

Table of Contents

1	Introduction	9
1.1	Background.....	9
1.2	Purpose.....	9
1.3	Scope.....	10
1.4	Key Concepts.....	11
1.5	Structure	12
2	Regulatory Considerations for Biopharmaceutical Process Development and Manufacturing.....	13
2.1	Introduction	13
2.2	Regulatory Organizations	14
2.3	Specific GMP Regulatory Requirements for Non-US Markets and Non-US Manufacturing Locations.....	18
2.4	Relationship to ICH Guidance Documents	23
2.5	Regulatory Considerations Across the Product Life Cycle.....	23
2.6	Differences Between the EU and FDA Approaches to Risk.....	27
3	Biopharmaceutical Processes, General	29
3.1	Introduction	29
3.2	Stages of Biopharmaceutical Product Development.....	31
3.3	Overview of the Regulatory Implications of Quality by Design and Quality Risk Management	39
3.4	Stability	43
4	Upstream Unit Operations	45
4.1	Cell Line Development.....	45
4.2	Cell Bank Preparation, Validation, and Maintenance.....	49
4.3	Fermentation and Cell Culture.....	52
4.4	Media Systems	57
4.5	Clarification and Recovery.....	58
5	Downstream Processing Unit Operations	63
5.1	Overview of Downstream Processing	63
5.2	Filtration in Downstream Processing	66
5.3	Chromatography Operations.....	70
5.4	Viral Clearance	71
5.5	Biopharmaceutical and Vaccine Conjugation.....	76
5.6	Bulk Formulation and Filling.....	77
5.7	Buffer Preparation and Storage	79
5.8	Special Topics	80
6	Scale-Up and Technology Transfer	87
6.1	Introduction	87
6.2	Scale-Up General Considerations	87
6.3	Upstream Scale-Up.....	88
6.4	Primary Recovery	90
6.5	Chromatography	91
6.6	Ultrafiltration/Diafiltration (UF/DF).....	91
6.7	Technology Transfer.....	92

7	Process Support and Utility Systems	103
7.1	Introduction	103
7.2	Regulatory Guidance	103
7.3	Materials of Construction	104
7.4	System Layout and Routing.....	106
7.5	Specific Service Considerations	106
7.6	Pharmaceutical Water.....	106
7.7	Pharmaceutical Steam.....	110
7.8	Equipment Cleaning.....	110
7.9	Process and Utility Gases.....	113
7.10	Process Temperature Control Systems	113
7.11	Cryogenics and Process Cooling.....	114
7.12	Process Bio-Waste Handling	114
7.13	Drains and Waste Collection.....	115
7.14	Potable Water Systems	115
7.15	Vacuum Systems	115
7.16	Electrical Services.....	116
8	Process Impact on Facilities	117
8.1	Introduction	117
8.2	Process Considerations.....	117
8.3	Application of Risk Assessment to Facility Design.....	124
8.4	Impact of Operational Philosophy and Process Definition on Facility Design.....	124
8.5	The Impact of Closed System Process Design on Facility Design	129
8.6	Automation and Control Philosophy Impacts on Facility Design.....	129
8.7	Pilot Plant Items for Consideration.....	130
9	Appendix 1 – Non-US Manufacturing and Non-FDA Regulated Market Requirements.....	135
9.1	Introduction	136
9.2	Occupational Health and Safety Regulatory Organizations and Standards	136
9.3	Environmental Regulatory Organizations and Standards	139
9.4	Specific GMP Regulatory Requirements for Non-US Markets and Non-US Manufacturing Locations....	140
9.5	Residual DNA.....	143
9.6	Drug Development and Clinical Trials.....	144
9.7	Specific Safety Requirements for Non-US Manufacturing Locations.....	145
9.8	Environmental Aspects Specifically Related to Biopharmaceutical Processing.....	145
9.9	Particular Engineering Items Affecting Bio-Equipment and Process Systems Design	145
9.10	General Commentary on Specific Environmental Health and Safety Issues	146
10	Appendix 2 – Equations	149
10.1	Growth Curve Equation for Batch Fermentations	150
10.2	Design Equations for a Fermentation System	153
11	Appendix 3 – Detailed Information.....	155
11.1	Bacterial and Mammalian Cell Types.....	156
11.2	Stirred Tank Reactor Scale-Up	156
11.3	Cell Disruption.....	161
11.4	Homogenization	162
11.5	Centrifugation.....	166
11.6	Filtration	171
11.7	Chromatography Operations.....	184

12	Appendix 4 – References	197
13	Appendix 5 – Glossary	207
	13.1 Acronyms and Abbreviations	208
	13.2 Definitions	214

