Drugmakers' Guide to Global Quality API Manufacturing

Table of Contents

About the Authors **5**

Introduction **7**

Differences Between API Manufacturing and Drug Manufacturing **9**

How Regulators Define Active Substances **15**

Global Active Substance Regulations **19**

- ICH Q7: GMP for Active Substances 19
- ICH Q11: Development of Drug Substances 19
- PIC/S Guidelines 20
- APIC Guidelines 20
- WHO Guidelines 21
- U.S. Regulations 21
- European Regulations 22

Global Biotech Active Substance Regulations **23**

- PIC/S Guidelines 24
- WHO Guidelines 24
- U.S. Regulations 24
- European Regulations 25

Compulsory Registration of Active Substances **29**

Required Authorizations **31**

- Import Authorization 31
- Written Confirmation for EU Imports 32
- Release for Distribution 35
- Official Supervision 35

Marketing Authorization Documentation for Active Substances **37**

- EDMF/ASMF 38
- CEP 39
- Additional EDMF/ASMF and CEP Details 39

GMP Certificates **41**

- EU GMP Certificate 41
- PIC/S and WHO GMP Certificates 42
- Other GMP Certificates 42

Auditing Active Substance Manufacturers **43**
Europe or Third Countries (Such as China or India) 43
Audits 46
Preparing for an Audit 46
Conducting the Audit 47
Audit Findings 49
Third-party Audits 51
Requirements for Third-party Audits 51
Audit Checklists 52
Chemical Active Substances **55**
Definition of Terms 55
Scope of GMP Regulations 57
Special Risks 62
Impurities: Genotoxic or Potentially Genotoxic Substances 64
Impurities: Residual Solvents 66
Class 1 Solvents in Active Substance Starting Materials 67
Class 1 Solvents as Contaminant in Other Solvents 67
Impurities: Heavy Metals or Residues from Metal Catalysts or Reactants 68
Other Impurities 70
Typical GMP Deficiencies in Chemical Active Substance Manufacturing 71
Quality Management 71
Buildings and Facilities 72
Process Equipment 72
Documentation and Records 73
Materials Management 73
Packaging and Identification Labeling of APIs and Intermediates 73
Laboratory Controls 73
Validation 73
Biotech Active Substances **75**
Types of Biotech Active Substances 75
Definition of Biotech Terms 76
Scope of Biotech GMP Regulations 80
Special Biotech Risks 83
Basic GMP Regulations for Biotech Active Substances 84
Personnel 84
Premises and Equipment 86

Containment 86
Environmental Monitoring 87
Dedicated/Multiproduct Facility 88
Ventilation Technology 89
Machines and Equipment 90
Cleaning and Facility Hygiene 90
Documentation 91
Production and Control Strategy 92
Starting and Raw Materials 92
Seed Culture and Cell Bank System 95
Cell Bank System Characterization 96
Working Principles and Production 97
Deviations 97
Contamination 98
Fermentation 98
Harvest, Isolation and Purification 100
Viral Inactivation and Removal 101
Cleaning Validation 102
Quality Control 102
Characterization 102
In-process Controls 103
Other Aspects 104
Animals 104
Specific GMP Regulations for Biotech Active Substances 107
Allergenic Products 107
Immunosera of Animal Origin 108
Vaccines 108
Recombinant Products 109
Monoclonal Antibodies 109
Transgenic Plant Products 110
Gene Therapy Drugs 111
Somatic and Xenogeneic Cell Therapy Drugs and Tissue-engineered Products 113
Appendices *(can be found on the CD in the back of this report)*