

Contents

File 1 to 3

1	Quality Management	
1.A	Quality management in the pharmaceutical environment	
1.A.1	Quality assurance in the GMP regulations	1.A (1)
1.A.2	From quality assurance to quality management	1.A (3)
1.A.3	Position of quality assurance in the company	1.A (4)
1.A.3.1	<i>Quality Unit as a staff function</i>	1.A (4)
1.A.3.2	<i>Quality Unit as a matrix function</i>	1.A (5)
1.A.4	Responsibility of the Quality Unit	1.A (7)
1.A.5	Tasks of a Quality Unit	1.A (9)
1.B	Documentation of a QM system	
1.B.1	Structure of a documentation system	1.B (1)
1.B.1.1	<i>Management board level</i>	1.B (3)
1.B.1.2	<i>Management/superiors</i>	1.B (4)
1.B.1.3	<i>Staff level</i>	1.B (4)
1.B.1.4	<i>Quality unit documents</i>	1.B (4)
1.B.1.5	<i>Procedure description and procedure instruction</i>	1.B (5)
1.B.1.6	<i>Operating procedure</i>	1.B (6)
1.B.2	Documents required in accordance with GMP	1.B (7)
1.B.3	Quality management handbook	1.B (9)
1.B.3.1	<i>Site master file</i>	1.B (9)
1.B.3.2	<i>Handbook in accordance with EN ISO 9001:2000</i>	1.B (11)
1.B.3.3	<i>Combined handbooks in accordance with GMP and ISO</i>	1.B (13)
1.B.3.4	<i>Functions of the quality management handbook</i>	1.B (17)
1.C	Quality management system in accordance with GMP	
1.C.1	Management responsibility	1.C (2)
1.C.1.1	<i>Responsibility of key personnel</i>	1.C (2)
1.C.1.2	<i>Responsibility of the management board</i>	1.C (2)
1.C.1.3	<i>Definition of quality policy</i>	1.C (5)
1.C.1.4	<i>Definition of quality objectives</i>	1.C (6)
1.C.1.5	<i>Support of the quality management system</i>	1.C (6)
1.C.1.6	<i>Deciding on resources</i>	1.C (7)
1.C.1.7	<i>Management review</i>	1.C (8)
1.C.2	Change management system	1.C (9)
1.C.2.1	<i>Definition of terms</i>	1.C (9)
1.C.2.2	<i>Processing of changes and deviations</i>	1.C (10)

1.C.2.3	<i>Processing of OOS results</i>	1.C (13)
1.C.2.4	<i>Involvement of external companies</i>	1.C (14)
1.C.3	Complaints and recall	1.C (15)
1.C.3.1	<i>Definition of terms</i>	1.C (15)
1.C.3.2	<i>Processing of complaints</i>	1.C (16)
1.C.3.3	<i>Responsibilities</i>	1.C (16)
1.C.3.4	<i>Compilation of a standard operating procedure (SOP)</i>	1.C (17)
1.C.3.5	<i>Recall</i>	1.C (21)
1.C.3.6	<i>Trend analysis</i>	1.C (22)
1.C.4	Corrective and Preventive Actions (CAPA)	1.C (22)
1.C.4.1	<i>Definitions</i>	1.C (23)
1.C.4.2	<i>Quality management system for CAPA</i>	1.C (23)
1.C.5	Risk management	1.C (26)
1.C.5.1	<i>Aims of risk management</i>	1.C (27)
1.C.6	Qualification and validation	1.C (28)
1.C.6.1	<i>Tasks of the Quality Unit</i>	1.C (29)
1.C.6.2	<i>Tasks of the management board</i>	1.C (29)
1.C.6.3	<i>Quality management system for qualification</i>	1.C (30)
1.C.6.4	<i>Quality management system for validation</i>	1.C (34)
1.C.7	Training	1.C (35)
1.C.7.1	<i>Compilation of a standard operating procedure (SOP)</i>	1.C (36)
1.C.7.2	<i>Compilation of an annual program</i>	1.C (36)
1.C.7.3	<i>Compilation of a training plan</i>	1.C (36)
1.C.7.4	<i>Guaranteeing participation</i>	1.C (37)
1.C.8	Inspection	1.C (37)
1.C.8.1	<i>Compilation of a standard operating procedure</i>	1.C (38)
1.C.8.2	<i>Contents of the audit program</i>	1.C (38)
1.C.8.3	<i>Contents of an audit plan</i>	1.C (39)
1.C.9	Batch record review and annual product review	1.C (42)
1.C.9.1	<i>Batch record review</i>	1.C (42)
1.C.9.2	<i>Annual product review</i>	1.C (44)
1.C.10	Qualification of suppliers and service providers	1.C (45)
1.C.10.1	<i>Responsibilities</i>	1.C (50)
1.C.10.2	<i>Risk analysis for grading</i>	1.C (50)
1.C.10.3	<i>Carrying out</i>	1.C (51)
1.C.10.4	<i>Requalification</i>	1.C (54)

