log reduction in these impurity concentrations. They are highly effective in sterilizing the feedwater.”

Chapter 8 of this Guide is dedicated to a discussion of microbial risks as well as mitigation and control measures for membrane-based WFI generation and storage and distribution systems. Microbiological contamination represents the greatest perceived risk with membrane-based WFI systems simply because the lethality of continuous heat is either reduced or missing from these WFI systems.

In summary, the risk assessment and the resulting strategy must mitigate the risks associated with membrane-based WFI generation systems to attain a risk profile that ensures the safety of patients. The CQAs, Critical Process Parameters (CPPs), and Critical Aspects (CAs) must be linked together as illustrated in Figure 3.1.

Figure 3.1: Linking Patient Safety to the Water Quality



3.5 Procedural Controls and Personnel Expertise

Ambient generation (via membrane-based technology) and storage and distribution of WFI do not have the inherent self-sanitizing capability that distilled and heated WFI storage and distribution systems have. Thus, the operation and sanitization Standard Operating Procedures (SOPs) for these ambient systems need to ensure adequate, robust system control. The experience of the personnel that operate the system is also critical.

3.6 Incoming Source Water Considerations

The water used to produce WFI must start with a feed water that meets the standards for municipal drinking water at the country or region where water enters the system, e.g., Europe [1], US [2], Japan [3], WHO [8] or other. Multiple variables can affect municipal drinking water distribution, such as aging infrastructure, drought, and the growing need for multiple sources to keep up with population growth. Thus, the water quality entering a specific facility can vary widely from region to region and even within the same city, industrial sector, or facility. More information on specific source/feed water and pretreatment topics is given in Chapter 4.

The characteristics of the incoming source water that should be considered during the risk assessment of the WFI system include:

- Seasonal variability in all characteristics
- Municipal disinfectant type, concentration, and variability
- Source(s) of the drinking water (e.g., private sources or municipal sources, well or surface water)
- Microbial composition

- Chemical composition
- Temperature

Incoming source water that is known to be regularly higher in microbial load requires more risk mitigation in system design and operation, as compared with a system with a reliably low microbial source water content. Similar risk mitigation measures may be required for other source water variables including temperature fluctuations or variations of dissolved/suspended solids concentrations. Seasonal variability should be understood and considered, especially with respect to microbial composition of the source water.

3.7 Process and Equipment Risks

There is no single membrane-based design that is guaranteed to make WFI quality water from all possible variations in source water. There is also no single design that will minimize all possible risks to acceptable levels for every application. A combination of unit operations needs to be properly selected and combined into an integrated system to ensure a risk profile that is equal to or better than a distillation-based system. This requires SMEs with specific knowledge in all of the different unit operations to ensure a robust, reliable combination is selected based on the source water characteristics for a given site or location.

Refer to Appendix 2 for a summary of the major risks associated with the most commonly found unit operations in a membrane-based ambient WFI system. The risks included are not all inclusive and a thorough risk assessment executed per an established method/procedure should be performed as part of the design process to ensure proper mitigation measures are in place.

3.8 Elastomeric Sealing Materials

Although necessary for sealing and isolation of surfaces in pretreatment, generation, and storage and distribution systems, the degradation of elastomeric sealing compounds within a system over time presents some of the greatest risks to WFI quality. Proper material selection is crucial to the reliable operation of any WFI system.

Material selection includes evaluating the risks associated with:

- Chemical compatibility
- Temperature ratings and operating ranges
- Pressure ratings
- Leachables and extractables

Risk assessments should consider where the elastomers are used within the membrane-based WFI system. Improper selection of materials of construction can result in cracking, flaking, drying, stiffening, melting, etc. and can eventually lead to gasket failure, particle shedding, or a void/surface where microbial proliferation occurs. Additionally, a risk-based program for replacement of water contact materials (including gaskets, seals, O-rings, and valve diaphragms) should be established.

3.9 Risks Specific to the Use of Ambient Storage and Distribution and Ozone

There are two unique WFI quality risks associated with membrane-based WFI generation systems coupled with ozone sanitized storage and distribution systems that typically are not found in distillation-based WFI generation systems coupled with hot storage and distribution systems:

- Elevated oxygen levels
- Elevated carbon dioxide levels

Ozone introduced into a system or generated from within the system decomposes or is reduced down to oxygen and water. The net result is elevated oxygen levels in a storage and distribution system. If a product is subject to oxidation, elevated oxygen levels represent a risk that is not found in traditional WFI systems. The risk of elevated oxygen should be assessed as it could be a potential risk to the process or product.

Carbon dioxide may also be present at elevated levels in ambient systems because the solubility of carbon dioxide increases at lower temperatures. The increase in WFI conductivity due to carbon dioxide can be mistaken for an increase caused by other more critical ionic compounds. Critical changes in the water quality can be overlooked because of this effect. Prevention of uptake of carbon dioxide in cold systems presents a larger issue than with hot systems. Traditional hot systems have lower overall dissolved gas concentrations as compared with ambient systems.

Ozone is a potent oxidizing agent with a relatively high oxidation potential that effectively breaks down chemical bonds in complex molecules and is lethal to bacteria [35]. Additionally, ozone may be the method of choice for loop sanitization for facilities with a focus on sustainability and reduction of carbon footprint. See Chapter 6 of this Guide and Section 2.2 of the *Ozone Good Practice Guide* [32] for more information.

3.10 Sampling and Monitoring

Every water treatment system comprises several unit operations that operate together to ensure that the overall system produces WFI in a reliable and repeatable manner. In addition to water quality attribute monitoring for quality control purposes, pharmaceutical companies should be prepared to demonstrate that each unit operation is operating under a state of control by establishing an effective and rigorous process monitoring program that monitors appropriate water quality attributes and establishes alert and action limits to ensure each unit process is functioning within its intended operating limits. See Chapter 11 and the *Sampling Good Practice Guide* [33] for additional details.

Sampling should be done at a variety of frequencies (from online to grab) at different locations and for different parameters depending on the level of risk mitigation required.

This concept of monitoring for process control purposes is discussed in the *Sampling Good Practice Guide* [33] as well as in USP <1231> Chapter 6.2 [2] which states:

“The tests being performed on the samples are relevant to the sampling location and purpose of the sample. In-process monitoring of non-monograph attributes may be indicated for specific unit operations. For instance, before and after a softener, it may be important to determine water hardness to verify softener efficacy...”

SMEs and water system engineers should identify the CQAs for each unit process to be monitored. It is important to understand that the CQAs for each process may differ from the compendial requirements. Identified water quality attributes determined to be critical should be monitored with online instrumentation if possible.

