

GMP Manual

Contents

1	Pharmaceutical Quality System (PQS)	
1.A	Preface	
1.B	The road to a Pharmaceutical Quality System	
1.C	Introduction to the PQS	
1.C.1	General requirements	1.C (1)
1.C.2	Documentation	1.C (2)
1.D	Main elements of a PQS	
1.D.1	Management responsibility	1.D (1)
1.D.2	Resource management	1.D (4)
1.D.3	Manufacturing operations	1.D (7)
1.D.4	Evaluation activities	1.D (10)
1.E	Essentials of a PQS	
1.E.1	Principles of a process	1.E (1)
1.E.2	Process mapping	1.E (8)
1.E.3	Responsibilities	1.E (25)
1.E.4	Key Performance Indicators (KPIs)	1.E (26)
1.F	Practical implementation of a PQS	
1.F.1	Assistance for implementation	1.F (1)
1.F.2	Organizational aspects	1.F (3)
1.F.3	Process of developing documents	1.F (5)
1.F.4	Document hierarchy	1.F (7)
1.G	Structure of a PQS quality manual – example	
1.H	Correlation between GMP requirements (WHO) and ISO 9001:2000	
1.I	References	
2	Personnel	
2.A	Place of work and job descriptions	
2.B	Requirements of the personnel	
2.B.1	Qualification requirements	2.B (1)
2.B.2	Health requirements	2.B (2)

2.C	Training	
2.C.1	Purpose of training	2.C (1)
2.C.2	Responsibility for training	2.C (1)
2.C.3	Requirements profiles/learning objectives	2.C (2)
2.C.4	Training contents and target groups	2.C (3)
2.C.5	Training planning	2.C (4)
2.C.6	Carrying out	2.C (4)
2.C.7	Reviewing the training and the training system	2.C (8)
2.C.8	Documentation	2.C (11)
2.D	Function owners subject to public law	
2.D.1	Qualified Person (QP)	2.D (1)
2.D.2	Head of Production	2.D (12)
2.D.3	Head of Quality Control	2.D (17)
2.D.4	Qualified Person in Accordance with Article 103 of Guideline 2001/83/EC	2.D (21)
2.D.5	Scientific Service in Charge of Information	2.D (24)
2.D.6	Medical sales representatives	2.D (26)
3	Premises	
3.A	Official Requirements	
3.A.1	Location, connection to other rooms	3.A (4)
3.A.2	Size, area, height	3.A (5)
3.A.3	Installation and supply of utilities	3.A (7)
3.A.4	Lighting, ventilation, air-conditioning	3.A (7)
3.A.5	Hygienic construction	3.A (8)
3.A.6	Room book and layout	3.A (8)
3.B	Material flow, personnel flow and layout	
3.B.1	Material flow	3.B (1)
3.B.2	Personnel flow	3.B (4)
3.B.3	Layout	3.B (4)
3.B.4	Design concepts in FDA's Sterile Drug Products Produced by Aseptic Processing guideline	3.B (5)
3.C	Room classes	
3.C.1	General GMP Requirements for Premises	3.C (1)
3.C.2	GMP Requirements for Cleanrooms: Air Cleanliness Grades	3.C (1)
3.C.3	Corresponding FDA Determinations	3.C (4)
3.C.4	GMP Requirements for Premises	3.C (6)
3.C.5	Room-specific Allocation of Air Cleanliness Stipulations	3.C (7)
3.C.6	Cleanliness Zoning Concepts	3.C (9)
3.C.7	Converting GMP Stipulations into Reality	3.C (12)

3.D	Construction elements	
3.D.1	Walls	3.D (1)
3.D.2	Doors and windows	3.D (6)
3.D.3	Floors	3.D (8)
3.D.4	Ceilings	3.D (10)
3.E	Barrier systems and isolators	
3.E.1	Protection concepts for maximized sterility assurance	3.E (1)
3.E.2	Pharmaceutical isolator technology	3.E (2)
3.E.3	Restricted access barrier systems (RABS technology)	3.E (8)
3.E.4	Application options for RABS and isolators	3.E (12)
3.F	Building services	
3.F.1	Basic requirements for installation	3.F (1)
3.F.2	Heating	3.F (3)
3.F.3	Sanitary plumbing and sewage	3.F (3)
3.F.4	Electrical installations incl. IT-management and control systems	3.F (3)
3.F.5	Qualification	3.F (4)
3.G	Heating Ventilation Air Conditioning (HVAC)	
3.G.1	Introduction	3.G (1)
3.G.2	Room ventilation systems	3.G (3)
3.G.3	Filters	3.G (11)
3.G.4	Principles for the design and planning of air conditioning ventilation systems	3.G (23)
3.G.5	Design criteria for the ventilation of premises	3.G (26)
3.G.6	Maintenance of air ventilation systems	3.G (37)
3.H	Process Gases	
3.H.1	Quality Requirements	3.H (2)
3.H.2	Generation, Storage and Distribution	3.H (4)
3.H.3	System design	3.H (5)
3.H.4	Qualification and monitoring	3.H (8)
3.I	Qualification of premises and air-conditioning systems	
3.I.1	Objectives of qualification	3.I (1)
3.I.2	Regulatory and normative fundamentals of qualification	3.I (2)
3.I.3	Project development and qualification	3.I (3)
3.I.4	Qualification Master Plan	3.I (4)
3.I.5	Qualification Plans and Qualification Reports	3.I (5)
3.I.6	Qualification checklists	3.I (6)
3.I.7	Requirements for measurement and test reports	3.I (29)
3.I.8	Requalification	3.I (30)
3.J	Monitoring of HVAC systems	
3.J.1	Objectives of process monitoring	3.J (1)
3.J.2	Data management stipulations	3.J (1)
3.J.3	Air cleanliness and other room air data	3.J (3)

3.J.4	Risks of microbiological monitoring	3.J (4)
3.J.5	Alarm and action limits	3.J (4)
3.J.6	Operation and maintenance	3.J (5)