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.6.1	<i>External factors</i>	2.C (4)
2.C.6.2	<i>Qualification of the trainer</i>	2.C (5)
2.C.6.3	<i>Training methods</i>	2.C (5)
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.1.1	<i>Requirements of the Qualified Person in accordance with European law</i>	2.D (1)
2.D.1.2	<i>Area of responsibility of the Qualified Person in accordance with European Law</i>	2.D (3)
2.D.1.3	<i>Organisational appointment/substitution regulations</i>	2.D (7)
2.D.2	Head of Production	2.D (12)
2.D.2.1	<i>Individual requirements for Head of Production</i>	2.D (12)
2.D.2.2	<i>Areas of Responsibility of the Head of Production</i>	2.D (12)
2.D.3	Head of Quality Control	2.D (17)
2.D.3.1	<i>Individual Requirements for the Head of Quality Control</i>	2.D (17)
2.D.3.2	<i>Areas of Responsibility of the Head of Quality Control</i>	2.D (17)
2.D.4	Qualified Person in Accordance with Article 103 of Guideline 2001/83/EC	2.D (21)
2.D.4.1	<i>Individual Requirements for the Qualified Person in Accordance with Article 103</i>	2.D (21)
2.D.4.2	<i>Areas of Responsibility of the Qualified Person in Accordance with Article 103 of Directive 2001/83/EC</i>	2.D (22)
2.D.5	Scientific Service in Charge of Information	2.D (24)
2.D.5.1	<i>Individual Requirements for the Scientific Service in Charge of Information</i>	2.D (24)
2.D.5.2	<i>Areas of Responsibility of the Scientific Service in Charge of Information</i>	2.D (24)
2.D.6	Medical sales representatives	2.D (26)
2.D.6.1	<i>Individual requirements for medical sales representatives</i>	2.D (26)
2.D.6.2	<i>Areas of responsibility of the medical sales representative</i>	2.D (26)
3	Premises	
3.A	Official requirements	
3.B	General requirements	
3.B.1	Location, connection to other rooms	3.B (2)
3.B.2	Size, area, height	3.B (3)
3.B.3	Installation and supply of utilities	3.B (3)
3.B.4	Lighting, ventilation, air-conditioning	3.B (5)
3.B.5	Hygienic construction	3.B (5)
3.B.6	Room book and layout	3.B (5)

3.C	Material flow, personnel flow and layout	
3.C.1	Material flow	3.C (1)
3.C.2	Personnel flow	3.C (4)
3.C.3	Layout	3.C (4)
3.C.4	Design concepts in FDA's Sterile Drug Products Produced by Aseptic Processing guideline	3.C (5)
3.D	Room classes	
3.D.1	EU Aseptic Processing GMPs	3.D (1)
3.D.2	Critical areas in the FDA's Sterile Drug Products Produced by Aseptic Processing guideline	3.D (3)
3.D.2.1	<i>Critical Areas</i>	3.D (3)
3.D.2.2	<i>Supporting Clean Areas</i>	3.D (5)
3.E	Construction elements	
3.E.1	Walls	3.E (1)
3.E.2	Doors and windows	3.E (6)
3.E.3	Floors	3.E (8)
3.E.4	Ceilings	3.E (10)
3.F	Building services	
3.G	Room qualification	
3.H	Heating Ventilation Air Conditioning (HVAC)	
3.H.1	Introduction	3.H (1)
3.H.2	Room ventilation systems	3.H (2)
3.H.2.1	<i>Pure (100%) external air conditioning system</i>	3.H (3)
3.H.2.2	<i>Central recirculating air/mixed air conditioning system</i>	3.H (4)
3.H.2.3	<i>Decentralized recirculating air/mixed air conditioning system with central external air preparation</i>	3.H (5)
3.H.2.4	<i>Pure recirculating air conditioning system</i>	3.H (6)
3.H.2.5	<i>Systems for tempering and volume flow regulation</i>	3.H (7)
3.H.2.6	<i>Control-systems of the air volume flows</i>	3.H (8)
3.H.2.7	<i>Utilities for the operation of room ventilation systems</i>	3.H (8)
3.H.3	Filters	3.H (10)
3.H.3.1	<i>Particle air filter</i>	3.H (11)
3.H.3.2	<i>Suspended matter filter – HEPA-Filter</i>	3.H (13)
3.H.3.3	<i>Air Filtration in the FDA's Sterile Drug Products Produced by Aseptic Processing guideline</i>	3.H (20)
3.H.4	Principles for the design and planning of air conditioning ventilation systems	3.H (22)
3.H.5	Design criteria for the ventilation of premises	3.H (27)
3.H.5.1	<i>Air technology design of a sterile room with negative pressure plenum</i>	3.H (28)
3.H.5.2	<i>Pressure stages and design of the pressure differential measurement for a sterile area</i>	3.H (29)
3.H.5.3	<i>Pressure Differentials in the FDA's Sterile Drug Products Produced by Aseptic Processing guideline</i>	3.H (30)

