

CONTENTS

<i>Foreword</i>	(v)
<i>Preface</i>	(vii)

CHAPTER 1

GMP Regulations for Pharmaceutical Industry

1.1 Basic Requirements of GMP	1
1.2 Organization Pillars in cGMP.....	2
a. Management Responsibilities	2
b. Resources.....	2
c. Manufacturing Operations	2
d. Evaluation Activities	2
1.3 Six Quality System in GMP.....	3
A. Pharmaceutical Quality Management System.....	3
B. Production Management System.....	3
a. Technical Measures	4
b. Organizational Measures.....	5
C. Facilities and Equipment Management System.....	6
D. Laboratory Controls Management System.....	6
E. Materials Management System.....	7
F. Packaging and Labelling Management System.....	7
1.4 Quality Culture and Pharmaceutical Industry	9

CHAPTER 2

Good Laboratory Practices in Pharmaceutical Industry

2.1 Good Laboratory Practice Equipment.....	11
2.2 Documentation in Good Laboratory Practice	12

2.3 Sampling in Good Laboratory Practice.....	12
A. Approaches for sampling plans will be discussed for	13
2.4 Testing in Good Laboratory Practice.....	13
2.5 Laboratory Reagents, Solutions, Reference Standards and Culture Media in Good Laboratory Practice	14
2.6 Glassware in Good Laboratory Practice	15
2.7 On-going stability programme in Good Laboratory Practice	15
2.8 Technical Transfer of Testing Methods in Good Laboratory Practice	16
2.9 Measures in Good Laboratory Practice.....	16

CHAPTER 3

Good Microbiology Practice in Pharmaceutical Industry

3.1 Premises, Layout and Zone	18
3.2 Laboratory Environmental Monitoring	19
3.3 Laboratory Equipment	19
3.4 Personnel	20
3.5 Media and Preparation.....	20
A. Media procurement and Storage	20
B. Media Preparation	20
C. Media Incubation Time	21
3.6 Reference Culture.....	22
3.7 Sampling.....	22
3.8 Laboratory Testing.....	23
3.9 Disposal of Contaminated Waste.....	23
3.10 Laboratory Data Management	24

CHAPTER 4

Good Aseptic Practices in Pharmaceutical Industry

4.1 The Industry's Approach to Validation of Aseptic Manufacturing	25
4.2 Cleanroom Classification	26
4.3 Environmental Monitoring	26

4.4 Methods of Microbiological Monitoring.....	26
4.5 Microbial Identification.....	26
4.6 Identification of Isolates	27
4.7 Essential Elements of the Environmental Control and Facility Management Program.....	27
4.8 Training for Aseptic Operations	28
4.9 Process Simulating Testing	28
4.10 Measure of Good Aseptic Practices	29

CHAPTER 5

Good Clean Room Monitoring in Pharmaceutical Industry

5.1 Content of ISO 14644-1:2015	32
5.2 Sampling and Location Evaluations.....	32
5.3 Sampling	33
5.4 Sampling Procedure.....	33
5.5 Sampling Instruments: LSAPC - Light Scattering Airborne Particle Counter	33
5.6 Recording and Evaluations of Airborne Particle Concentration	34
5.7 ISO Class Number.....	34
5.8 Test Reports and Interpretation of Results	35
5.9 Out of Specifications	35

CHAPTER 6

Good Engineering Practices in Pharmaceutical Industry

6.1 Good Engineering Practice Overview	37
6.2 Key Concepts in Pharmaceutical Engineering	37
6.3 Using Good Maintenance Practice in Good Engineering.	38
6.4 Spares Management in Good Engineering Practice	39
6.5 Maintenance Qualification.....	40
6.6 Cost Cutting becomes the Pharma Industry's Mantra.....	40
6.7 Simplicity is the Ultimate Sophistication.....	41
6.8 Measures in Good Engineering Practices	42

CHAPTER 7

Good Alarm Management Practices in Pharmaceutical Industry

7.1 Key aspects of Alarm Management Program	44
7.2 Regulators Expectation of Alarm Management System...	44
A. FDA and Alarming	44
B. ISA-18.2 Alarm System Management Lifecycle	45
7.3 Element of a Good Alarm on Risk Assessment in Pharmaceutical Industry	47
7.4 Categorization of Alarm	47
7.5 Principle of Alarm Management System	48