3.K References

4 Facilities and Equipment

4.A Introduction

4.B Mechanical components

4.B.1	Construction and installation materials	4.B (1)
4.B.2	GMP-compliant design characteristics	4.B (2)
4.B.3	Electrical and pneumatic components	4.B (3)

4.C Control

4.D Facility concepts

4.D.1	CIP (Cleaning in Place)	4.D (1)
4.D.2	Isolator technology	4.D (2)
4.D.3	Connected facilities	4.D (2)

4.E Examples of facility qualification

4.E.1	Design qualification	4.E (1)
4.E.2	Installation qualification	4.E (5)
4.E.3	Operational qualification	4.E (12)

4.F Technical documentation

4.F.1	Necessity	4.F (1)
4.F.2	Scope and content	4.F (2)
4.F.3	Administration of the technical documentation	4.F (9)
4.F.4	Log book	4.F (12)

4.G Calibration

4.G.1	Definitions	4.G (1)
4.G.2	Procedure	4.G (3)
4.G.3	Documentation	4.G (4)
4.G.4	Administration of scheduled calibration dates/ times	4.G (5)

4.H Maintenance

4.H.1	Types of maintenance	4.H (2)
4.H.2	GMP-conforming maintenance	4.H (2)
4.H.3	Systems for maintenance	4.H (3)

4.I CIP (Cleaning in Place)

4.I.1	Introduction	4.I (1)
4.I.2	CIP systems	4.I (3)
4.I.3	GMP-conforming design of CIP facilities	4.I (6)
4.I.4	Nozzle heads for container cleaning	4.I (11)

4.I.5	Measuring technology	4.I (13)
4.I.6	Realisation of cleaning systems	4.I (15)
4.J	Containment (personnel protection) in solids handling	
4.J.1	Significance	4.J (1)
4.J.2	Definition of terms	4.J (3)
4.J.3	Containment grades of products	4.J (3)
4.J.4	Measurement of the residue limits (OEL)	4.J (6)
4.J.5	Example of containment facility planning	4.J (7)
4.J.6	Containment weak points	4.J (15)
4.J.7	Containment systems for filling and emptying drums	4.J (16)
4.J.8	Container systems	4.J (23)
4.J.9	Filter systems	4.J (27)
4.J.10	Sampling	4.J (28)
4.J.11	Containment on equipment	4.J (30)
4.K	Process control systems	
4.K.1	Definitions	4.K (1)
4.K.2	Features of process control systems	4.K (2)
4.K.3	How to use process control systems	4.K (5)
4.K.4	Carrying out a process control system project	4.K (6)
4.K.5	Qualification of process control systems	4.K (7)
4.L	Hygienic (sanitary) design when using solids	
4.L.1	Introduction	4.L (1)
4.L.2	Surfaces	4.L (3)
4.L.3	Material: stainless steel	4.L (6)
4.L.4	Connections	4.L (11)
4.L.5	Hoists and roller conveyors	4.L (22)
4.L.6	Pneumatic conveyor system	4.L (25)
4.L.7	Dosing systems	4.L (26)
4.L.8	Platforms and stands	4.L (28)
4.L.9	Clean room installations	4.L (31)
5	Pharmaceutical Water	
5.A	Water types	
5.A.1	Potable water	5.A (2)
5.A.2	Purified water	5.A (3)
5.A.3	Highly purified water	5.A (5)
5.A.4	Water for injection	5.A (7)
5.B	Generation of pharmaceutical water	
5.B.1	Purified water (PW)	5.B (2)
5.B.2	Water for injection (WFI)	5.B (11)
5.B.3	Purification of pharmaceutical water treatment systems	5.B (14)

5.C	Distribution and storage of pharmaceutical water	
5.C.1	Loop	5.C (1)
5.C.2	Fixtures	5.C (6)
5.C.3	Measuring technique	5.C (7)
5.C.4	Formation of biofilms	5.C (21)
5.C.5	Rouging	5.C (23)
5.C.6	Buffering of ultra pure water	5.C (27)
5.C.7	Loop with subloops	5.C (29)
5.D	Qualification of water supplies	
5.D.1	Introduction	5.D (1)
5.D.2	Risk analysis	5.D (3)
5.D.3	Design qualification	5.D (8)
5.D.4	Installation qualification	5.D (17)
5.D.5	Operational qualification (OQ)	5.D (28)
5.D.6	Transfer to the user	5.D (36)
5.D.7	Process validation/performance qualification (PQ)	5.D (42)
5.D.8	Qualification report	5.D (47)
5.E	Operation of water supplies	
5.E.1	Procedures to reduce microbial counts	5.E (1)
5.E.2	Maintenance of a water supply	5.E (4)
5.E.3	Calibration of measuring systems	5.E (10)
5.E.4	Change control	5.E (11)
5.E.5	Requalification	5.E (13)
5.E.6	Decommissioning/uninstalling	5.E (14)
5.F	Pure steam systems	
5.F.1	Physical principles	5.F (1)
5.F.2	Quality requirements for pure steam	5.F (3)
5.F.3	Pure steam generation	5.F (6)
5.F.4	Pure steam distribution system	5.F (10)
6	Qualification	
6.A	Official requirements	
6.A.1	Legal aspects of qualification	6.A (1)
6.A.2	Documentation of the qualification	6.A (4)
6.A.3	Design Qualification (DQ)	6.A (5)
6.A.4	Installation Qualification (IQ)	6.A (8)
6.A.5	Operational Qualification (OQ)	6.A (9)
6.A.6	Performance Qualification (PQ)	6.A (10)
6.A.7	Qualification of established facilities	6.A (11)
6.A.8	Requalification	6.A (13)

