



GOOD PRACTICE GUIDE:

Membrane-Based Water for Injection Systems

Pharmacopeia

Reverse Osmosis

Ultrafiltration

Microbial Control

Operating Cost





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Membrane-Based Water for Injection Systems

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ISBN 978-1-946964-56-4

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.

Acknowledgements

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The work was supported by the ISPE Critical Utilities Community of Practice (CoP).

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Special Thanks

The Leads would like to thank ISPE for technical writing and editing support by Nina Wang (ISPE Guidance Documents Technical Editor) and production support by Lynda Goldbach (ISPE Publications Manager).

The Team Leads would also like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

Company affiliations are as of the final draft of the Guide.

Cover photo: courtesy of Endress+Hauser (www.endress.com/en/endress-hauser-group) and BWT (www.btw.com/en).



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Table of Contents

1	Introduction	9
1.1	Background.....	9
1.2	Purpose and Scope	10
1.3	Sustainability.....	10
1.4	Key Concepts.....	11
2	Regulatory Requirements	13
2.1	Introduction	13
2.2	Pharmacopeial Monographs on WFI Quality and Manufacturing Methods.....	13
2.3	Regional Guidelines – European Union.....	15
2.4	Regional Guidelines – US.....	19
2.5	Regional Guidelines – Japan	20
2.6	International Organizations.....	21
3	Risk Considerations	23
3.1	Introduction	23
3.2	Regulatory Concerns	24
3.3	Quality Risk Management.....	24
3.4	Risk Profile.....	25
3.5	Procedural Controls and Personnel Expertise.....	26
3.6	Incoming Source Water Considerations	26
3.7	Process and Equipment Risks	27
3.8	Elastomeric Sealing Materials.....	27
3.9	Risks Specific to the Use of Ambient Storage and Distribution and Ozone.....	28
3.10	Sampling and Monitoring	28
3.11	Setting Appropriate Alert and Action Limits for WFI Systems	29
3.12	Operating Model and Control Strategy	29
4	Pretreatment.....	31
4.1	Introduction	31
4.2	Pretreatment Risks	31
4.3	Pretreatment Controls.....	34
5	Generation.....	41
5.1	Introduction	41
5.2	Materials and Construction	44
5.3	Final Treatment Processes	44
5.4	System Configuration Options	55
6	Storage and Distribution.....	65
6.1	Introduction and Purpose.....	65
6.2	Microbial Control and Water Quality	65
6.3	Design and Operational Considerations	67
6.4	Testing and Risk Control.....	70

7	Process Analytical Technology	73
7.1	Definition	73
7.2	FDA Guidance for Industry.....	73
7.3	European Pharmacopoeia Chapter 5.25	74
7.4	Online and Off-line Sampling	74
7.5	Statistical Applications Usage	74
7.6	Process Control Monitoring and Real-time Release	75
7.7	Process Knowledge and Control.....	75
8	Microbiological Considerations	77
8.1	Introduction	77
8.2	Pretreatment System Microbial Control	78
8.3	Primary Purification System Microbial and Endotoxin Control.....	81
8.4	Storage and Distribution System Microbial and Endotoxin Control	87
8.5	Water System Attribute Monitoring	97
8.6	Contamination Control Strategy.....	102
9	Commissioning and Qualification.....	105
9.1	Introduction	105
9.2	User Requirements Specification.....	105
9.3	Risk Assessment.....	105
9.4	C&Q Plan	106
9.5	Design Review and Design Qualification	106
9.6	Special Considerations for Commissioning	107
9.7	Qualification Documents	107
9.8	Special Considerations for Installation and Operational Qualification	107
9.9	Special Consideration for Performance Qualification	108
9.10	Summary Report.....	109
9.11	Change Control.....	109
9.12	Retrofits.....	110
9.13	Periodic Review/Requalification.....	110
10	Comparing Costs of Alternative Technologies	111
10.1	Introduction	111
10.2	Lifecycle Cost/Total Cost of Ownership	111
10.3	Cost Accounting Basics	112
10.4	Incremental Additional Costs for Support Utilities	114
10.5	System and Major Component Life Expectancy	115
10.6	System Utilization	117
11	Operation and Maintenance	119
11.1	Introduction	119
11.2	Water Purification Unit Processes	120
11.3	System-wide Operational and Maintenance Strategies and Approaches	133

12 Appendix 1 – Summary of Pharmacopeial Requirements	137
13 Appendix 2 – Process and Equipment Risks	141
13.1 Scale Control	141
13.2 Chlorine/Chloramine Removal	142
13.3 Reverse Osmosis.....	144
13.4 Electrodeionization.....	145
13.5 Ultrafiltration.....	146
13.6 Ozone Systems.....	148
14 Appendix 3 – Contamination Control Strategy Outline	151
15 Appendix 4 – Ozone Off-gassing and Worker Safety	155
16 Appendix 5 – Safety of Airborne Ozone Release During Outlet Flushing	157
17 Appendix 6 – Cost Analysis Case Study	159
17.1 Summary.....	159
17.2 Cost Inputs.....	160
17.3 System Configurations (Process Flow Diagrams)	165
17.4 Scenarios	167
17.5 Results and Analysis.....	168
18 Appendix 7 – Verifying the Intactness of Ultrafilters	171
18.1 Intactness Testing	172
18.2 Calculating the Ultrafilter Rejection Rate	172
19 Appendix 8 – References	175
20 Appendix 9 – Glossary.....	179
20.1 Acronyms and Abbreviations	179
20.2 Definitions	183

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.