3.H.6	Maintenance of air ventilation systems	3.H (36)
3.H.6.1	<i>Time intervals for carrying out inspections or servicing</i>	3.H (39)
3.H.6.2	<i>Tolerances for inspection and servicing deadlines</i>	3.H (40)
3.H.6.3	<i>Maintenance plan</i>	3.H (40)
3.H.6.4	<i>Forms for the inspection and servicing of ventilation systems</i>	3.H (41)
3.H.6.5	<i>Log book for air technology systems</i>	3.H (51)
3.H.7	Qualification of air conditioning ventilation systems	3.H (53)
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.1.1	<i>Definition</i>	4.I (1)
4.I.1.2	<i>Cleaning mechanisms</i>	4.I (2)

4.1.2	CIP systems	4.1 (3)
4.1.2.1	<i>CIP facility for stack cleaning</i>	4.1 (3)
4.1.2.2	<i>CIP facility for lost cleaning</i>	4.1 (4)
4.1.3	GMP-conforming design of CIP facilities	4.1 (6)
4.1.3.1	<i>Influences of the surfaces</i>	4.1 (6)
4.1.3.2	<i>Requirements for pipes and tanks</i>	4.1 (7)
4.1.3.3	<i>Requirements for bonding elements and seals</i>	4.1 (8)
4.1.3.4	<i>Requirements for pumps</i>	4.1 (9)
4.1.3.5	<i>Requirement for valves</i>	4.1 (10)
4.1.3.6	<i>Requirements for measuring instruments</i>	4.1 (10)
4.1.4	Nozzle heads for container cleaning	4.1 (11)
4.1.4.1	<i>Spray ball</i>	4.1 (12)
4.1.4.2	<i>Rotating nozzle head</i>	4.1 (12)
4.1.4.3	<i>Targeted jet/orbital cleaner</i>	4.1 (12)
4.1.5	Measuring technology	4.1 (13)
4.1.5.1	<i>Flow measurement</i>	4.1 (13)
4.1.5.2	<i>Pressure measurement</i>	4.1 (13)
4.1.5.3	<i>Temperature measurement</i>	4.1 (14)
4.1.5.4	<i>Conductivity measurement</i>	4.1 (14)
4.1.6	Realisation of cleaning systems	4.1 (15)
4.J	Containment (personnel protection) in solids handling	
4.J.1	Significance	4.J (1)
4.J.1.1	<i>Use of laminar flow units</i>	4.J (1)
4.J.1.2	<i>Working in the full protection suit</i>	4.J (2)
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.5.1	<i>The FIBC (Flexible Intermediate Bulk Container) as a containment system</i>	4.J (9)
4.J.5.2	<i>Isolators as a containment system</i>	4.J (10)
4.J.5.3	<i>Transport and docking system for the FIBC</i>	4.J (12)
4.J.5.4	<i>Feasibility study (mock-up)</i>	4.J (12)
4.J.5.5	<i>Particle measurement of facilities in accordance with SMEPAC</i>	4.J (13)
4.J.5.6	<i>Documentation and results</i>	4.J (15)
4.J.6	Containment weak points	4.J (15)
4.J.7	Containment systems for filling and emptying drums	4.J (16)
4.J.7.1	<i>Drum filling with endless liner</i>	4.J (16)
4.J.7.2	<i>Drum filling and emptying with DCS (Drum Containment System)</i>	4.J (17)
4.J.7.3	<i>Big Bag emptying and filling with a protective liner system</i>	4.J (20)
4.J.8	Container systems	4.J (23)
4.J.8.1	<i>Container with outlet cone for discharging</i>	4.J (23)
4.J.8.2	<i>Containment Transfer Unit at the container inlet for filling</i>	4.J (24)
4.J.8.3	<i>Split valve systems</i>	4.J (25)
4.J.8.4	<i>Laminar flow, Glove box systems (isolators)</i>	4.J (26)