Microbiological monitoring presents unique challenges which are discussed in Chapter 8 of this Guide and in the *Sampling Good Practice Guide* [33]. For process control purposes, the use of Online Water Bioburden Analyzers (OWBAs) offers a valuable tool for mitigating risk in ambient WFI systems, but should not be considered a replacement for traditional sampling for quality control and product release purposes at this time (current as of Guide publication). These monitoring methods bring significant advantages such as immediate results, improved troubleshooting, and giving operators the ability to detect and react quickly in times of elevated microbial counts to help ensure the system is maintained under a state of control. Guidance on OWBAs as well as Rapid Microbial Methods (RMM) can be found in PDA Technical Report No. 33 [36], Ph. Eur. Chapter 5.1.6 [1], USP <1223> [2], and the *Sampling Good Practice Guide* [33]. The EMA Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies [21] also suggests the use of these devices for water system control.

Although the *Sampling Good Practice Guide* [33] was published prior to the widespread acceptance of membrane-based systems for producing WFI water, it remains as a valuable resource for additional details regarding sampling for process control and for quality control purposes.

The overall sampling and monitoring locations and frequency must be clearly identified in the CCS for a given WFI system. Additional details regarding the requirements for a CCS are provided in Appendix 3.

3.11 Setting Appropriate Alert and Action Limits for WFI Systems

The selection of appropriate alert and action limits for CPPs of various purification processes represent effective risk reduction techniques that may be utilized. As described in USP <1231> Section 9.4 [2], two or three-tier concepts are common practices in this application and are accepted. A two-tier approach relies on action (or alert) and specification limits whereas a three-tier approach relies on action, alert, and specification limits. USP advises against the use of a single-tier system as it is seen to be risky and difficult to manage.

See Chapters 4, 5, 7, and 11 and Appendix 2 for additional discussion.

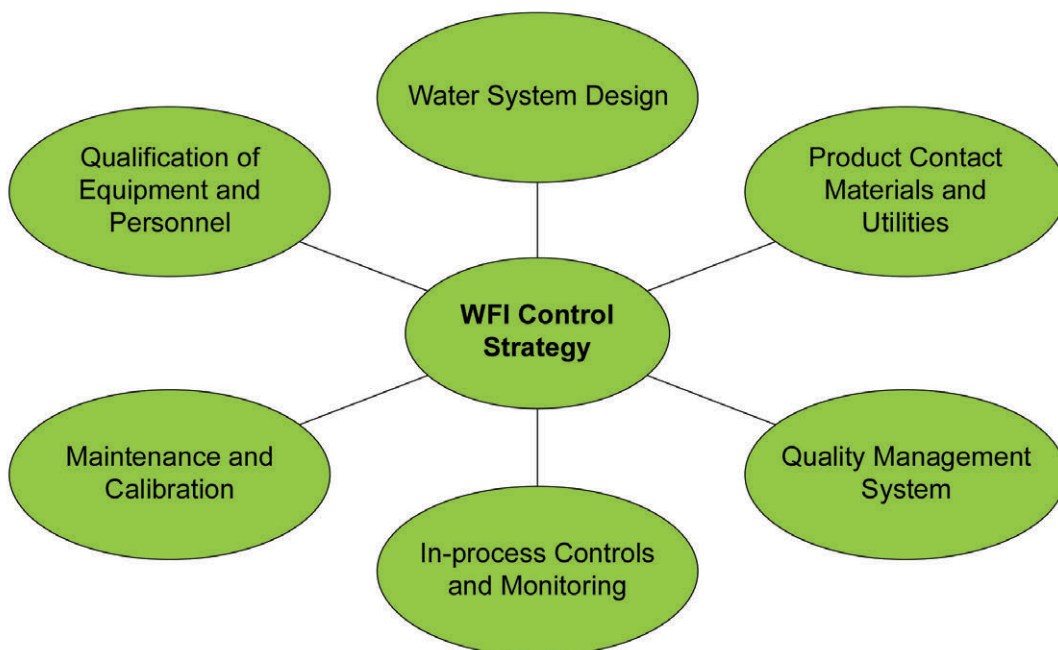
3.12 Operating Model and Control Strategy

For any water system, the operating model and control strategy must be fully developed. The process typically starts during the design phase of the new system. This is particularly important for membrane-based WFI systems as these systems may come under closer scrutiny by regulators until these systems are more widely used and accepted. It is crucial to involve representatives from the appropriate departments (e.g., Quality Assurance, Quality Control, Manufacturing/Operations, Facilities, Engineering, etc.) during the design phase of an ambient WFI system. These stakeholders will get to know how the system works and what they will have to do later when the routine operations start. Care should be taken during construction, start-up, and commissioning and qualification to ensure that the system is operated and sanitized regularly. Failure to properly operate and sanitize any WFI system can lead to unreliable operation, equipment damage, and microbial control problems.

The selected degree of equipment monitoring and automation has a direct impact on the capital cost as well as the level of operator involvement for ongoing monitoring during system operation. It is the responsibility of the pharmaceutical companies to demonstrate that their membrane-based WFI systems are operating under a state of control, and this may lead to an increase in the number of control points identified for monitoring.

The control strategy should be developed during the design phase and properly documented. Figure 3.2 illustrates an example of the elements to include in a control strategy, based on the requirements outlined in the EMA Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies [21]. An example outline for a WFI control strategy is provided in Appendix 3.

Figure 3.2: Example of the Control Strategy Elements for a Membrane-based WFI System



4 Pretreatment

This chapter is the first of three chapters that discuss equipment design attributes for pretreatment, generation (Chapter 5), and storage and distribution (Chapter 6).

This Guide uses the term “source water” to refer to the water entering the facility from its supplier (municipal supply, well, etc.) to align with the common compendia term while the *Water and Steam Baseline Guide* [5] uses the term “feed water”. In the context of water supplied to the facility, these two terms can be considered equivalent.

Note: See Appendix 9 glossary definitions for feed water and source water.

4.1 Introduction

This chapter discusses the unique considerations of pretreatment for membrane-based WFI systems. This chapter is not intended to be a general discussion of pretreatment systems, which can be found in the *Water and Steam Baseline Guide* [5].

Pretreatment systems are found in all pharmaceutical water purification systems. Pretreatment is a series of unit operations to condition the source water so that it will be of adequate quality to ensure performance of the final treatment. The pretreatment system must condition the source water to ensure long-term operation of downstream equipment such as RO membranes and EDI resins and membranes.

For WFI systems, bacterial control in downstream equipment is a primary concern. With distillation processes, bacteria is destroyed with the elevated temperatures of a still and, to a lesser extent, removed in the separation and blowdown process. For a membrane-based final treatment for generation of WFI, microbial and bacterial growth reduction strategies should be established and applied to reduce loading of downstream components.