6.B	Preparation of the qualification	
6.B.1	Commissioning	6.B (1)
6.B.2	Sequence	6.B (5)
6.B.3	Qualification team	6.B (6)
6.B.4	Responsibilities	6.B (6)
6.B.5	Qualification by external service providers	6.B (6)
6.B.6	Risk analysis	6.B (10)
6.C	Qualification documentation	
6.C.1	Qualification master plan	6.C (2)
6.C.2	Qualification plan	6.C (3)
6.C.3	Qualification report	6.C (9)
6.C.4	Labeling of the qualification status	6.C (10)
6.C.5	SOP – “Qualification of facilities and equipment”	6.C (11)
6.D	Design qualification (DQ)	
6.D.1	User requirements (user specifications)	6.D (3)
6.D.2	Technical specification	6.D (12)
6.E	Installation qualification (IQ)	
6.E.1	Examples of IQ plans	6.E (3)
6.E.2	Example: Fluid bed equipment	6.E (22)
6.F	Operational qualification(OQ)	
6.F.1	Examples of OQ plans	6.F (3)
6.F.2	Example: Fluid bed dryer	6.F (13)
6.G	Performance qualification (PQ)	
6.H	Special cases of qualification	
6.H.1	Retrospective qualification	6.H (1)
6.H.2	Requalification	6.H (2)
6.H.3	Content of a review	6.H (3)
6.H.4	Maintenance of the qualified status	6.H (5)
6.H.5	Qualification of simple equipment	6.H (7)
7	Process Validation	
7.A	Official requirements	
7.A.1	Regulative aspects	7.A (1)
7.A.2	Principles of process validation	7.A (11)
7.A.3	Types of process validation	7.A (18)
7.A.4	Maintaining the validated status	7.A (23)
7.A.5	Documentation of process validation	7.A (27)
7.B	Validation – a key element of quality assurance	

7.C	Process validation approaches	
7.C.1	Prospective validation	7.C (1)
7.C.2	Retrospective validation	7.C (3)
7.C.3	Concurrent validation	7.C (5)
7.D	Revalidation	
7.D.1	Time intervals for periodic revalidations	7.D (2)
7.D.2	Incidences requiring revalidation	7.D (2)
7.E	Planning of process validation projects	
7.E.1	Responsibilities and task assignment	7.E (1)
7.E.2	Validation team	7.E (4)
7.E.3	Timing of validation	7.E (6)
7.E.4	Prerequisites for carrying out a validation project	7.E (6)
7.F	Validation master plan	
7.F.1	Validation matrix	7.F (4)
7.F.2	Example of a validation master plan	7.F (6)
7.F.3	Example for a validation matrix	7.F (17)
7.F.4	Example for a test plan	7.F (24)
7.G	Risk analysis	
7.G.1	Finding out the adequate extent of validation	7.G (1)
7.G.2	Carrying out risk analysis	7.G (1)
7.H	Validation protocol and report	
7.H.1	Elements of the validation protocol	7.H (1)
7.H.2	Content of a validation report	7.H (9)
7.I	Quality by Design	
7.I.1	Process development	7.I (1)
7.I.2	Design space	7.I (3)
7.I.3	Statistical Design of Experiments (DoE)	7.I (6)
7.I.4	Multivariate Data Analysis (MVDA)	7.I (9)
7.J	Process Analytical Technology (PAT)	
7.J.1	Process-analytical measurements	7.J (1)
7.J.2	Evaluation of the data	7.J (3)
7.J.3	Possible applications	7.J (4)
7.J.4	Implementations of PAT	7.J (6)
7.J.5	Advantages of PAT implementation	7.J (6)
7.J.6	PAT in the USA and Europe	7.J (7)

8	Cleaning Validation	
8.A	Official requirements	
8.B	How to validate cleaning procedures	
8.B.1	Optimization of cleaning procedures	8.B (1)
8.B.2	Compilation of cleaning instructions	8.B (5)
8.B.3	Validating manual and automated cleaning procedures	8.B (8)
8.C	Cleaning validation master plan	
8.D	Establishing the scope of validation	
8.D.1	Bracketing: determination of critical substances	8.D (1)
8.D.2	Matrixing: determination of equipment-specific validation protocols	8.D (5)
8.E	Acceptance criteria and limit calculation	
8.E.1	Calculation of active pharmaceutical ingredient residues	8.E (1)
8.E.2	Calculation of cleansing agent residues	8.E (10)
8.E.3	Determination of the microbial status	8.E (11)
8.F	Sampling procedures	
8.F.1	Swab test	8.F (1)
8.F.2	Rinse test	8.F (4)
8.F.3	Other procedures	8.F (6)
8.F.4	Selection of the appropriate sampling procedure	8.F (7)
8.F.5	Microbiological testing of surfaces	8.F (9)
8.G	Analytical procedures	
8.G.1	Requirements for method validation	8.G (1)
8.G.2	Selection of the appropriate analytical procedure	8.G (6)
8.H	Documentation	
8.H.1	Validation protocol	8.H (1)
8.H.2	Validation report	8.H (5)
8.H.3	Other documents	8.H (7)
8.I	Maintenance of the validated status	
8.I.1	Changes and deviations	8.I (2)
8.I.2	Change control	8.I (3)
8.I.3	Revalidation	8.I (4)
8.I.4	New products and equipment	8.I (9)
8.I.5	Deviations	8.I (12)
8.J	Cleaning validation documentation (example)	
8.K	References	

