

# Table of Contents

<b>1</b>	<b>Introduction .....</b>	<b>9</b>
1.1	Background.....	9
1.2	Scope of this Guide.....	9
1.3	Key Topics Included in this Guide .....	10
1.4	Guide Structure.....	12
<b>2</b>	<b>Key Design Philosophies .....</b>	<b>15</b>
2.1	Introduction .....	15
2.2	Pharmacopeial Water and Steam .....	16
2.3	Specification of Pharmaceutical Water Quality – Establishing Acceptance Criteria .....	17
2.4	Critical Quality Attributes and Critical Process Parameters .....	18
2.5	GMP Compliance Issues .....	18
2.6	Design Range versus Operating Range .....	18
2.7	Process Analytical Technology.....	19
<b>3</b>	<b>Water Options and System Planning.....</b>	<b>21</b>
3.1	Introduction .....	21
3.2	Incoming or Source Water Characteristics .....	21
3.3	Water Quality Options .....	22
3.4	System Planning .....	29
3.5	System Design.....	35
<b>4</b>	<b>Pretreatment Options.....</b>	<b>37</b>
4.1	Introduction .....	37
4.2	Process Design of Pretreatment .....	38
4.3	Feed Water and Pretreatment Testing .....	40
4.4	Pretreatment Unit Operations .....	41
4.5	Control of Fouling: Removal of Turbidity and Particulates .....	44
4.6	Control of Scaling: Removal of Hardness and Metals .....	47
4.7	Control of Dissolved Gases – Contact Membrane Degasification .....	50
4.8	Organic Material and Removal .....	50
4.9	System Design for Control of Microbial Growth.....	53
4.10	Removal of Microbial-Control Agents.....	56
4.11	Changes in Anion Composition/Concentration .....	59
4.12	Materials of Construction and Construction Practices .....	61
4.13	Water Conservation .....	62
<b>5</b>	<b>Final Treatment Options for Production of Compendial Purified Water, Compendial Water for Injection, and Non-Compendial Waters .....</b>	<b>63</b>
5.1	Introduction .....	63
5.2	Ion Exchange .....	64
5.3	Reverse Osmosis.....	68
5.4	Distillation.....	75
5.5	Polishing and Removal of Specific Contaminants .....	85
5.6	Continuous Electrodeionization .....	89

<b>6</b>	<b>Systems for Production of Compendial Purified Water, Water for Injection, and Non-Compendial Water.....</b>	<b>93</b>
6.1	Introduction .....	93
6.2	Purified Water .....	94
6.3	Water for Injection .....	96
6.4	Non-Compendial Waters.....	99
<b>7</b>	<b>Pharmaceutical Steam.....</b>	<b>101</b>
7.1	Introduction .....	101
7.2	Common Steam Terms and Definitions .....	101
7.3	Types of Pharmaceutical Steam .....	102
7.4	Regulatory and Industry Guidance .....	103
7.5	Background and Industry Practices .....	104
7.6	System Planning .....	105
7.7	Steam Generation .....	108
7.8	Steam Attributes and Condensate Sampling .....	110
7.9	Materials of Construction .....	112
7.10	Distribution .....	112
<b>8</b>	<b>Storage and Distribution Systems .....</b>	<b>115</b>
8.1	Introduction .....	115
8.2	Purpose.....	115
8.3	System Components.....	115
8.4	Materials of Construction/Finishes.....	130
8.5	Microbial-Control Considerations.....	136
8.6	System Designs.....	138
8.7	Sampling at Point of Use and Dedicated Sample Valves .....	154
<b>9</b>	<b>Laboratory Water.....</b>	<b>155</b>
9.1	Introduction .....	155
9.2	System Design Considerations.....	155
9.3	Determining User Needs.....	156
9.4	Water Purification Technologies.....	168
9.5	Laboratory Water Supply Options .....	170
9.6	Maintenance .....	180
9.7	Instruments and Calibration .....	180
9.8	Commissioning and Qualification.....	180
<b>10</b>	<b>Rouge and Stainless Steel.....</b>	<b>183</b>
10.1	Introduction .....	183
10.2	Regulatory Stance .....	184
10.3	Surface Conditions and Treatments.....	186
10.4	Rouge Formation .....	188
10.5	Rouge Detection (Methodology) .....	193
10.6	Risk Analysis – Rouge and Its Remediation .....	194
10.7	Rouge Remediation (Methodology) .....	197
10.8	Conclusions .....	198

<b>11 Control and Instrumentation .....</b>	<b>199</b>
11.1 Introduction .....	199
11.2 Principles and Purpose of Measurements and Instrumentation .....	200
11.3 General Instrumentation Requirements .....	201
11.4 Design Conditions versus Operating Range .....	211
11.5 Responses to Measurements .....	211
11.6 Control Systems .....	212
<b>12 Commissioning and Qualification .....</b>	<b>215</b>
12.1 Introduction .....	215
12.2 Sampling for Water and Steam Systems .....	217
12.3 Acceptance Criteria .....	218
12.4 Change Control and Maintaining the Qualified State of the System .....	219
<b>13 Microbiological Considerations for Pharmaceutical Water Systems .....</b>	<b>221</b>
13.1 Introduction .....	221
13.2 The Microbial Growth Process in High Purity Water Systems .....	221
13.3 Detrimental Effects of Biofilm .....	225
13.4 Microbial and Biofilm Control Strategies .....	227
13.5 Sanitizer Choices .....	233
13.6 Assessing Microbial-Control Success .....	249
13.7 Functional Microbiological Pharmacopeial Compliance .....	251
13.8 Microbial and Endotoxin Control in Pure Steam Systems .....	253
<b>14 Appendix 1 – References .....</b>	<b>255</b>
<b>15 Appendix 2 – Glossary .....</b>	<b>261</b>
15.1 Acronyms and Abbreviations .....	261
15.2 Definitions .....	266