This microbial growth reduction strategy in pretreatment can be considered in three aspects:

- Control of bacterial loading on downstream membrane system
- Reduction of nutrients that can support bacterial growth in downstream equipment
- Control of chemicals that may inhibit the efficacy of downstream equipment to remove and control bacteria

4.2 Pretreatment Risks

While chemical and particulate controls in a pretreatment system are a major concern for any membrane system, this Guide focuses on the microbial growth control strategy for membrane-based WFI systems. Control strategies for chemical and particulates are outlined in the *Water and Steam Baseline Guide* [5].

The presence of bacteria is common and expected in pretreatment systems. They are not expected to be sterile nor hygienic. High levels of bacteria in a pretreatment system does not constitute a system failure; however, steps should be taken to keep levels under control and within a range that is manageable by the membrane-based WFI system. Keeping bacteria levels and growth under control within the pretreatment system reduces the potential for biofouling of membrane surfaces. Conversely, having a system designed only for bacterial control might come at a cost to other pretreatment functions such as scale and particulate control. A balance between bacterial control and other pretreatment functions must be established. The bacterial control strategy should include design and operation considerations to minimize growth, monitoring of bacteria with established alert levels, and a mitigation plan to perform sanitizations in the event of unacceptable levels of bacterial proliferation.

Endotoxins, while not explicitly discussed in this chapter, are removed in downstream equipment. Their removal and control are not typically the role of a pretreatment system. Endotoxins are formed in the Extracellular Polymeric Substance (EPS) of biofilms that can be released into the water as the bacteria is killed. A robust bacterial control strategy in pretreatment that focuses on controlling both bacteria proliferation and biofilm formation will additionally result in controlling endotoxin loading of downstream equipment. As such, the control mechanisms for bacteria are also the control mechanisms for endotoxins.

4.2.1 Extraneous Sources of Contamination – Source Water

Table 4.1 presents the potential impact on final treatment operations due to impurities typically found in source water and in the absence of a robust pretreatment system.

Table 4.1: Potential Risks to Final Treatment Operations Caused by Source Water Impurities

Final Treatment Operation	Source Water Impurity					
	Particulates	Bacteria	Organic	Hardness / Minerals	Chlorides	Chlorine and Chloramine
Reverse Osmosis (RO)	Clogging, abrasive damage to membranes	Biofouling of membranes	Organic fouling of membranes	Scaling, clogging, abrasive damage to membranes	None	Membrane degradation, pass through of contaminants
Electrodeionization (EDI)	Clogging, abrasive damage to membranes	None	Resin fouling	Resin scaling (chemical)	None	Resin degradation, membrane degradation, pass through of contaminants
Single Effect and Multiple-Effect (ME) Distillation	None	None	Carryover of volatile carbons	Scaling of heat exchange surfaces	Degradation of stainless steel surfaces	Degradation of stainless steel surfaces, carry over of chloramine to final product
Vapor Compression (VC) Distillation	None	None	Carryover of volatile carbons	Scaling of heat exchange surfaces	Degradation of stainless steel surfaces	Degradation of stainless steel surfaces, carry over of chloramine to final product
Ultrafiltration	Clogging, abrasive damage to membranes	Biofouling of membranes	Organic fouling of membranes	None	None	None

Source water for membrane-based WFI systems must meet drinking water standards regulations by the competent authority (such as US Environmental Protection Agency (EPA) [37], WHO [8], European Union, or Japan). Water sourced from an unregulated supply (such as a well) should be quality tested and monitored on a routine basis to ensure compliance to the relevant potable water standard. Source water that does not meet drinking water standards must first be treated to ensure compliance upstream of the pretreatment purification train in order to be considered suitable source water for a pharmaceutical water system. The design and operation of source water that does not meet drinking water standards is outside the scope of this Guide.

Source water, while meeting drinking water standards, is not sterile. Many species of bacteria and high levels of endotoxin can be present in source water despite treatment and residual disinfectants. Additionally, nutrients that support growth and proliferation of bacteria and formation of biofilms are present in source water. The source water attributes that affect microbial quality should be well understood and monitored.

Where fluctuations in source water quality occur, the quality should be closely monitored. The closer the water source is to the surface, the more significantly the conditions on the surface can impact water quality. These conditions include seasonal fluctuations and acute weather/environment events such as fires, rain, and droughts. Source water considerations may include source type, temperatures, rain falls, hurricanes, monsoons, influences by nearby industries, algae blooms, temperature inversions in reservoirs, etc. Water quality fluctuations may present itself in varying monitoring attributes, including but not limited to bacteria, hardness, disinfectant levels, organic levels and types, conductivity, silt density, etc.

Quality fluctuations may also include changes in treatment or changes of sources by the supplier. It is common in some areas for the source to change between surface and ground supplies or from different geographic regions. Knowledge of water supply influences and source water treatment is critical and should be fully understood by the system owners. Considerations include whether the supply is consistent or changes periodically and whether sources are treated differently.

The system owner or other facility representative should continually be in contact with the water supplier and proactively anticipate changes in supplies and/or fluctuations in water quality, both natural and manmade. The design and operation of the pretreatment system should be adequate for the source water scenario. In certain areas, it is common for the water supplier to periodically treat their distribution network, e.g., shock chlorination. Preparations should be made for these periodic treatments.

The type of residual disinfectants present in the water, if any, should be understood. This includes understanding how the raw water treatment is performed and what form of residual disinfection treatment is used. In the US, it is common to have residual chlorine (free) or residual chloramine. In Europe, it is not as common to have residual chlorine.

The residual disinfectant dissipates over time leading to lower efficacy. Free chlorine is relatively reactive and is prone to being consumed in byproduct reactions. The chemistry for these reactions can be complex, involving organic and inorganic compounds and can be dependent on time, temperature, and/or pH. It is expected that the chlorine levels at the entrance to the pretreatment system is lower than the level at the source water supplier. Additionally, the same dissipation can be observed in facilities with water storage tanks and complex distribution piping.

Free and total chlorine can be easily measured using hand test kits, online analyzers, and laboratory testing, and should be incorporated as a component of the risk mitigation. Sampling and monitoring are further discussed in Section 4.3.1.

4.2.2 Other Extraneous Sources of Contamination

Like the other parts of the water treatment system, the pretreatment system can be subject to contamination from outside sources. Chemical preparation tanks should be managed in a manner that minimizes the potential for extraneous contamination and may require periodic sanitization.

After fabrication and especially if wetted at the factory, the components and piping should be drained, dried, and/or preserved (as necessary) prior to shipment of the system. If not done correctly, contaminants may be introduced. After installation, the system should be flushed and/or sanitized prior to being put in service. Similarly, following routine, minimally intrusive maintenance activities, the system should be flushed prior to being put into service. For significant maintenance activities to membrane-based WFI pretreatment systems that involve breaches to the system integrity (such as changing media or resin), sanitization (if available) should be performed for affected components prior to being put in service to mitigate potential introduction of bacteria.