9 Computer Validation

9.A	Introduction and basic terminology	
9.A.1	Introduction	9.A (1)
9.A.2	Basic terminology	9.A (2)
9.B	Regulatory aspects	
9.B.1	Europe	9.B (1)
9.B.2	PIC/S	9.B (4)
9.B.3	USA	9.B (4)
9.B.4	Electronic signature / Electronic records	9.B (6)
9.B.5	GAMP® Good Automated Manufacturing Practice	9.B (8)
9.C	Life cycle of software and systems	
9.C.1	“V-Model”	9.C (2)
9.C.2	Software development	9.C (4)
9.C.3	Purchasing commercial of the shelf systems	9.C (6)
9.C.4	Configuration and customisation	9.C (7)
9.D	Risk analysis and system classification	
9.D.1	GAMP® classification	9.D (1)
9.D.2	Risk indexes	9.D (6)
9.D.3	Risk management at the level of user requirements	9.D (14)
9.E	Validation of computerised systems	
9.E.1	Responsibility and organisation	9.E (1)
9.E.2	Validation plan	9.E (4)
9.E.3	Specifications (user requirements/technical specification) for hardware and software	9.E (8)
9.E.4	Unit, integration and acceptance tests	9.E (11)
9.E.5	Documentation for validation (validation plan and report)	9.E (17)
9.E.6	Data migration and start-up	9.E (18)
9.E.7	Examples	9.E (19)
9.E.8	Dealing with existing systems (legacy systems)	9.E (34)
9.F	Operation of computerised systems	
9.F.1	System description	9.F (1)
9.F.2	User training	9.F (1)
9.F.3	Standard operating procedures (SOPs)	9.F (1)
9.F.4	Authorised access and security (virus protection)	9.F (2)
9.F.5	Data backup and archiving	9.F (5)
9.F.6	Contingency plans and data recovery	9.F (7)
9.F.7	Change management and error reporting	9.F (8)
9.F.8	Periodic review	9.F (10)
9.F.9	Retirement of computerised systems	9.F (11)

9.G	External service providers	
9.G.1	Relocation of activities (outsourcing, offshoring, nearshoring, backshoring)	9.G (1)
9.G.2	Service level agreement	9.G (2)
9.G.3	Auditing of suppliers and service providers	9.G (8)
9.H	References	
10	Considerations on Risk Management	
10.A	Introduction and Principles	
10.A.1	Advantages of Risk Management	10.A (2)
10.A.2	Considerations on the Risk-Based Approach	10.A (4)
10.A.3	Regulatory Environment	10.A (7)
10.A.4	Objectives	10.A (12)
10.A.5	Science-Based Approach	10.A (13)
10.A.6	Summary	10.A (14)
10.B	Basic Consideration on Implementing Risk Management Into a Process	
10.B.1	Areas of Hazards	10.B (1)
10.B.2	Prerequisites	10.B (3)
10.B.3	Use of Knowledge and Experience	10.B (5)
10.B.4	Consideration on Manual Operations	10.B (5)
10.B.5	Elements of Risk Management	10.B (6)
10.B.6	Implementation of a Risk Management Process	10.B (7)
10.B.7	Commitment of Management	10.B (7)
10.B.8	Project Team	10.B (8)
10.B.9	Analysis of Existing Risk Management Approaches	10.B (8)
10.B.10	Standardization of Methods and Tools	10.B (9)
10.B.11	Considerations on Risk Based Behavior	10.B (9)
10.B.12	Additional Training Required?	10.B (10)
10.C	Details on Using Risk Management Principles as Behavior	
10.C.1	Application to the QM System	10.C (1)
10.C.2	The Team	10.C (2)
10.C.3	Assessment Criteria	10.C (3)
10.C.4	Procedure to Determine Conclusions	10.C (4)
10.C.5	Evaluation on Individual Topics (Detailed Evaluation) Using Risk Management	10.C (4)
10.C.6	Example on Process Validation	10.C (6)
10.D	Methodologies to be Used to Facilitate Risk Management	
10.E	Using Process Mapping	
10.F	Using a Fishbone Diagram	
10.F.1	Create a Fish Bone Diagram	10.F (2)
10.F.2	Advantages and Disadvantages	10.F (4)

10.G	Informal Use of Risk Management	
10.H	Fault Tree Analysis (FTA)	
10.H.1	Basic Principles	10.H (1)
10.H.2	Objective: What a FTA Can Do and Where to Use It	10.H (1)
10.H.3	How to Run the Process of a FTA	10.H (2)
10.H.4	Prerequisites for an FTA	10.H (2)
10.H.5	Execution of an FTA	10.H (3)
10.H.6	Advantages and Disadvantages of an FTA	10.H (5)
10.I	Failure Mode Effects Analysis (FMEA)	
10.I.1	Objectives and Areas of Application	10.I (2)
10.I.2	General Items on the FMEA Process	10.I (3)
10.I.3	Implementation of FMEA in a Project	10.I (18)
10.I.4	Advantages and Disadvantages of an FMEA	10.I (18)
10.I.5	Application Example of a Modified FMEA	10.I (23)
10.J	Hazard Analysis of Critical Control Points (HACCP)	
10.J.1	Prerequisite and Result to be Expected	10.J (2)
10.J.2	Advantages and Disadvantages	10.J (8)
10.J.3	Application Example	10.J (9)
10.K	Conclusion	
11	Production	
11.A	Sanitation	
11.A.1	Organisational prerequisites	11.A (1)
11.A.2	Sources of contamination	11.A (2)
11.A.3	Responsibilities and implementation	11.A (3)
11.B	Personnel hygiene	
11.B.1	Clothing	11.B (1)
11.B.2	Code of Conduct	11.B (11)
11.B.3	Hand disinfection	11.B (14)
11.B.4	Health requirements	11.B (15)
11.B.5	Training	11.B (16)
11.C	Production hygiene	
11.C.1	Sources of contamination	11.C (4)
11.C.2	Cleaning	11.C (11)
11.C.3	Disinfection	11.C (13)
11.D	Sanitation programme	
11.D.1	Organisation of room cleaning	11.D (1)
11.D.2	Documentation	11.D (5)
11.E	Environmental monitoring	
11.E.1	General	11.E (1)