CHAPTER 8

Good Computer Validation System Practices in Pharmaceutical Industry

8.1 Computer Validation Master Plan.....	50
8.2 Computer Qualification	50
A. System Requirement Specifications (SRS) or User Requirement Specifications (URS).....	50
B. Design Qualification and Specifications	51
C. Installation Qualification	51
D. Operational Qualification	53
E. Performance Qualification	53
8.3 Validation Protocol/Report.....	54
8.4 Validation of Hardware and Software	55

CHAPTER 9

Good Distribution Practices – Supply Chain Integrity in Pharmaceutical Industry

9.1 Key components of Good Distribution Practice	57
A. Quality Management System	57
B. Supplier Qualification	58
C. Internal Audit	58
D. Storage Management System	58

E. Environmental Condition Management	58
F. Temperature Mapping	59
G. Distribution Management System	60
9.2 Counterfeit	60
9.3 Supply Chain Integrity and Security	60
9.4 Category of Supply Chain Integrity and Security	61

CHAPTER 10

Good Data Management System in Pharmaceutical Industry

10.1 Regulatory Expectations	64
10.2 When does Electronic Data become a CGMP Record?	64
10.3 CIA or AIC Triangle.....	65
10.4 The Data Governance System.....	65
10.5 Designing Systems to Assure Data Quality and Integrity	66
10.6 Triggers of Data Integrity Loss.....	66
10.7 Data Integrity Metrics.....	67
10.8 Measures of Good Data Management System	67

CHAPTER 11

Quality Agreements in Pharmaceutical Industry

11.1 Elements of a Quality Agreement.....	68
11.2 Activities in Quality Agreements.....	69

CHAPTER 12

Change control Management and its Applications

12.1 Benefits of Change Control System	72
12.2 ICH Q8 and ICH Q9 to Change Management in ICH Q10	73
12.3 Steps involved in Change Control Management.....	73
12.4 E-Change Control System	74

CHAPTER 13

Technology Transfer of Pharmaceutical Product

13.1 Different Types of Technology Transfer	75
13.2 Technology Transfer Protocol and Report.....	77

CHAPTER 14

Pharmaceutical Annual Product Quality Review

14.1 Importance of Annual Product Quality Review.....	78
14.2 Contents of APQR.....	79
14.3 Data Trend and Analyzation.....	80

CHAPTER 15

Statistical Tools for Pharmaceutical Industry

15.1 Concept of Six Sigma and Lean Manufacturing	82
15.2 Common Statistical Tools Pharmaceutical Industry can use to Meet Regulatory Requirements.....	83
15.3 Other Statistical Tools used in Pharmaceutical Industry .	85
15.4 Qualitative and Quantitative Analysis.....	88
A. Patterns and Trends.....	88
15.5 Measures of Statistical Tools Analysis	89

CHAPTER 16

Application of Different Quality Tools in Investigation of Non-Conformance Observations

16.1 Deviation Management	90
A. Steps involved in Deviation Investigation	91
B. Deviation Categorization.....	91
16.2 Complaint.....	92
A. Steps involved in Complaint Handling	92
16.3 Recall.....	93
A. Classification of Recall.....	93
B. Recall Strategy	93
C. Recall Communication	94
D. Recall Status Reports	95
E. Effectiveness Checks.....	95

16.4	Out of Specification (OOS).....	96
A.	Phase I: Laboratory Investigation	96
B.	Phase II: Full Scale Investigation	97
a.	Production Review	97
b.	Additional Laboratory Testing	98
16.5	Field Alter Report (FAR)	99
16.6	Out of Trend (OOT)	100
16.7	Investigations Tools	100
A.	Root Cause Analysis (RCA).....	100
B.	Corrective and Preventive Action (CAPA)	101
C.	Risk Management Program.....	102
a.	Quality Risk Management Tools	103
16.8	Verification Program	105

CHAPTER 17

New Approach to the Internal Audit from Traditional to Risk based Approach

17.1	Traditional Approach to IA	107
17.2	Forecasting Approach to IA.....	107
17.3	Benefits of QRM to IA Program	108
17.4	IA Approach to Organization.....	109
I.	System based Approach.....	109
A.	Full Inspection Option	110
B.	Abbreviated Inspection Option	110
II.	Linked based -Process Approach	110
III.	Risk based approach for IA Program.....	111
IV.	Forensic Audit	111
V.	For-Cause-Audit.....	112
17.5	Planning.....	113
17.6	Audit Sampling	114
17.7	Audit Tools.....	115
17.8	Audit Evidence and Analysis Phase	116
17.9	Audit CLOSE-OUT and FOLLOW-UP	116