4.2.3 Internal Sources of Contamination – Nutrients in Pretreatment Systems

As discussed previously, there is no expectation for the pretreatment system to be sterile and the presence of bacteria is common and varies by source water and location. It is typical to have source water with low bacteria but then to observe growth in the pretreatment system components that exceeds drinking water levels. Enumeration techniques, different from those employed for WFI, may be necessary to yield quantifiable bacteria data. In order to control growth in a facility, it is important to understand both where the growth occurs in a system and the factors that affect it.

Whereas PW and WFI systems may present a hostile environment for bacterial growth, pretreatment systems readily have nutrients available to support growth. The nutrients may be entrained in the source water or on the high surface areas present in the pretreatment system components. Carbonaceous material can accumulate on filtration surfaces, providing a nutrient rich environment for bacteria proliferation. Additionally, some media itself (such as water softener resin and carbon media) provide ample amounts of nutrients to support bacterial growth. As residual disinfectants dissipate or are removed and in the presence of nutrients, it is expected that bacteria levels may be higher than at the feed to the pretreatment system. Monitoring of the bacteria should be performed and mitigation levels established for higher risk components. Mitigations may include but are not limited to sanitizations, backwashes, and media/filter replacements.

4.3 Pretreatment Controls

A robust control strategy must be in place for pretreatment systems and be documented in a risk assessment. The strategy must address the risks to the final treatment process from the pretreatment system. The sampling program and operating and maintenance procedures must also be documented. A sampling and monitoring program should be in place regardless of the final treatment. The control strategy must take into consideration the system as installed and the source water attributes.

4.3.1 Sampling and Monitoring

Sampling and monitoring need to be indicative of the system as installed but should not be excessive. The sampling program, including attributes and frequency, must reflect both the risks identified for the specific source water and the pretreatment system installed. In other words, there is no “one size fits all” approach. For example, a system with residual chlorine may pose lower bacteria in a water softener compared to a system that has no residuals, thus microbial monitoring may not be necessary with the presence of chlorine. However, the residual chlorine poses an oxidation risk to the downstream RO membranes, requiring chlorine monitoring that would not be required of a system free of residual chlorine.

Sampling ports used for bacterial monitoring should be designed to ensure representative sample streams. Excessive dead legs, threads, and ball valves should be avoided. Valves should be right-sized for sample collection and be self-draining.

Periodic source water sampling should establish baseline trends, consider season fluctuations, and identify any deviating results that may require modifications to system design, maintenance, and/or operation. Periodic intercomponent sampling should also be performed to ensure positive performance per design (e.g., TOC reduction) or identify negative impacts (e.g., high bacteria growth).

Typical testing parameters are summarized in Table 4.2. Sampling plans should be determined based on the facility's source water and pretreatment system installed.

Table 4.2: Typical Monitoring Parameters and Methodology for Pretreatment Sampling

Monitoring	Grab/ Laboratory Sample	In-line/Online	At-line/ Handhelds/ Test Kits	Sampling Frequency Considerations
Total and Free Chlorine	X	X	X	Routine
Total Organic Carbon (TOC)	X	X		Routine
Microorganisms	X			Routine
Endotoxin	X			Routine
Conductivity and/or Total Dissolved Solids (TDS)	X	X	X	Routine
Total Hardness	X	X	X	Routine
pH	X	X	X	Routine
Silt Density Index (SDI)			X	Infrequent
Turbidity	X			Infrequent
Total Suspended Solids	X			Infrequent
Silica	X			Infrequent

4.3.2 Component Operating/Design Considerations

This section presents the advantages, disadvantages, and operating or design considerations for common pretreatment system components with respect to microbial control. The tables included in this section are not intended to be comprehensive listings of all types of pretreatment available.

4.3.2.1 Materials of Construction

The materials of construction for a pretreatment system are varied and should be safe for drinking water consumption, meet local drinking water requirements, and should not adversely affect the quality of the water. A pretreatment system does not need to be hygienic in design, but should be fit for its purpose and be safe for personnel. Commonly used materials for vessels include Fiberglass Reinforced Plastic (FRP), epoxy lined carbon steel, and stainless steel. Commonly used materials for piping include copper, stainless steel, Polyvinyl Chloride (PVC), and Chlorinated Polyvinyl Chloride (CPVC).

4.3.2.2 Particulate Removal

Table 4.3 provides a comparison of particulate removal methods.

Table 4.3: Comparison of Particulate Removal Methods

Component	Advantages	Disadvantages	Considerations
Media Filters	- Ability to backwash - Good for chlorinated source water supply	- Heavy organics, turbidity might consider another technology - High surface area to support growth - Susceptible to bacteria growth if water is unchlorinated	- If combined with flocculation or coagulation, ensure tight controls - Utilize residual disinfectants to control bacteria - Backwashing at proper flow rates should be considered as part of control strategy to help dislodge bacteria and remove from the system - Operating flow rates should be within specified range to prevent channeling and ensure performance
Cartridge and Bag Filters	- Low investment costs - Good for chlorinated source water supply	- Not good for unchlorinated source water supply - Frequent replacements required	Monitor pressure drop across filters to ensure operation
Ultrafiltration	- Organic removal depending on the molecular weight cut-off of membrane - Chlorine tolerant - Bacteria reduction	Backwash of membranes	- Backwashes and cleaning sanitizations should be employed and frequency set by procedure - Chlorine dosing should be considered and monitored especially if break tanks are used - Chlorine enhanced backwash
Backwashable Screen Filters	Simple and small footprint	Limited capacity between backwashes	- Typically used for large particulate removal only - Perform sample analysis to identify particle size array prior to installation to avoid excessive backwashing

4.3.2.3 Scale Control

Table 4.4 provides a comparison of scale control methods.

Table 4.4: Comparison of Scale Control Methods

Component	Advantages	Disadvantages	Considerations
Softener	Good with low levels of chlorine	- Large surface area - High bacteria growth on media - Potential addition of organic carbon due to oxidation - High chloride content can be problematic where waste water chloride restrictions are in place	- If there is no residual disinfectant, perform periodic heat (hot water or steam) sanitization ensuring full contact with resin and vessel surfaces - Use series operation for > 1 softener to promote water flow through system and reduce stagnation - Ensure continuous flow through system to reduce stagnation - Salt tanks should not pass light (to reduce algae growth) - Perform disinfection UV downstream for non-chlorinated water to minimize the effect of resulting planktonic bacteria - Backwashing at proper flow rates should be considered as part of control strategy to help dislodge bacteria and remove from the system - Specialty regenerant salt with disinfection agents may be used when infrequently used brine solutions exhibit microbial growth - Operating flow rates should be within specified range to prevent channeling and ensure performance
Antiscalant	- Low surface area for growth - Inexpensive capital investment	- Overdosing may promote growth and result in RO membrane fouling - No feedback control to ensure proper dosing - Proprietary composition sometimes unknown to the end user	Ensure antiscalants are intended for use in drinking water applications and monitored for removal downstream of RO system
Electric/ Electrolytic Scale Control	- Low surface area for growth - Potentially hostile environment for bacteria growth	- Kinetics chemistry of technology is less understood than alternative/ side reaction of free chlorine among others - Limited sources of components - High investment cost	N/A

4.3.2.4 Chlorine and Chloramine Removal

Table 4.5 provides a comparison of chlorine and chloramine removal methods.

