

Table of Contents

1	Introduction	7
1.1	Overview	7
1.2	Purpose.....	7
1.3	Scope.....	8
1.4	Key Terms	8
2	Critical Utilities Viewed from a Regulatory Perspective.....	11
2.1	Drinking/Potable Water	11
2.2	Compendial Water Pretreatment	14
2.3	Purified Water	14
2.4	Water for Injection.....	15
2.5	Pure Steam.....	15
2.6	Clean Compressed Air.....	16
2.7	Process Gases.....	17
3	Validation Lifecycle and Quality Systems	21
3.1	Validation	21
3.2	Change Control.....	24
3.3	Risk Management.....	25
3.4	Drawings and Documentation.....	27
3.5	Investigations and Corrective Actions and Preventive Actions	32
3.6	Sampling and Testing.....	36
4	Ongoing Operations	39
4.1	Data Integrity, Handling, and Automation.....	39
4.2	Sanitization and Microbial Control In Pharmaceutical Water Systems	43
4.3	Maintenance	47
4.4	Hoses.....	49
4.5	Routine System Reviews.....	50
4.6	Calibration.....	52
4.7	Training	54
5	Legacy Water Systems	57
5.1	Sources of Legacy Systems	57
5.2	Types of Deficiencies and What Can Be Done	57
5.3	Regulatory Impact of Legacy Systems	60
6	Appendix 1 – Typical Regulatory Citations/Warning Letters	61
6.1	Letter 1 – Failure to Validate and Monitor the Water Purification System.....	61
6.2	Letter 2 – Failure to Test Water Used in Drug Product Manufacture	62
6.3	Letter 3 – Inadequate Purified Water System Controls.....	62
6.4	Letter 4 – Water System Failures	63
6.5	Letter 5 – Inadequate Investigations.....	64
6.6	Letter 6 – Failure to Validate and Monitor the Water Purification System	65
6.7	Letter 7 – Failure to Validate Purified Water System	66
6.8	Letter 8 – Data Integrity Failures.....	67
6.9	Letter 9 – Lack of or Insufficient Investigation of Water System Failures	68

7 Appendix 2 – Inspection Hosting Good Practices and Readiness Checklist.....	69
7.1 Inspection Hosting and Behaviors	69
7.2 Opportunities for Improvement	70
7.3 Inspection Readiness Checklist.....	72
8 Appendix 3 – Sampling Practice and Planning Supplemental Information	75
8.1 Testing SOP and Test Materials Preparation	75
8.2 Examples of Good and Poor Water Sampling and Water Use Practices.....	75
8.3 Microbial Discrepancies Caused by Poor Sampling Methods	76
8.4 Sampling Plan.....	77
9 Appendix 4 – Compendial Water Specifications	79
10 Appendix 5 – Microbial Enumeration: Consideration of Nutrient Media, Incubation Temperature, and Incubation Time	85
10.1 Growth Medium Choice	85
10.2 Incubation Conditions (Temperature and Duration)	86
11 Appendix 6 – References	87
12 Appendix 7 – Glossary.....	93
12.1 Acronyms and Abbreviations	93
12.2 Definitions	95