CHAPTER 18

Quality by Design (QbD) Approach in the Product Life Cycle

18.1 Elements of QbD	118
18.2 Steps involved in QbD Development Process.....	118
18.3 The Principle Steps in QbD are	119
18.4 QbD Documents	120
18.5 Process Analytical Technology (PAT) Frame Work.....	121
18.6 Use of PAT Tools in Continuous Manufacturing Process.....	121
A. PAT Tools	122
B. Risk-Based Approach	122
C. Integrated Systems Approach.....	122
D. Real Time Release	122
E. Strategy for Implementation	122
F. PAT Regulatory Approach.....	123
18.7 Product Life Cycle.....	123
A. Pharmaceutical Development	123
B. Technology Transfer.....	124
C. Commercial Manufacturing	124
D. Product Discontinuation.....	124
18.8 Definition.....	124

CHAPTER 19

Process Validation in Pharmaceutical Industry

19.1 Approach of Process Validation.....	127
A. Stage 1 – Process Design	127
B. Stage 2 – Process Qualification.....	128
C. Stage 3 – Continued Process Verification	129
D. Revalidation.....	129
19.2 Content of Validation Protocol/Report	129

CHAPTER 20

Cleaning Validation and Cross Contamination Approach on Risk MaPP Concept

20.1	Types of Cleaning	131
A.	Manual Cleaning	132
B.	Semi-Automated Processes Cleaning.....	132
C.	Automated Processes Cleaning.....	132
20.2	Approach for Cleaning Validation	132
20.3	Addition of New Product and Equipment to Validated Chain.....	133
20.4	Equipment Hold Study Approaches	133
20.5	Selection of Worst Case Product	133
20.6	Cleaning Validation Protocol	134
A.	Indirect Sampling: Rinse Sampling	134
B.	Direct Sampling: Swab Sampling	135
20.7	Quality Risk based Approach for Cleaning Validation..	136
20.8	European Union Expectation on Cross Contamination .	137
A.	EU chapter 5 expectation	137
B.	EMA	138
20.9	Selection & Reporting of the PDE Determination Strategy	139
20.10	Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination	139
20.11	Definitions	139

CHAPTER 21

Pharmaceutical Water Generation and Distribution System and Regulatory Expectation

21.1	Design and Process Flow	143
21.2	Steps involved in Pharmaceutical Water Preparations...	144
21.3	Possible Pretreatment Method for Pharmaceutical Water Preparation	144

21.4 Possible Purification Method for Pharmaceutical Water Preparation	144
21.5 Qualification.....	145
A. User Requirement Specification (URS)	145
a. Process water	145
b. Purified water/water for injection	145
c. Pure steam.....	145
B. Functional Design Specification (FDS).....	145
a. Process water	146
b. Purified water/WFI	146
c. Pure steam	146
C. Design Specification (DS).....	147
a. Process Water	147
b. Purified Water/WFI	147
c. Pure Steam	148
D. Performance Qualification for purified water / WFI/Pure Steam	148
a. Phase 1 :Test period : 2–4 weeks	148
b. Phase 2 : Test Period : 2–4 weeks	148
c. Phase 3: Test Period: 1	148
E. Validation Cycle of Qualification and Validation of Water System	149
21.6 Component for Pharmaceutical Water System.....	150
A. Pretreatment System	150
a. Raw Water.....	150
b. Chlorination.....	150
c. Filtration	150
d. Dechlorination.....	150
e. Softener.....	150
f. Hardness	151
g. Oxidation Reduction Potential (ORP).....	151
h. Silt Density Indicator.....	151
i. Microbial-Retentive Filtration	151