Table 4.5: Comparison of Chlorine and Chloramine Removal Methods

Component	Advantages	Disadvantages	Considerations
Carbon Filtration	- Removal of low molecular weight carbon - Tolerant to water supply fluctuations	- Large surface area - High bacteria growth on media - Removal of residual disinfectant - Carbon beds for chloramine removal are much larger due to slower reaction kinetics and require more contact time	- Heat (hot water/steam) sanitization highly recommended - Backwash unit following sanitization - Backwash at proper flow rates as part of control strategy to help dislodge bacteria and remove from the system - Backwash to reset beds and reduce likelihood of channeling and ensure contact time - Perform disinfection UV downstream to reduce planktonic bacteria - Perform scheduled carbon replacement - Operating flow rates should be within specified range to prevent channeling and ensure performance - Use catalytic carbon for chloramine removal
Sodium Metabisulfite (SMBS) (also referred to as bisulfite or sulfite)	Low surface area for growth	- Does not reduce organic carbons in water - Less tolerant to variations in source water and/or chlorine levels - Growth in bulk SMBS preparation tanks - Chloramine reduction requires significantly higher injection - Difficult to monitor and accurately control	- Injection rates should be reliable and respond to changes in chlorine levels and may require frequent calibration - Over injection can increase susceptibility to bacteria growth on RO system - Under injection can result in RO membrane damage that could pass bacteria into the permeate and EDI damage - Perform periodic cleaning of preparation tanks - Establish expiration dates for SMBS solutions due to growth in solution
UV Dechlorination	- Does not have surface area of carbon filter - Disinfection for planktonic bacteria	- High capital and operating costs - Less tolerant to variations in source water and/or chlorine levels - Chloramine reduction requires significantly higher dosage of UV intensity than for disinfection and higher for chloramine than for chlorine - Potential for trace amounts of residual chlorine	- Designed for worst-case scenario, interferences possible with other chemicals/particulates absorbing UV light - Seasonal fluctuations must be considered - Wavelengths and UV intensity need to be specifically designed for chlorine reduction

4.3.2.5 Miscellaneous Functions

Table 4.6 provides a comparison of miscellaneous unit operations.

Table 4.6: Comparison of Miscellaneous Unit Operations

Component	Advantages	Disadvantages	Considerations
UV Disinfection	Reduction of planktonic bacteria	Does not address biofilms	Intensity and lamp status should be monitored
pH Adjustment (caustic and/or acid)	Inexpensive capital investment	Less tolerant to variations in source water CO₂ levels	- Perform periodic cleaning of preparation tanks - Process measurements need to be placed in proper process location and allow for mixing and control loop adjustments - Dosing of acid and caustic may be required if source water is shifted between surface and well supplies
Chlorine Injection	Low costs	By-products (trihalomethanes, chloramines)	- Concentrated chlorine may dissipate over time in storage - Natural ammonia in water may inadvertently form chloramine - Chlorine levels should be considered in conjunction with contact time and pH to be effective - Chlorine should be evenly distributed through the system to ensure contact with wetted surfaces - Injection should be by process feedback (Oxidation Reduction Potential (ORP) or free chlorine)
Pretreated Water Tanks (upstream of RO)	Buffer for pressure/flow fluctuations	Microbial growth in tanks where residual disinfectant is not present	- Requires recirculation for tank turnover, continuous movement - Ensure tank is part of sanitization circuit - Must be capable of being sanitized - Must be drainable
Heat Exchangers (coolers and heaters)	- For cooling of hot water supplies - For heating of cold water supplies	Cost of equipment and utility supplies	- Plate and frame and shell and tube type heat exchangers are acceptable - Select material of construction to minimize leaks

4.3.3 Operations

4.3.3.1 Temperature

The operating temperature of the pretreatment system may affect filtration performance and chemical reaction rates, which affect bacterial growth. Warmer water typically supports bacterial growth more than cooler water. The source water temperature is not typically a parameter that the facility can control, but it should be monitored. If the source water is warm, particularly in warmer climates or during summer months, it may be desirable to cool the source water or increase sanitization frequencies. Conversely, in colder climates or during winter months, it may be necessary to heat the source water or increase operating pressure to maintain system capacity.

4.3.3.2 Sanitization

Residual disinfectants in the source water should be removed as close to the downstream RO membranes as practical so that the disinfectants can be more fully leveraged. Where residual disinfectants are not present, either from an absence in the source water or from removal in subsequent steps, the pretreatment system should be sanitized on a periodic basis. Hot water is typically used for sanitizations; however, a site can also consider steam or chemical sanitization where practical. Sanitization methodology may vary by unit operation based on compatibility (e.g., carbon beds are not typically chemically sanitized). Sanitizations are typically operated between 65–80°C. For some systems, such as carbon media that have a high mass and surface area, it may be advisable to increase the temperature to 80–85°C to achieve sanitization in a timely manner. The facility should have a documented program for routine sanitizations.

See Chapter 8 for microbial control details.

4.3.3.3 Maintenance

Following intrusive maintenance or other extended periods of downtime, a full flush should be performed on the pretreatment system. The flush should include backwashes of all back washable components as well as sanitizations as available.

See Chapter 11 for maintenance details.

5 Generation

5.1 Introduction

5.1.1 Background

WFI generation systems must improve the quality of water meeting local primary drinking water quality requirements to a quality that meets or exceeds the appropriate regulatory WFI monographs for the application. The CQAs include conductivity, TOC, endotoxin, and microbial limit at a minimum and can include additional physicochemical parameters (e.g., nitrates, nitrites, ammonium, etc.).

While distillation with appropriate pretreatment processes has proven capable of reliably producing WFI for decades, alternative processes have been proven to be capable of generating WFI with CQA levels equal or superior to distillation. These alternative systems require appropriate process selection, equipment construction, operation, and maintenance to produce WFI consistently and reliably. Although there are many combinations of unit processes that can be used to produce WFI, most alternative systems incorporate multiple membrane processes in the design. These membrane processes have been proven in pharmaceutical applications and in many other non-pharmaceutical applications where water quality parameters are much stricter than WFI [38, 39, 40, 41]. The materials of construction, sanitization methods, and operation/maintenance practices of these systems often exceed those used in similar process designs to produce PW. Distillation has the advantage of continuous high temperature in the evaporation process which provides superior microbial control. Alternative systems typically operate at ambient temperatures and rely on proper design, construction, sanitization, operation, and maintenance to compensate for non-lethal temperature in production mode.