11.E.2	Sampling plan	11.E (3)
11.E.3	Establishment of limits and frequencies	11.E (4)
11.E.4	Methods	11.E (9)
11.E.5	Investigation areas	11.E (11)
11.E.6	Evaluation	11.E (16)
11.F	GMP in the production process	
11.G	Weigh-in	
11.G.1	Legal requirements	11.G (1)
11.G.2	Weigh-in principles	11.G (3)
11.G.3	Weigh-in procedure	11.G (7)
11.G.4	Documentation	11.G (11)
11.H	Identification	
11.H.1	Handling of labels	11.H (1)
11.H.2	Labelling of starting materials	11.H (2)
11.H.3	Labelling of equipment and containers	11.H (3)
11.H.4	Labelling of rooms	11.H (7)
11.I	In-process control	
11.I.1	Objectives	11.I (2)
11.I.2	Organisation and responsibilities	11.I (3)
11.I.3	Carrying out	11.I (4)
11.I.4	Documentation and evaluation of data	11.I (8)
11.J	Prevention of cross-contamination	
11.J.1	Causes of cross-contamination	11.J (1)
11.J.2	Measures to prevent cross-contamination	11.J (5)
11.J.3	Manufacture of critical products	11.J (6)
11.K	Deviations	
11.K.1	Definition	11.K (1)
11.K.2	Procedure	11.K (2)
11.K.3	Responsibilities	11.K (4)
11.K.4	Measures	11.K (4)
11.K.5	Failure investigation report	11.K (5)
11.K.6	Evaluation of measures	11.K (7)
11.K.7	SOP "deviations" – (example)	11.K (9)
11.K.8	Check-list for deviation handling	11.K (14)
11.L	Reworking	
11.L.1	Definitions	11.L (1)
11.L.2	Procedure	11.L (2)
11.L.3	Rework / Reprocessing of rejected products	11.L (4)
11.L.4	Rework of returned products	11.L (8)
11.L.5	Rework of products that have not been rejected	11.L (8)

11.M	Warehouse and logistics	
11.M.1	Regulatory requirements	11.M (1)
11.M.2	Stock management system	11.M (2)
11.M.3	Responsibilities	11.M (6)
11.M.4	Personnel	11.M (6)
11.M.5	Storage areas	11.M (7)
11.M.6	Storage conditions	11.M (13)
11.M.7	Sanitation and pest control	11.M (16)
11.M.8	Material Flow	11.M (18)
11.M.9	Process Flow	11.M (22)
11.N	Transportation	
11.N.1	Requirements for logistic service providers	11.N (2)
11.N.2	Transportation challenges and monitoring devices	11.N (5)
11.N.3	Cool/Cold Chain Distribution	11.N (9)
11.N.4	Temperature Profiles	11.N (13)
11.N.5	Transportation Risks	11.N (18)
11.O	References	
12	Sterile Production	
12.A	Introduction	
12.A.1	Manufacturing products that can be sterilised in the final container	12.A (2)
12.A.2	Aseptic processing	12.A (3)
12.A.3	Production areas/premises	12.A (4)
12.A.4	Production equipment	12.A (7)
12.B	Air Lock Concepts	
12.B.1	Personnel locks in the clean area	12.B (1)
12.B.2	Material locks	12.B (7)
12.C	Manufacturing the solution	
12.C.1	Starting materials	12.C (1)
12.C.2	Solution batch	12.C (4)
12.C.3	Testing the bioburden	12.C (8)
12.C.4	Sterile filtration	12.C (9)
12.D	Washing processes	
12.D.1	Stoppers	12.D (1)
12.D.2	Particulate impurities	12.D (3)
12.D.3	Glass containers (ampoules, bottles)	12.D (5)
12.D.4	Transport	12.D (8)
12.E	Filling	
12.E.1	Filling equipment for solutions	12.E (1)
12.E.2	Process for filling LVP containers in cleanliness grade C	12.E (5)
12.E.3	Process for filling ampoules with solution in cleanliness grade A/B	12.E (8)

12.E.4	Filling ampoules in cleanliness grade C and laminar flow	12.E (8)
12.E.5	Culture medium filling (Media Fill)	12.E (8)
12.E.6	Filling with powders	12.E (13)
12.F	Steam sterilisation	
12.F.1	Sterilisers	12.F (1)
12.F.2	Description of the procedure	12.F (2)
12.F.3	Qualification of a steam steriliser	12.F (6)
12.F.4	Validation of the steam sterilisation process	12.F (11)
12.G	Microbiological monitoring	
12.G.1	Sources of contamination	12.G (1)
12.G.2	Room classification	12.G (2)
12.G.3	Monitoring program	12.G (4)
12.G.4	Sampling	12.G (17)
12.G.5	Sampling points	12.G (20)
12.G.6	Measure if levels are exceeded	12.G (22)
12.G.7	Organism identification	12.G (24)
12.H	Test for sterility	
12.H.1	Parametric release	12.H (1)
12.H.2	Sterility test	12.H (3)
12.H.3	Method description	12.H (10)
12.H.4	Number of samples	12.H (11)
12.H.5	Sample quantity	12.H (12)
12.H.6	Reading and evaluating	12.H (12)
12.H.7	Procedure in the event of culture medium turbidity	12.H (15)
12.H.8	Culture media	12.H (16)
12.H.9	Culture media controls	12.H (17)
12.H.10	Method validation	12.H (18)
12.I	Testing for tightness and particles	
12.I.1	Testing for tightness	12.I (1)
12.I.2	Particle test	12.I (5)
12.I.3	Sequence of operation	12.I (12)
12.J	Freeze drying	
12.J.1	Description of the procedure	12.J (1)
12.J.2	Qualification of a freeze dryer	12.J (6)
12.J.3	Validation of the freeze drying process	12.J (9)
12.K	Dry Heat Sterilisation	
12.K.1	Description of the procedure	12.K (2)
12.K.2	Sterilisation kinetics	12.K (3)
12.K.3	Qualification of a sterilisation tunnel	12.K (5)
12.K.4	Validation of the sterilisation process	12.K (8)

13 Packaging

13.A Packaging material

13.A.1	Responsibilities	13.A (2)
13.A.2	Contents	13.A (2)
13.A.3	Materials	13.A (2)
13.A.4	Protection against counterfeit medicinal products	13.A (6)
13.A.5	Packaging material testing	13.A (7)

