
CONTENTS

I	Essential Background Microbiology	I
	What Microorganisms Are	2
	Types of Microorganism	4
	Moulds (Fungi)	6
	Yeasts	8
	Bacteria	10
	Detailed Infrastructure of Bacteria	14
	Bacterial Nomenclature	16
	The Gram Reaction	18
	Cultivation of Bacteria	22
	Pure and Mixed Cultures	24
	The Bacterial Growth Curve	26
	Microbial Ecology	28
	Aerobes and Anaerobes	30
	Microorganisms in Nature	32
	Microorganisms and Pharmaceutical Products	34
	Some Microorganisms Mentioned in this Chapter	36
2	Contamination Control	39
	Principles of Contamination Control	40
	Major Sources of Contamination	42
	Controlling Air as a Source of Contamination	44
	Controlling Materials as a Source of Contamination	46
	Controlling Personnel as a Source of Contamination	48
	Controlling Services as a Source of Contamination	50

	Specific Contamination Control Technologies	54
	HEPA Filtration	56
	Air-Flow Protection — Air Cascades	58
	Air-Flow Protection — Air Movement (Turbulence)	60
	Air-Flow Protection — Localised Unidirectional Protection	62
	Closed (“Hard-Piped”) Manufacturing Systems	64
	Isolation and Restricted Access Technologies	66
	Some Microorganisms Mentioned in this Chapter	68
3	Microbiological Quality Control	69
	Principles	70
	Sampling	72
	Sampling — The Test for Sterility	74
	Sampling — Microbial Limits Tests	76
	Conducting the Test for Sterility	78
	Validating the Test for Sterility	80
	Conducting Microbial Limits Tests	82
	Microbial Limits Tests — Conducting and Validating TVCs by Membrane Filtration	84
	Microbial Limits Tests — Conducting TVCs by Plate Count Methods	86
	Microbial Limits Tests — Validating TVCs by Plate Count Methods	88
	Microbial Limits Tests — Conducting Tests for Selected Microorganisms	90
	Microbial Limits Tests — Validating Tests for Selected Microorganisms	92
	Microbial Limits Tests — Objectionable Microorganisms	94
	Out-of-Specification Results — Test for Sterility	96
	Out-of-Specification Results — Microbial Limits Tests	98
	Some Microorganisms mentioned in this Chapter	100
4	Water Microbiology	101
	Microorganisms in Natural Waters	102
	How Microorganisms Have Evolved to Live in Water	104
	Formation and Control of Biofilm	106
	Microbiological Limits Applying to Pharmacopoeial Grade Waters	108
	Pharmacopoeial Requirements Applying to Testing Water for Compliance With Microbiological Limits	110
	Pharmaceutical Water Systems	112
	Microbiology of Water Pre-Treatment Processes	114

Microbiology of Pharmaceutical Water Preparation Processes	116
Deionisation	118
Reverse Osmosis (RO)	120
Microbiology of Water Storage and Distribution Systems	122
Primary Design of Water Storage Systems for Microbiological Control	124
Primary Design of Water Distribution Systems for Microbiological Control	126
Sanitisation of Water Storage and Distribution Systems	128
Microbiological Sampling and Monitoring of Pharmacopoeial Water Systems — Routine	130
Microbiological Sampling and Monitoring of Pharmacopoeial Water Systems — Validation	132
Some Microorganisms Mentioned in this Chapter	134
5 Manufacture of Sterile Products	135
Definitions and Essential Background Information	136
Sterile Products and Presentations	138
Container-Closure Integrity	140
Aseptic Processing and Terminal Sterilisation	142
Terminal Sterilisation	144
Aseptic Processing: Principles	146
Clean Rooms: Limits on Particle Concentrations in Air	148
Classification of Clean Rooms to IS 14644	150
Clean Rooms: Microbiological Limits (Air)	152
Clean Rooms: Microbiological Limits (Surfaces)	154
Clean Rooms: Grades A and B	156
Clean Rooms: Grades C and D	158
Interfaces between Clean Rooms: Air Locks	160
6 Sterilisation and Depyrogenation	163
Killing (Inactivating) Microorganisms	164
Kinetics of Inactivation of Populations of Microorganisms	166
Semi-Logarithmic Inactivation and Sterility Assurance	168
Resistance of Microorganisms to Sterilisation Treatments	170
Measures of Resistance to Sterilisation Treatments (D-Values)	172
The Choice Among Sterilisation Processes	174
Steam Sterilisation in Autoclaves: The Cycle	176
Steam Sterilisation in Autoclaves: Porous Load Cycles	178
Steam Sterilisation in Autoclaves: Fluid Load Cycles	182
Sterilisation-in-Place (SIP)	184
Steam Sterilisation: Validation	186

	Steam Sterilisation: F_0 Concept	188
	Scientific Basis of F_0	190
	Steam Sterilisation: Parametric Release	192
	Dry Heat Sterilisation/Depyrogenation in Ovens and Tunnels	194
	Sterilisation by Gamma Radiation	196
	Sterilisation by Ethylene Oxide	198
	Sterilisation by Filtration	202
	Some Microorganisms Mentioned in this Chapter	204
7	Disinfectants	205
	Disinfectants	206
	Use of Disinfectants	208
	Preparation of Disinfectants	210
	Rotation of Disinfectants	212
	Validation of Disinfectants	214
	Practicalities of Disinfection	216
8	Endotoxins and the LAL Test	219
	Pyrogens	220
	The LAL Reaction	222
	Endotoxin Limits	224
	The LAL Test by the Gel Clot Method	226
	The LAL Test by Other Methods	228
9	Simulation (Media Fills)	231
	The Purpose of Simulation	232
	The Study Design	234
	Placebos and Media	236
	Media — Growth Support	238
	Simulation — Numbers of Units and Duration of Runs	240
	Validation of Maintenance of Asepsis over Time	242
	Personnel Involvement in Simulation	244
	Anti-Microbial Stages in Aseptic Processes	246
	Incubation	248
	Validation Media Fills	250
	Routine Media Fills	252
	Some Microorganisms Mentioned in this Chapter	254
10	Preservative Efficacy	255
	Inclusion of Preservatives in Pharmaceutical Products	256
	Anti-Microbial Effectiveness Testing	258
	Some Microorganisms Mentioned in this Chapter	260

11	Modern Methods	261
	Microbiological Technique	262
	Counting Numbers of Microorganisms	264
	Identifying Microorganisms by Biochemical Tests	266
	Identifying Microorganisms by Complex Methodology	268
12	Microbiological Assay	271
	Zones of Inhibition	272
	Variables	274
	Small Plate and Large Plate Assays	276
	Slope, Parallelism, and Linearity	278
	Fiducial Limits	280
	Three-point and Two-point Microbiological Assays	282
	Appendix <i>Bruce Vernon</i>	285
	Introduction to Biological Medicinal Products	286
	Immunity and Vaccines	288
	Recombinant DNA (rDNA) Products	290
	Other Methods of Manufacture and Control of Biological Medicinal Products	292
	Microbiological Risks in Regard to Biological Medicinal Products	294
	About the Authors	297
	Index	301

