

Table of Contents

1	Introduction	9
1.1	Background.....	9
1.2	Purpose.....	9
1.3	Scope.....	10
1.4	Rationale for the Second Edition	10
2	Use of Ozone in the Pharmaceutical Industry	11
2.1	Introduction	11
2.2	Background.....	11
2.3	Overview of Ozone Use – Advantages and Disadvantages	12
3	Regulatory and Industry Guidance.....	15
3.1	Introduction	15
3.2	United States Pharmacopeia (USP)	15
3.3	United States Food and Drug Administration (FDA)	17
3.4	European Regulations	18
3.5	World Health Organization (WHO).....	20
3.6	International Society for Pharmaceutical Engineering (ISPE).....	20
4	Ozone Characteristics	21
4.1	Introduction and Properties.....	21
4.2	Ozone Generation and Introduction.....	22
4.3	Ozone Reactivity.....	25
4.4	Ozone Destruction	26
4.5	Ozone Detection and “Added Substances” Considerations.....	26
5	Effectiveness of Ozone for Microbial Control.....	27
5.1	Introduction	27
5.2	Ozone Use in Pharmaceutical Water Systems	27
5.3	Mechanisms and Targets of Ozone Attack.....	27
5.4	Factors Affecting Ozone Efficacy	28
5.5	Ozone Sanitization Strategies.....	29
5.6	Ozonated System Microbial Sampling.....	32
5.7	Determining Ozone Sanitization Efficacy and Frequency.....	33
5.8	Summary Elements of Optimal Microbiological Control Using Ozone.....	35
6	Ozone Generation	37
6.1	Introduction	37
6.2	General Considerations	37
6.3	Electrolytic Ozone Generation	37
6.4	Corona Discharge Ozone Generation.....	41
6.5	Ozone Generator Sizing	46
7	Ozone Sensors.....	49
7.1	Introduction	49
7.2	Polarographic Sensors.....	49
7.3	UV Photometers.....	50
7.4	Ozone Sensor Properties and Related Term Definitions	52
7.5	Calibration.....	53
7.6	Sensor Verification	57
7.7	Servicing	57

8	UV Light for Ozone Destruction	59
8.1	Introduction	59
8.2	Electromagnetic Spectrum.....	60
8.3	Mercury Arc Lamps	61
8.4	Conventional Low-Pressure Lamps	61
8.5	Low-Pressure High Output (Amalgam) Lamps	62
8.6	Medium-Pressure HG Arc Lamps	62
8.7	Ozone Absorbance of UV Light.....	63
8.8	UV Dose.....	64
8.9	Sizing of UV System for Ozone Destruction	65
8.10	UV Intensity Monitors.....	67
8.11	UV Lamp Aging.....	67
8.12	Equipment Maintenance, Safety and Parts Replacement	69
8.13	UV and Water Temperature	71
8.14	Frequency of Lamp On/Off (Cycling) and Power Fluctuations.....	71
8.15	Flow and Pressure Related Concerns	72
8.16	UV Selection Process	72
9	System Design	73
9.1	Introduction	73
9.2	Ozone Introduction.....	73
9.3	Vent Filter and Gas Blanketing Considerations	79
9.4	Vent Gas Destruction	83
9.5	Water Temperature Control.....	83
9.6	Ozone Sensor Location and Configuration	84
9.7	UV Unit Location and Configuration.....	84
9.8	Materials of Construction	85
9.9	Feed Gas Purity and Control	85
9.10	Safety.....	85
9.11	Additional Design References.....	87
9.12	Retrofitting Water Systems with Ozone Sanitization Capability.....	88
10	System Operation and Control.....	93
10.1	Introduction	93
10.2	Ozone Dispensing Options	93
10.3	Storage Tank Dissolved Ozone Levels	94
10.4	UV Operation for Ozone Destruction	95
10.5	Dissolved Ozone Monitoring and Verification of Removal	95
10.6	Distribution Loop Sanitization and Frequency	96
10.7	System Shock Sanitization Capability.....	98
10.8	Conductivity Monitoring.....	99
10.9	TOC Monitoring.....	99
10.10	Point of Use Sampling and Maintenance for Microbiological Control	100
10.11	Safety.....	100
10.12	Ozone Related Process Parameter Summary.....	103
10.13	Rouge	103
10.14	Deviations	104

11 Commissioning and Qualification.....	105
11.1 Introduction	105
11.2 Design Requirements	106
11.3 Commissioning and Qualification Verification	108
11.4 Installation Qualification/Verification	109
11.5 Operational Verification/Operational Qualification	109
11.6 Performance Qualification.....	110
12 Ozone and Heat Sanitization Comparison	113
12.1 Introduction	113
12.2 Importance of Considering All User Requirements	114
12.3 Heat Versus Ozone Sanitization Considerations	114
12.4 Comparison of Heat Versus Ozone Sanitization Configurations.....	115
12.5 Lifecycle Cost Development	116
13 Ozone and Chemical Sanitization Comparison	119
13.1 Introduction	119
13.2 Comparing Ozone to Other Sanitization Approaches	119
13.3 Justification for Considering Changes in Sanitization Approaches.....	119
13.4 Common Challenges of All Chemical Sanitants.....	120
13.5 Comparison of Conventional Chemical and Ozone Sanitization Approaches	120
14 Appendix 1 – Estimating a Lower LOD for Sensors Using System Specific Data	125
15 Appendix 2 – Ozone Off-Gassing During Flushing of Points of Use and Impact on Worker Safety	129
15.1 Worker Exposure Limits.....	130
16 Appendix 3 – Safety of Airborne Ozone Release During Outlet Flushing	133
17 Appendix 4 – References	137
18 Appendix 5 – Glossary	141
18.1 Acronyms and Abbreviations	141
18.2 Definitions	143