5.1.2 Pharmacopeial Considerations

There is no single consensus membrane-based WFI production method recommended or allowed, as shown in Table 2.1. Many of the individual pharmacopeia are not explicit about what is required and are not prescriptive as to state the specific methods (e.g., method A+B+C) that must be used to reliably produce WFI. Some require a specific process such as RO or UF along with additional processes, so the process selection may be limited to some degree. All have various versions of language that allow significant end user flexibility to determine what technology is “equivalent to” or “superior to” distillation in the removal of chemical and biological attributes. It is important to clarify that it is the responsibility of the pharmaceutical/biotechnology manufacturers to qualify the membrane-based WFI systems and generate adequate data to prove equivalence or superiority to distillation.

While there is currently no harmonized requirement for redundant membrane barriers (see Table 2.1), the authors of this Guide believe that the combination of two membrane barriers provides the lowest risk for chemical and microbial contamination. The potential combinations as well as the advantages and disadvantages of single versus two membrane barriers are discussed at length in Section 5.4.

5.1.3 Process/Technology Selection and System Design

WFI systems can be configured in many ways with the multitude of pretreatment and final treatment combinations. This chapter provides the following information to assist readers in the selection and design of WFI systems:

- Overview of the individual final treatment process operations, including an understanding of process capabilities, limitations, sanitization options, advantages, and disadvantages (Section 5.3)
 - Additional details regarding specific unit operations can be found in the USP <1231> [2].

- Most common system configurations to reliably produce WFI (Section 5.4)
 - Figures 5.13 and 5.14 are technology maps that show the options for pretreatment and final treatment. Pretreatment tends to be more variable than the final treatment steps used in the most common system configurations and is directly correlated to the physicochemical and microbial properties of the feed water. Additional details regarding pretreatment can be found in Chapter 4 of this Guide and in the *Water and Steam Baseline Guide* [5].
 - Other configurations are possible; the configurations presented are based on the experience of the authors, the commercially available solutions, and the systems that are in current WFI production or previously operated as HPW prior to elimination of this grade of water from Ph. Eur. [1] in 2019.

As with the design of any WFI system, the selection of technology will be driven by many factors including, but not limited, to:

- Ability to meet WFI CQAs
- Capital expense costs
- Operating expense costs
- Total cost of ownership
- Utility availability
- Utility costs
- Spatial requirements and accessibility
- Equipment lead time
- Service availability
- Maintainability
- Feed water conditions
- Staff expertise (e.g., engineering and maintenance)
- Sustainability requirements (e.g., greenhouse gas goals or water conservation targets)
- Familiarity and comfort with the technologies
- WFI usage
- Risk assessment

Process selection and sizing are key steps in system design. The generation system design must accommodate peak end user water consumption demands, so the instantaneous flow rate and storage capacity must be optimized to ensure water availability and cost effectiveness. Equipment redundancy is part of the optimization considerations. The process selection impacts system capital cost but other factors such as surface finishes, instrumentation type and quantity, controls, process sanitization methods, and equipment customization may impact cost more than process selection.

The selection of sanitization methods, materials of construction, instrumentation, controls, and other features impacts cost but can also significantly impact the robustness and reliability of the system. Construction should minimize areas that are conducive to biofilm formation and difficult to properly sanitize. Hot water sanitization at 65–80°C for final treatment and some pretreatment is common. All areas of the system should be able to be sanitized with a minimum of one method and ideally two methods. Replacement of components may be used in areas where sanitization may be impractical.

Flow, pressure, temperature, and conductivity are almost always monitored continuously with online instruments. Online monitoring of TOC at the generation stage is optional. Consideration of rapid detection methods for microbial level and endotoxin is suggested by some bodies such as EMA [21]. Controls can impact performance as automated sanitization procedures are often more likely to be performed regularly. Data acquisition can aid in trending and early problem detection and resolution. See Chapter 11 for additional information.

5.1.4 WFI Quality Attributes

All regulatory pharmacopeias require compliance with limits for conductivity, TOC, endotoxin, and microbial level. These limits drive the selected processes in most cases. Depending on feed water chemical composition, compliance with nitrates and/or ammonium or other physicochemical parameters may impact the unit processes selected to ensure compliance.

Membrane-based systems are generally as reliable, if not better than distillation, in attainment of the chemical CQAs of WFI [38, 39, 40, 41]. WFI system design elements are similar or identical to PW systems regarding attaining chemical quality requirements.

Consistent attainment of the microbial and endotoxin CQAs typically drives the enhanced design aspects of alternative WFI systems. The microbial control reliability of distillation is a result of distillation occurring at a temperature above 100°C rather than perfection of microbial separation during evaporation. It is not currently practical to operate typical alternative systems continuously at self-sanitizing temperatures. Some unit operations such as media filtration, softening, activated carbon filtration, submicron filtration, and UF can be operated continuously at elevated temperatures. Other unit operations such as RO, EDI, and anion exchange resin are either not capable of continuous high temperature operation or suffer performance deterioration. It is not practical to operate parts of the pretreatment and generation systems at high temperatures (65–80°C) while having to cool the water for processing in many other system unit operations. The microbial/endotoxin attainment concerns are primarily based upon possible microbial growth/biofilm formation between unit process sanitization and the effectiveness of the sanitization procedures.

Conductivity attainment is achieved through implementation of RO, nanofiltration, and/or ion exchange technologies. RO and nanofiltration are similar in pretreatment requirements, capital costs, and operating costs but RO provides significantly superior conductivity reduction. Implementation of nanofiltration is rare in WFI production due to these factors. Most membrane-based WFI systems implement RO as the primary process for conductivity attainment. As stated in USP <1231> [2], a single pass of RO rarely produces product water meeting WFI conductivity requirements so further treatment downstream with another RO pass, an ion exchange process, or both is typical for conductivity attainment.

WFI TOC level compliance is achieved in most membrane-based systems with RO. A single RO pass typically reduces TOC to levels well below the compendial 500 ppb limit for almost all feed waters [41]. Additional TOC reduction might be accomplished with pretreatment activated carbon, an additional RO pass, TOC reduction UV light, and EDI.

Endotoxin limit compliance is primarily attained with one or two passes of RO. Most membrane-based WFI systems implement a final UF stage to ensure production of low endotoxin water.

Microbial control is provided by multiple technologies. Systems utilize a combination of microbial reduction processes including UV light, RO, microbial retentive filters, and ultrafilters. Systems should be designed in a manner that limits final filtration requirements to trace removal of microbes and not reduction of high microbial levels (e.g., final filtration being the unit operation getting the system to operate in a state of control). The sanitization methods and components selected for the unit processes impact microbial control significantly and must be sufficiently robust for reliable WFI production.