13.B Packaging process

13.B.1	Allocation of packaging material	13.B (2)
13.B.2	Line clearance	13.B (3)
13.B.3	Labelling	13.B (6)
13.B.4	Control functions	13.B (6)
13.B.5	Release for production	13.B (8)
13.B.6	In-process controls	13.B (15)
13.B.7	Cleaning primary containers	13.B (21)
13.B.8	Labelling	13.B (21)
13.B.9	Variable data	13.B (22)
13.B.10	Imprints	13.B (23)
13.B.11	Reconciliation	13.B (24)
13.B.12	Safety features	13.B (26)
13.B.13	Completion of a packaging process	13.B (26)

13.C Qualification of a packaging line

13.C.1	Master qualification plan	13.C (2)
13.C.2	Design qualification (DQ)	13.C (8)
13.C.3	Installation qualification (IQ)	13.C (24)
13.C.4	Operational qualification (OQ)	13.C (34)
13.C.5	Performance qualification (PQ)	13.C (46)

14 Laboratory Controls

14.A Sampling

14.A.1	Requirements	14.A (2)
14.A.2	Sampling plan (instructions)	14.A (3)
14.A.3	Notes for the sampling process	14.A (8)

14.B Reagents

14.B.1	Labeling	14.B (2)
14.B.2	Usage and stability	14.B (2)
14.B.3	Documentation	14.B (4)

14.C Standards and reference substances

14.C.1	Definition of different standards and their areas of use	14.C (1)
14.C.2	Handling, storage and stability	14.C (5)

14.D	Qualifying laboratory instruments	
14.D.1	Qualification protocols and reports	14.D (2)
14.D.2	System suitability test (SST)	14.D (5)
14.E	Calibration in the lab	
14.E.1	Definitions	14.E (1)
14.E.2	Calibration instructions and record	14.E (4)
14.E.3	Examples	14.E (5)
14.E.4	Decision	14.E (20)
14.F	Validation of analytical methods	
14.F.1	Principles	14.F (1)
14.F.2	Definitions of the parameters	14.F (3)
14.F.3	Documentation	14.F (6)
14.F.4	Revalidation	14.F (6)
14.G	Stability testing	
14.G.1	ICH guidelines for stability tests	14.G (2)
14.G.2	Storage and storage conditions	14.G (4)
14.G.3	Analyses	14.G (13)
14.G.4	Reduction of the study design	14.G (20)
14.G.5	Stability testing in the marketing phase	14.G (24)
14.G.6	Defining the retest period for an active pharmaceutical ingredient and the shelf life for a drug product through evaluation of stability data (ICH Q1E)	14.G (37)
14.G.7	Decision tree for data evaluation for retest period or for APIs or drug products (excluding frozen products)	14.G (40)
14.G.8	Procedure for statistical analysis	14.G (40)
14.G.9	Examples of the statistical evaluation of stability data	14.G (42)
14.H	Out-of-specification results	
14.H.1	Significance	14.H (1)
14.H.2	Definitions	14.H (4)
14.H.3	FDA OOS Guidance	14.H (4)
14.H.4	Example for handling of an OOS result	14.H (12)
14.H.5	Trend tracking	14.H (13)
14.I	Raw data documentation	
14.I.1	Principles	14.I (1)
14.I.2	Single sheet documentation system	14.I (3)
14.J	Batch release	
14.J.1	Certification by a Qualified Person and release in accordance with EC GMP Guidelines	14.J (4)
14.J.2	Responsibility for issuing the release	14.J (8)
14.J.3	Publication of release	14.J (9)
14.J.4	Release procedures in practice	14.J (10)

14.K	Microbiological testing	
14.K.1	Total microbial count	14.K (2)
14.K.2	Specified microorganisms	14.K (24)
14.K.3	Testing frequencies	14.K (48)
14.K.4	Miscellaneous tests	14.K (52)
14.L	Pharmacopoeias	
14.L.1	Structure of Pharmacopoeias	14.L (1)
14.L.2	General considerations	14.L (2)
14.L.3	Development of Monographs	14.L (3)
14.L.4	European Pharmacopoeia (Ph Eur)	14.L (4)
14.L.5	British Pharmacopoeia (BP)	14.L (7)
14.L.6	United States Pharmacopoeia (USP)	14.L (9)
14.L.7	Japanese Pharmacopoeia (JP)	14.L (11)
14.L.8	International Pharmacopoeia (Ph Int)	14.L (13)
14.L.9	Harmonization	14.L (14)
14.M	References	
15	Documentation	
15.A	Official requirements	
15.A.1	GMP-requirements managed and reviewed according to German pharma business regulations	15.A (1)
15.A.2	Requirements of the EU GMP Guideline	15.A (4)
15.A.3	Requirements of the US GMP Regulations	15.A (8)
15.A.4	Formal requirements	15.A (13)
15.A.5	Management and revision documentation	15.A (17)
15.B	GMP-conforming documentation	
15.B.1	Handwritten entries	15.B (1)
15.B.2	Archiving	15.B (2)
15.B.3	Master-SOP – “GMP-conforming documentation”	15.B (3)
15.C	Batch documentation	
15.C.1	Manufacturing instructions/record	15.C (3)
15.C.2	Packaging instruction and batch packaging record	15.C (26)
15.C.3	Electronic batch recording	15.C (28)
15.C.4	Testing procedures and test protocol	15.C (31)
15.C.5	Batch record review	15.C (36)
15.D	Standard operating procedures (SOPs)	
15.D.1	Compilation	15.D (2)
15.D.2	Approval and implementation	15.D (7)
15.D.3	Training	15.D (7)
15.D.4	Usage	15.D (8)
15.D.5	Review	15.D (9)