B.	Purification System	152
a.	Ion Exchange	152
b.	Mixed bed dimineralizers.....	152
c.	Reserve Osmosis	153
d.	Continuous Electro deionization (CEDI) or Electron De-ionization (EDI)	153
C.	Storage and Distribution	153
a.	Storage Tanks	153
b.	Ultraviolet Light.....	154
c.	Distribution Systems	154
d.	Sanitization	155
e.	Total Organic Carbon (TOC)	155
f.	Conductivity	155
g.	Flow of distribution loop	155
h.	Pressure	155
i.	Microfiltration	156
j.	Ultrafiltration.....	156
k.	PureSteam	156
21.7	Methods used for Preparation of Pharmaceutical Water	156
21.8	Test Performed for Potable Water and its Recommended Limits.....	157
21.9	Type of water is used in the Pharmaceutical Sterile Medicine Product as an Excipient as per EMEA/CVMP/115/01 Note for Guidance on Quality of Water for Pharmaceutical Use	157
21.10	Type of water is used in the Pharmaceutical Non-Sterile Medicine Product as an Excipient as per EMEA/CVMP/115/01 Note for Guidance on Quality of Water for Pharmaceutical Use	157

21.11	Type of Water is used in the Manufacturer of Active Pharmaceutical Ingredients (APIs) as per EMEA/CVMP/115/01 Note for Guidance on Quality of Water for Pharmaceutical Use.....	158
21.12	Type of Water is used for Cleaning/Rinsing of Equipment, Containers and Closure as per EMEA / CVMP/115/01 Note for Guidance on Quality of Water for Pharmaceutical Use.....	159
21.13	Potable Water as per Reference ISPE Baseline Guide, Volume- 4 Water and Steam System, WHO TRS 929 WHO TRS 937	160
	A. Construction Requirement of Underground and Overage Storage Tank	160
	B. Control of Microbial load in Potable Water	161
	C. Dechlorination of Feed Water	161
	D. Procedure and limit of Hardness	161
	E. Procedure and limit of Oxidation Reduction Potential (ORP)	161
	F. Procedure and limit of Silt Density Indicator:	162
	G. Procedure for Microbial-Retentive Filters in Potable Water Line	162
	H. Potable Water Sampling and Testing	162
21.14	Purified Water and WFI System as per ISPE Baseline Guide, Volume 4 Water and Steam System, WHO TRS 929 WHO TRS 937	162
	A. Design Requirement for Distribution of Purified Water and WFI System.....	162
	B. Storage Tank Design Requirement for Purified Water / WFI System	163
	C. Welding document Requirement during Design Qualification	163
	D. Flow velocity of Purified Water and WFI in Distribution Loop.....	163
	E. Conductivity Sensor	163

F. Pressure and Compound Gauge available in Purified Water and WFI System	163
G. Sampling procedure is for Purified and Water for Injection as per USP Chapter <1231>	163
H. Alert and Action levels defined for Purified and Water for Injection	164
I. Continuous System Monitoring of Purified Water and Water for Injection System	164
J. System Reviews of Purified Water and Water for Injection System	165
21.15 Planned Preventive Maintenance Programme	165
A. Potable/Purified/WFI/Pure Steam	165
B. Alarm Management for Purified/WFI/Pure Steam	165
C. RO Membrane Maintenance.....	165
D. Ion Exchange Membrane Maintenance.....	166
E. Continuous Electro deionization (CEDI) or Electron De-ionization (EDI) Maintenance	166
F. Total Organic Carbon (TOC)	166
G. Sanitization for Purified and Water for Injection System	166
H. Ultra Violet lamp.....	167
I. Cleaning.....	167
21.16 Definition	167

CHAPTER 22

Pharmaceutical Heating, Ventilation and Air Conditionings (HVAC) and Regulatory Expectations

22.1 Qualification	170
A. Designed Qualification.....	170
I. Aseptic Dosage Form Facility	174
II. Check Points for Design Qualification for Aseptic and Biologics area	175
III. Design Criteria for Solid /Semi Solids/Liquids/ Final API	182

IV.	Design Criteria for Potent Solid/Semi Solids/ Liquids/ Final API Form.....	183
V.	Design Acceptance Criteria.....	186
VI.	Check Points for Design Qualification Solid / Semi Solids/Liquids/ Final API (Potent and Non Potent).....	186
	A. Installation Qualification.....	191
	B. Operational Qualification	191
	C. Performance Qualification	191
22.2	Regular Check Points of HVAC System	191
22.3	Definition.....	194

