

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