15.D.6	Changes	15.D (9)
15.D.7	Withdrawing an operating procedure	15.D (10)
15.D.8	Administration	15.D (10)
15.D.9	Archiving	15.D (12)
15.D.10	Example of an SOP "Compilation and administration of operating procedures"	15.D (13)
15.E	Site master file	
15.E.1	Introduction	15.E (1)
15.E.2	Design	15.E (1)
15.F	Annual product review / Product quality review	
15.F.1	Documents required for an annual product review	15.F (4)
15.F.2	Annual product review report	15.F (6)
15.F.3	Collaboration with a contract manufacturer	15.F (8)
15.F.4	Example: annual product review	15.F (9)
15.F.5	Master-SOP for the annual product review	15.F (14)
16	Research and Development	
16.A	General conditions and legal requirements	
16.B	Development phases and GMP requirements	
16.B.1	Formulation development	16.B (4)
16.B.2	Analytical development	16.B (7)
16.B.3	Manufacturing and testing of stability samples	16.B (11)
16.B.4	Packaging development	16.B (14)
16.B.5	Process development	16.B (16)
16.B.6	Cleaning verification and validation	16.B (19)
16.B.7	Process optimization: Basic principles for process validation	16.B (22)
16.B.8	Up scaling to pilot plant and production scale	16.B (25)
16.B.9	Handover to other manufacturing sites	16.B (27)
16.C	Interfaces to GLP and GCP	
16.C.1	GLP –Good Laboratory Practice	16.C (1)
16.C.2	GCP –Good Clinical Practice	16.C (5)
16.C.3	Interfaces between the areas regulated by GMP and those regulated by GCP	16.C (10)
16.D	Manufacture and control of clinical samples	
16.D.1	Prerequisites for the approval of clinical investigations	16.D (1)
16.D.2	Manufacturing of clinical samples and comparator drugs	16.D (2)
16.D.3	Packaging and labeling	16.D (6)
16.D.4	Control and release of investigational medicinal products	16.D (11)
16.D.5	Storage and shipment of investigational drugs	16.D (14)
16.D.6	Returns, recalls and destruction of clinical samples	16.D (15)

16.E Documentation and recording of changes during development

16.F Development report

17 Contractors and Suppliers

17.A Contract manufacture

17.A.1	Reasons for contract manufacture	17.A (1)
17.A.2	Procedure for assigning manufacturing contracts	17.A (3)
17.A.3	Duties of the contract giver	17.A (9)
17.A.4	Duties of the contract acceptor	17.A (12)
17.A.5	Contract manufacturer agreement	17.A (17)
17.A.6	Audits of contract manufacturers	17.A (21)
17.A.7	SOP for assigning manufacturing contracts	17.A (30)
17.A.8	Framework contract for contract manufacture and quality control	17.A (36)

17.B Contract Analysis

17.B.1	Introduction	17.B (1)
17.B.2	Legal background	17.B (2)
17.B.3	Selection of an external testing laboratory	17.B (3)
17.B.4	Liability limitation contract	17.B (5)
17.B.5	Certificate of Analysis	17.B (14)
17.B.6	Transfer of the test to the contract laboratory	17.B (15)

17.C Suppliers

17.C.1	Introduction	17.C (1)
17.C.2	Definitions	17.C (4)
17.C.3	Quality systems	17.C (5)
17.C.4	Records	17.C (14)
17.C.5	Contracts and quality agreements	17.C (17)
17.C.6	Supplier review and controls	17.C (19)
17.C.7	Supplier audits	17.C (21)
17.C.8	Re-evaluation of Suppliers	17.C (26)
17.C.9	GMP Manual Cross References to Suppliers	17.C (28)

17.D References

18 Inspections

18.A Principles

18.B Inspection procedures

18.B.1	System-based	18.B (1)
18.B.2	Product-based	18.B (2)
18.B.3	Procedure-based	18.B (2)
18.B.4	Area-based	18.B (3)

18.C	Inspectors	
18.C.1	Technical qualification requirements	18.C (1)
18.C.2	Personal requirements	18.C (3)
18.D	Organization of inspections	
18.D.1	Inspection planning	18.D (1)
18.D.2	Inspection preparation	18.D (3)
18.D.3	Carrying out the inspections	18.D (4)
18.D.4	Evaluation and documentation	18.D (8)
18.E	Self-inspection	
18.E.1	Purpose of self-inspection	18.E (1)
18.E.2	Carrying out the self-inspection	18.E (1)
18.E.3	Self-inspection documentation	18.E (3)
18.E.4	Errors and remedial action	18.E (9)
18.E.5	Follow-up activities	18.E (11)
18.F	Inspection of contract manufacturers	
18.F.1	Purpose of the inspection of contract manufacturer	18.F (1)
18.F.2	Carrying out inspections of contract manufacturer	18.F (1)
18.F.3	Handling of changes and deviations	18.F (3)
18.G	Inspection of suppliers	
18.G.1	Purpose of the supplier inspection	18.G (1)
18.G.2	Carrying out the supplier inspection	18.G (2)
18.H	Questionnaire for preparing GMP-inspections	
18.I	References	
19	Quality Unit	
19.A	General	
	This chapter will be part of a later update.	
19.B	The “Qualified Person” according to Directive 2001/83/EC	
19.B.1	Introduction	19.B (1)
19.B.2	Legal background of the European “Qualified Person” regulations	19.B (2)
19.B.3	Qualification and experience	19.B (5)
19.B.4	Duties and responsibilities	19.B (8)
19.B.5	Qualified Person and Pharmaceutical Quality Systems	19.B (26)
19.C	Change control	
19.C.1	Principles of change control	19.C (1)
19.C.2	Introduction and operation of change control programs	19.C (4)
19.C.3	Documentation	19.C (9)
19.D	References	

20 Continual Improvement

20.A Preface

20.B Six Sigma

20.B.1	Definition	20.B (1)
20.B.2	What it is / what it does / how it works	20.B (1)
20.B.3	Goals/Objectives/Benefits	20.B (19)
20.B.4	Implementation	20.B (21)
20.B.5	Tools	20.B (24)
20.B.6	Variations	20.B (25)
20.B.7	Examples	20.B (26)

20.C Statistical Process Control (SPC)