5.2 Materials and Construction

Selection of appropriate materials is critical to successful system operation. Selection parameters include temperature, pressure, chemical tolerance, cost, availability, and additional factors. Hygienic construction using type 316L stainless steel tubing and valves is implemented in the majority of systems constructed to date (at the time of Guide publication). Non-metallic materials such as PVDF may be used in lieu of stainless steel where suitable for pressure, temperature, and other application considerations.

Material selection is just one factor in component selection. System locations that are higher risk, such as areas with no residual disinfectant, require additional design considerations to minimize areas conducive to biofilm formation and provide resistance to sanitant penetration. Minimization of dead legs is also a design consideration.

Surface finish is typically based upon component location in the system. Components in low risk systems such as chlorinated pretreatment units generally do not have any particular surface finish requirements. Stainless steel components in the high purity section of the system, often the post-membrane and/or low residual chlorine sections, are typically specified with mechanical polish and in some cases electropolishing requirements. Surface finish selection should be consistent with the risk factors identified. Additional details regarding surface finish can be found in the *Water and Steam Baseline Guide* [5]. Unit process components selection is covered in Section 5.3.

Chemical and physical compatibility of the materials of construction of any equipment or component (e.g., tank, filter housing, pump, valve, instrument, pipe, etc.) within the membrane-based WFI system is of paramount importance. Considerations for chemical and physical compatibility include the following:

- If the system will be periodically sanitized using heat, then the equipment or component would need to be compatible with the temperature and duration regularly introduced during the sanitization process.
- Routine exposure of polymeric-based filter elements to heat, chemicals, or ozone can impact life expectancy, so it is important to follow all manufacturers' requirements.
- Regardless of the sanitant used (ozone or chemical), the materials of construction of the equipment or component need to be compatible with the sanitant levels introduced continuously or during the sanitization process.

5.3 Final Treatment Processes

For simplicity and ease of discussion, the membrane-based unit processes presented in this section are in order of decreasing pore size (microfiltration, UF, nanofiltration, and RO) and the remaining processes (ion exchange, EDI, UV treatment, membrane degasification) are described afterwards.

Note: The order of the unit processes presented in this Guide should not be misinterpreted as any suggested sequences. This order should not be used to form the basis for determining the sequence of unit operations for final treatment processes.

5.3.1 Microfiltration (*Absolute Membrane Filtration*)

Microfiltration, or absolute membrane filtration, typically refers to filtration utilizing media with pore sizes ranging from below 1 µm down to 0.02 µm or slightly below and possessing a removal efficiency of at least 99.9% (3-log reduction). In the pharmaceutical industry, microfiltration is commonly used for sterile filtration during aseptic filling operations and bacterial removal in water purification systems. Microfiltration media is available in a variety of materials, and some media is available in hydrophobic or hydrophilic forms (or both) to satisfy different application requirements. Some media may also be charge enhanced to improve performance. Microfilters are available in both hollow fiber and pleated configurations, with pleated forms being the most common. Microfilters utilized in pharmaceutical water systems are typically provided as cartridges but are also available in other forms for other uses. The most common pore sizes utilized in pharmaceutical water systems are 0.2 and 0.1 µm absolute.

Microfilters operate in a dead ended fashion, i.e., retained particles stay on the media and there is no reject stream or waste. Pleated microfilters suitable for pharmaceutical use typically utilize two layers of the same barrier membrane in series for additional robustness and to ensure performance. For pharmaceutical applications, these filters typically are required to remove 99.999% or more of bacteria present in the system (about 100 to 1,000 times the maximum level of contamination expected), but manufacturers tend to generate validation data showing much higher removal ratings. Manufacturers have made great efforts to establish nondestructive means to verify the integrity and thereby the implied performance of their microfilters.

Microfilters are utilized primarily for their bacteria removal capabilities, although some charge modified microfilters may exhibit some endotoxin removal capabilities. Microfilters are generally not rated to remove endotoxins, so additional treatment is required to meet endotoxin requirements. For this reason, microfilters are typically not used as the final barrier in the production of WFI. However, microfilters may be utilized as part of a comprehensive microbial control strategy and may be installed at different locations in a system for microbial control. For additional discussion, refer to Chapter 8.

5.3.2 Ultrafiltration

UF utilizes smaller pore sizes as compared to microfilters. UF is capable of bacteria and endotoxin (cell fragment) removal. UF encompasses a wide range of pore sizes and additional rejection techniques, such as surface charge, to reject a wide range of molecular weight molecules (Molecular Weight Cut-off (MWCO) of 1,000–100,000 Daltons). Higher MWCO filters are used in pretreatment for organic and colloidal removal, while smaller MWCO filters are utilized for final treatment of WFI. The industry generally utilizes membranes with MWCO of ≤ 20,000 Daltons for this purpose when MWCO is specified. Compliance with the JP [3] requires MWCO of ≤ 6,000 Daltons. See Chapter 8 for additional information.

Ultrafilters are available in several different configurations with the most common being spiral wound and hollow fiber. Hollow fiber ultrafilters are available in complete modules with housings (as shown in Figure 5.1) or in basic filter elements for use in stainless steel housings (as shown in Figure 5.2). Most UF membranes are manufactured from polymers, but ceramic UF membranes are also available. Because of their small pore sizes, the vast majority of ultrafilters are tangential flow devices, i.e., they generate a reject or waste stream as they process material. Some ultrafilters are operated as dead ended devices and flushed periodically whereas others have no reject stream at all.

Figure 5.1: Example Hollow Fiber UF Module with Housing

Courtesy of Koch Separation Solutions, www.kochseparation.com.

**Figure 5.2: Example Hollow Fiber UF Filter for Use in Stainless Steel Housing**

Courtesy of Evoqua Water Technologies, www.evoqua.com.



Because of the increased surface area required with ultrafilters, particularly at the finer end of the pore size spectrum, the nondestructive integrity test methods utilized for absolute membrane filters may be ineffective for UF membranes. Consult with manufacturers to determine the correct test method and conditions for the UF membrane for the application.

Ultrafilters for which integrity can be verified by nondestructive means provide an effective bacteria and endotoxin barrier and are commonly utilized as the final purification step in the generation of WFI quality water.

Sanitization methods for the UF system vary depending on the material of the UF membrane:

- If polymeric materials are used, the system should be hot water sanitized (65–80°C)
- If ceramic materials are used, the system should be either ozone sanitized or hot water sanitized

Sanitization of UF modules with heat, ozone, or chemical can reduce the life of the modules. When storage and distribution are included, the sanitization procedure would typically encompass the UF module with the balance of the system. UF modules that are not ozone compatible would have to be isolated from ozone during system ozone sanitization.