CHAPTER 23

Manufacturing Execution System (MES) in Pharmaceutical Industry

23.1	Overview of REPAC Model.....	198
23.2	Overview of Three-Layer-Model	199
23.3	Overview of Standards ISA S95.00.01/02/03 for MES ...	200
23.4	Systematic Planning Approach to MES Implementation in 14 Stages.....	201
23.5	MES Functions	202
23.6	Implementation Strategy	203

CHAPTER 24

Pharmaceutical Drug Master File

I.	Submissions to Drug Master Files	205
II.	Types of Drug Master File and its Contents.....	207
III.	General Information and Suggestions.....	208
IV.	Format, Assembly, and Delivery	208
V.	Drug Master File submissions and correspondence should be addressed as follows.....	208
VI.	Authorization to refer to a Drug Master File	208
VII.	Processing and Reviewing Policies.....	209
VIII.	Holder Obligations	209

IX.	Major Reorganization of a Drug Master File.....	211
X.	Closure of a Drug Master File	211
XI.	Submission Process of Drug Product	211

CHAPTER 25

Common Technical Document in Regulatory Filing

25.1	Organization of the Common Technical Document	213
	Module 1: Administrative Information and Prescribing Information	213
	Module 2: Common Technical Document Summaries	213
	Module 3: Quality	217
	Module 4: Nonclinical Study Reports	220
	Module 5: Clinical Study Reports	220
25.2	Electronic Common Technical Document	221

CHAPTER 26

European Union Marketing Authorization

A.	Mutual Recognition Procedure (MRP).....	223
a.	Steps involved in the mutual recognition procedure	223
b.	Flow chart for the Mutual Recognition Procedure....	224
B.	Decentralized Procedure	225
a.	Steps involved in the Decentralised procedure	226
b.	Flow Chart of the Decentralised Procedure	226
C.	Numbering System for the Procedures for Mutual Recognition and Decentralised Procedure	228
D.	Centralised authorisation procedure.....	229
a.	Flow Chart of the Centralised Procedure	230

CHAPTER 27

Site Master File

27.1	Content of Site Master File.....	231
A.	General Information on the Manufacturer	231

B.	Quality Management system of the Manufacturer ...	232
C.	Personnel.....	234
D.	Premises and Equipment	234
E.	Documentation	236
F.	Production.....	236
G.	Quality Control (QC)	237
H.	Distribution, Complaints, Product Defects and Recalls	237
I.	Self-inspections.....	238
27.2	Appendix.....	238

CHAPTER 28

Standard Operating Procedure (SOP)

28.1	Writing Styles	240
28.2	SOP Process.....	240
28.3	SOP Review and Approval.....	241
28.4	Frequency of Revisions and Reviews	241
28.5	Checklists.....	241
28.6	Document Control.....	242
28.7	SOP Document Tracking and Archival.....	242
28.8	SOP General Format	243
28.9	Definitions	245

CHAPTER 29

Quality Manual

I.	Contents of the Quality Manual.....	247
II.	Topics that should be covered in the final section on Quality Policies for Specific Regulation Elements.....	249

CHAPTER 30

Human Error Reduction: Pharma Industry Challenge

30.1	How Do Industry and Regulatory Expectations and Approaches Differ?	253
------	---	-----

30.2 Understanding, Investigation & Tackling of Human Error.....	254
30.3 Power of 5-WHY	255
30.4 Human Error and Retraining	255
30.5 What Can Be Done for Human Error?	256
30.6 Measure of Human Error	257

CHAPTER 31

Regulatory Inspections: Face Challenges through Proactive Measures

31.1 Regulatory Expectations?.....	258
31.2 Current Regulatory Audits Looking	259
31.3 Regulators Looks at...	260
31.4 Audit Trail Assessments	261
31.5 An Approach to Managing Regulatory Risks and Achieving Compliance	262
31.6 Measures of Regulatory Inspections	263

CHAPTER 32

Pharmaceutical GMP: Past, Present, and Future - A Review

32.1 Current Expectations for Pharmaceutical Quality Systems	264
32.2 A Quality Culture That Leads to Sustainable Compliance	265
32.3 Quality Culture.....	265
32.4 Building Knowledge, Effective Monitoring & Control Systems.....	266
32.5 Global Supply Chain and Vendor Qualification	266
32.6 Bundling GMP Enforcement with Other Violations	267
32.7 Quality Systems	267
32.8 Change Control: New FDA Expectations for Equipment Changes.....	268
<i>References</i>	269