4.J.9	Filter systems	4.J (27)
4.J.10	Sampling	4.J (28)
4.J.10.1	System 1: Sampling via a withdrawal screw fitted in the production area	4.J (28)
4.J.10.2	System 2: Sampling via a micro Powder Transfer System (MPTS)	4.J (29)
4.J.11	Containment on equipment	4.J (30)
4.J.11.1	Example 1: Shaft leadthroughs	4.J (30)
4.J.11.2	Example 2: Filling and discharging cone dryers	4.J (31)
4.J.11.3	Practical example of a containment API plant	4.J (31)
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.1.1	Weaknesses in facility planning	4.L (2)
4.L.2	Surfaces	4.L (3)
4.L.2.1	Product-contact surfaces	4.L (3)
4.L.2.2	Non-product-contact surfaces	4.L (4)
4.L.3	Material: stainless steel	4.L (6)
4.L.3.1	Coating of stainless steel surfaces	4.L (8)
4.L.3.2	Welds	4.L (8)
4.L.4	Connections	4.L (11)
4.L.4.1	Flange and quick release connections	4.L (11)
4.L.4.2	Flexible connections	4.L (17)
4.L.4.3	Screw connections	4.L (19)
4.L.5	Hoists and roller conveyors	4.L (22)
4.L.5.1	Hoists	4.L (22)
4.L.5.2	Roller conveyors	4.L (23)
4.L.6	Pneumatic conveyor system	4.L (25)
4.L.6.1	Vacuum conveyor with separator	4.L (25)
4.L.6.2	Powder transport system (PTS)	4.L (26)
4.L.7	Dosing systems	4.L (26)
4.L.7.1	Vibration dosing device	4.L (27)
4.L.7.2	Dosing screw	4.L (27)
4.L.7.3	Slide dosing gate (knife-gate)	4.L (27)
4.L.7.4	Flexidos dosing system	4.L (28)
4.L.7.5	Transbatch feeder	4.L (28)
4.L.8	Platforms and stands	4.L (28)
4.L.8.1	Platforms	4.L (28)
4.L.8.2	Stands	4.L (30)
4.L.9	Clean room installations	4.L (31)
4.L.9.1	Rail design	4.L (31)

4.L.9.2	Control panels	4.L (32)
4.L.9.3	Cable ducts	4.L (33)

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.2.1	Purified Water filled into containers (Packaged Purified Water)	5.A (5)
---------	---	---------

5.A.3	Highly purified water	5.A (5)
-------	-----------------------	---------

5.A.4	Water for injection	5.A (7)
-------	---------------------	---------

5.A.4.1	Sterilized Water for Injection	5.A (8)
---------	--------------------------------	---------

5.A.4.2	Water for Injection: special USP monographs	5.A (10)
---------	---	----------

5.B Generation of pharmaceutical water

5.B.1	Purified water (PW)	5.B (2)
-------	---------------------	---------

5.B.1.1		Airbreak 5.B (2)
---------	--	------------------

5.B.1.2	Softener	5.B (2)
---------	----------	---------

5.B.1.3	Removal of chlorine	5.B (2)
---------	---------------------	---------

5.B.1.4	Reverse osmosis	5.B (4)
---------	-----------------	---------

5.B.1.5	Electrodeionization (EDI, CDI)	5.B (6)
---------	--------------------------------	---------

5.B.1.6	Ultra filtration	5.B (8)
---------	------------------	---------

5.B.1.7	Ion exchanger	5.B (9)
---------	---------------	---------

5.B.1.8	Purification plants	5.B (9)
---------	---------------------	---------

5.B.2	Water for injection (WFI)	5.B (10)
-------	---------------------------	----------

5.B.2.1	Distillation technology	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.1.1	Flow rate and turbulent flow	5.C (2)
---------	------------------------------	---------

5.C.1.2	Pipes	5.C (3)
---------	-------	---------

5.C.1.3	Requirements of welds	5.C (4)
---------	-----------------------	---------

5.C.1.4	Dead end piping	5.C (5)
---------	-----------------	---------

5.C.1.5	Use of plastics (PVDF)	5.C (6)
---------	------------------------	---------