5.3.3 Nanofiltration

Nanofiltration utilizes pore sizes finer than UF and is typically considered to be filtration utilizing media with pore size ratings between MWCO of 2,000–3,000 Daltons down to about 300–500 Daltons. Nanofiltration is commonly used in pretreatment to remove hardness minerals that are primarily divalent and trivalent ions. Nanofilters provide limited monovalent ion (e.g., sodium and chloride) removal. Nanofiltration is effective at removing bacteria, endotoxin, and smaller molecular weight contaminants.

Nanofiltration membranes are most commonly cast in sheets and packaged into a spiral wound configuration to integrate as much surface area as possible into a given unit. Nanofilters are tangential flow devices. Nanofilters are typically effective at removing 20–98% of dissolved salts. Salts with monovalent anions (e.g., sodium chloride or calcium chloride) have rejections of 20–80% and salts with divalent anions (e.g., magnesium sulfate) have higher rejections of 90–98%, although there may be variations between manufacturers [42]. Verifying the integrity of nanofiltration membrane systems may be best accomplished by monitoring the changes in conductivity between the feed water and the product water, because conventional methods used on microfilters and ultrafilters are ineffective with nanofilters.

One major challenge faced by nanofilters is that they are subject to the same pretreatment requirements and fouling issues as RO, but their performance is significantly inferior to that of RO. For this reason, RO is the primary technology of choice, and nanofiltration is rarely used as part of a pharmaceutical water system design.

5.3.4 Reverse Osmosis

The next membrane filtration step that is finer than nanofiltration is RO. RO represents the membrane process with the finest pore size ratings and the greatest contaminant removal capabilities. For these reasons, RO is an extremely important unit process that is commonly integrated into most membrane-based WFI generation systems. RO systems are the workhorse of many pharmaceutical water purification systems, providing a consistent and reliable water that requires little additional treatment to meet the requirements for WFI. RO is a particularly valuable process when there are wide seasonal variations in the water quality, which typically occurs when the source water is from a surface water supply or a shallow well.

This section covers several general aspects of RO performance in greater detail. This information is not intended as a design guide, but rather to cover the fundamental concepts of how RO systems perform, what they are capable of, and what their limitations are.

5.3.4.1 Performance Characteristics

Because of its fine pore size, RO is another tangential flow filtration process and the reject stream is used to flush contaminants away continuously by creating turbulent flow along the membrane surface. RO is a process in which water is pumped under pressure through a semipermeable membrane that allows water to pass through but retains the vast majority of other contaminants. Due to its fine pore structure, RO is capable of removing minerals, TOC, bacteria, and endotoxin with high levels of efficiency. Most membranes have an approximate MWCO of 100–200 Daltons and are effective at removing all materials larger than the rated MWCO. Typical RO performance reduces the concentration of ions by 95–99% [42], the TOC levels by 80–95% and the microbial and endotoxin reduction by two to three logs (99–99.9%) [41].

RO is capable of removing the vast majority of the conductivity-based ions required to satisfy the conductivity requirements for WFI. RO is typically capable of removing enough TOC to satisfy the TOC requirements for WFI without the need for further treatment. The endotoxin and microbial removal properties of RO allows production of water that is meeting WFI CQAs or prepares the water for final trace contaminant reduction by UF or other suitable processes.

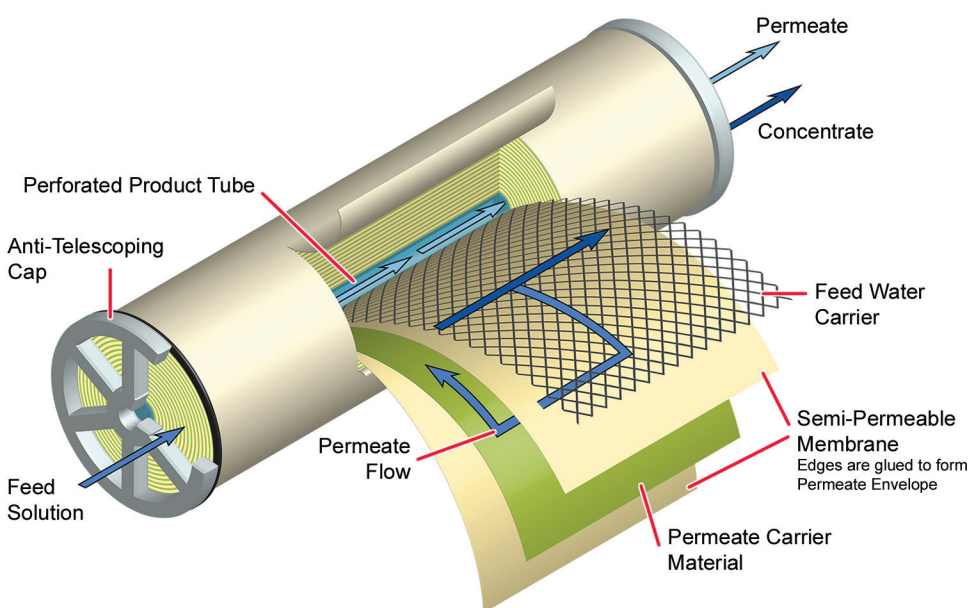
Predictable changes in RO system performance can be attributed to feed water temperature and transmembrane pressure. The changes in contaminant removal efficiency are relatively minor, but the changes in flow rates may be more prominent. This is discussed in greater detail in Chapter 11.

5.3.4.2 Materials and Construction

In pharmaceutical water generation systems, spiral wound polyamide Thin Film Composite (TFC) membrane configurations without a brine seal are utilized. RO membrane construction consists of a polyamide membrane layer applied on top of a polyethersulfone or polysulfone porous layer which is then attached to a non-woven backing support. This three-layer construction is also called a TFC membrane sheet. TFC sheets are then assembled into a spiral wound element or module as shown in Figure 5.3.

Figure 5.3: Example Spiral Wound Membrane Element Design

Courtesy of DuPont Water Solutions, www.dupont.com/water.html.



5.3.4.3 Configuration Design

RO systems are designed differently depending on whether the goal is:

- To maximize the percentage of feed water that is converted into product water,
- To maximize the quality of the water produced by the system, or
- Both

To maximize the percentage of feed water that is converted into product water, RO pressure vessels may be arranged using a reject staged configuration (also called tapered RO array), as shown in Figure 5.4. In this case, reject water from a set of vessels becomes feed water for the next vessels. This may be repeated to minimize the amount of discarded water from the system, but care must be taken to ensure adequate reject flow to prevent fouling of the RO membranes. Most RO arrays convert about 75%–85% of feed water to product water. Recovery or conversion of feed water to product water can exceed 90% when enhanced recovery techniques (e.g., recovery RO array or electrodialysis system) are implemented [42].