20.C.1	Definition	20.C (1)
20.C.2	What it is /what it does / how it works	20.C (1)
20.C.3	Goals/Objectives/Benefits	20.C (32)
20.C.4	Implementation	20.C (33)
20.C.5	Tools	20.C (36)
20.C.6	Variations	20.C (36)
20.C.7	Examples	20.C (36)

20.D Process Analytical Technology (PAT)

20.D.1	Definition	20.D (1)
20.D.2	The Role of PAT in Pharmaceutical Manufacturing	20.D (1)
20.D.3	Regulatory Perspective and Guidances	20.D (5)
20.D.4	PAT instrumentation	20.D (11)
20.D.5	Application of PAT in a GMP environment	20.D (13)
20.D.6	Examples of PAT Applications	20.D (19)

20.E References

21 Active and Inactive Ingredients

21.A GMP for Active Pharmaceutical Ingredients (APIs)

21.A.1	Introduction	21.A (1)
21.A.2	Quality management	21.A (6)
21.A.3	Personnel	21.A (13)
21.A.4	Buildings and facilities	21.A (15)
21.A.5	Process equipment	21.A (21)
21.A.6	Documentation and records	21.A (25)
21.A.7	Materials management	21.A (33)
21.A.8	Production and in-process controls	21.A (36)
21.A.9	Packaging and identification labelling of APIs and intermediates	21.A (43)
21.A.10	Storage and distribution	21.A (47)
21.A.11	Laboratory controls	21.A (49)
21.A.12	Validation	21.A (55)

21.A.13	Change Control	21.A (59)
21.A.14	Rejection and re-use of materials	21.A (63)
21.A.15	Complaints and Recalls	21.A (70)
21.A.16	Contract manufacturers, including laboratories	21.A (70)
21.A.17	Agents, brokers, traders, distributors, repackers, and relabellers	21.A (72)
21.A.18	Specific guidance for APIs manufactured by cell culture/fermentation	21.A (75)
21.A.19	APIs for use in clinical trials	21.A (81)
21.B	GMP for APIs – considerations on special topics	
21.B.1	Materials management	21.B (1)
21.B.2	Production and maintenance	21.B (9)
21.B.3	Re-use and recovery of materials	21.B (23)
21.B.4	Interaction with brokers	21.B (32)
21.C	Excipients	
21.C.1	Introduction	21.C (1)
21.C.2	Regulatory aspects and guidance documents	21.C (6)
21.C.3	Safety, toxicological, and precedence of use issues	21.C (36)
21.C.4	Compendial monographs	21.C (39)
21.C.5	Excipient Master Files and other filings	21.C (45)
21.C.6	Applicability of ICH guidance to excipients	21.C (48)
21.C.7	Other aspects critical to the marketing of excipients	21.C (50)
21.D	References	
22	Biologics	
	This chapter is left empty in order to facilitate later additions.	
23	Medical Devices	
23.A	Introduction	
23.A.1	Definition	23.A (2)
23.A.2	Types of medical devices	23.A (3)
23.A.3	Regulatory background	23.A (5)
23.A.4	Process approach to a Quality Management System	23.A (10)
23.B	Quality Management System (QMS)	
23.B.1	Management responsibility	23.B (1)
23.B.2	Quality manual	23.B (4)
23.B.3	Quality policy	23.B (5)
23.B.4	Quality planning	23.B (6)
23.B.5	Management review	23.B (7)
23.B.6	Audits	23.B (10)
23.C	Personnel	
23.C.1	General	23.C (1)
23.C.2	Training	23.C (2)

23.C.3	Health, hygiene, practices, and clothing	23.C (3)
23.C.4	Consultants and contractors	23.C (4)
23.D	Design control	
23.D.1	General	23.D (1)
23.D.2	Design planning	23.D (4)
23.D.3	Design input	23.D (5)
23.D.4	Design output	23.D (9)
23.D.5	Design review	23.D (10)
23.D.6	Design verification	23.D (12)
23.D.7	Design validation / Clinical evaluation	23.D (15)
23.D.8	Design transfer	23.D (17)
23.D.9	Design changes	23.D (18)
23.D.10	Design history file	23.D (20)
23.E	Human factors	
23.F	Statistical techniques	
23.G	Risk management	
23.H	Document and record control	
23.H.1	Control of documents	23.H (1)
23.H.2	Control of records	23.H (4)
23.I	Production and process controls	
23.I.1	Manufacturing materials	23.I (2)
23.I.2	Automated processes	23.I (2)
23.I.3	Sterile products	23.I (3)
23.I.4	Changes	23.I (4)
23.I.5	Material acceptance procedures	23.I (4)
23.J	Identification and traceability	
23.J.1	Identification	23.J (1)
23.J.2	Traceability	23.J (1)
23.K	Buildings, facilities, and equipment	
23.K.1	Buildings and facilities	23.K (1)
23.K.2	Environment	23.K (2)
23.K.3	Equipment	23.K (3)
23.L	Validation	
23.M	Purchasing/supplier control	
23.M.1	Purchase orders	23.M (3)
23.M.2	Quality agreements	23.M (3)
23.N	Packaging and labeling	
23.N.1	Packaging	23.N (1)
23.N.2	Manufacturer's information	23.N (1)

23.O	Handling, storage, distribution, installation and servicing	
23.O.1	Handling	23.O (1)
23.O.2	Storage	23.O (2)
23.O.3	Distribution	23.O (2)
23.O.4	Installation	23.O (3)
23.O.5	Servicing	23.O (3)
23.P	Nonconformance, Corrective Action and Preventive Action	
23.P.1	Definitions	23.P (1)
23.P.2	CAPA System	23.P (1)
23.P.3	Nonconforming product	23.P (5)
23.P.4	Advisory notice, device correction or product recall	23.P (5)
23.Q	Customer complaints	
23.Q.1	Complaint evaluation	23.Q (2)
23.Q.2	Complaint investigation	23.Q (2)
23.R	Combination products	
23.S	References	