5.C.2	Fixtures	5.C (6)
-------	----------	---------

5.C.2.1	Valves	5.C (6)
---------	--------	---------

5.C.2.2	Sensors	5.C (7)
---------	---------	---------

5.C.2.3	Sterile filter	5.C (7)
---------	----------------	---------

5.C.2.4	Sampling points	5.C (7)
---------	-----------------	---------

5.C.3	Measuring technique	5.C (7)
-------	---------------------	---------

5.C.3.1	Level measurement	5.C (8)
---------	-------------------	---------

5.C.3.2	Flow measurement	5.C (12)
---------	------------------	----------

5.C.3.3	Conductivity measurement	5.C (15)
---------	--------------------------	----------

5.C.3.4	Pressure measurement	5.C (16)
---------	----------------------	----------

5.C.3.5	Temperature measurement	5.C (18)
---------	-------------------------	----------

5.C.3.6	Ozone measurement (online)	5.C (19)
---------	----------------------------	----------

5.C.3.7	<i>TOC measurement (online)</i>	5.C (20)
5.C.4	Formation of biofilms	5.C (21)
5.C.5	Rouging	5.C (23)
5.C.5.1	<i>What is rouging?</i>	5.C (23)
5.C.5.2	<i>Impact on the water quality</i>	5.C (24)
5.C.5.3	<i>Handling rouging</i>	5.C (24)
5.C.5.4	<i>How can you detect rouging?</i>	5.C (25)
5.C.5.5	<i>Measures against rouging</i>	5.C (26)
5.C.6	Buffering of ultra pure water	5.C (27)
5.C.7	Loop with subloops	5.C (29)
5.C.7.1	<i>Cleanability of the loop for purified water</i>	5.C (29)
5.C.7.2	<i>Valve groupings</i>	5.C (30)
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.3.1	<i>User requirements</i>	5.D (8)
5.D.3.2	<i>Technical specifications</i>	5.D (10)
5.D.3.3	<i>Test protocol</i>	5.D (13)
5.D.3.4	<i>Test record</i>	5.D (14)
5.D.4	Installation qualification	5.D (17)
5.D.4.1	<i>Facility documentation</i>	5.D (17)
5.D.4.2	<i>Test protocol</i>	5.D (20)
5.D.4.3	<i>IQ test record</i>	5.D (24)
5.D.5	Operational qualification (OQ)	5.D (28)
5.D.5.1	<i>Test protocol (OQ)</i>	5.D (30)
5.D.5.2	<i>Test record</i>	5.D (32)
5.D.6	Transfer to the user	5.D (36)
5.D.6.1	<i>Transfer report</i>	5.D (36)
5.D.7	Process validation/performance qualification (PQ)	5.D (42)
5.D.7.1	<i>Microbiological tests for pharmaceutical water</i>	5.D (42)
5.D.7.2	<i>Determination of alert and action limits</i>	5.D (45)
5.D.7.3	<i>Sampling</i>	5.D (46)
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.1.1	<i>Sanitization</i>	5.E (1)
5.E.1.2	<i>Sterilization procedure</i>	5.E (2)
5.E.1.3	<i>Disinfection</i>	5.E (3)
5.E.2	Maintenance of a water supply	5.E (4)
5.E.2.1	<i>Quality-relevant maintenance</i>	5.E (6)
5.E.2.2	<i>Safety-relevant maintenance</i>	5.E (8)
5.E.2.3	<i>Value-maintaining maintenance</i>	5.E (9)
5.E.3	Calibration of measuring systems	5.E (10)

5.E.4	Change control	5.E (11)
5.E.4.1	<i>Major and minor changes</i>	5.E (11)
5.E.5	Requalification	5.E (13)
5.E.5.1	<i>Requalification after major changes</i>	5.E (13)
5.E.5.2	<i>Requalification after a defined interval</i>	5.E (13)
5.E.6	Decommissioning/uninstalling	5.E (14)
5.E.6.1	<i>Shutting down the water supply</i>	5.E (14)
5.E.6.2	<i>Disassembly work on the facility</i>	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.2.1	<i>Pharmacopeial requirements</i>	5.F (3)
5.F.2.2	<i>DIN EN 285 (1997-2)</i>	5.F (4)
5.F.2.3	<i>DIN 58950 part 7 (April 2003)</i>	5.F (5)
5.F.3	Pure steam generation	5.F (6)
5.F.3.1	<i>Degassing</i>	5.F (6)
5.F.3.2	<i>Natural circulation procedure</i>	5.F (7)
5.F.3.3	<i>Downdraft procedure</i>	5.F (8)
5.F.3.4	<i>Pure steam generator with external heat exchanger</i>	5.F (8)
5.F.3.5	<i>Separation systems</i>	5.F (9)
5.F.3.6	<i>Quality-relevant measuring points</i>	5.F (9)
5.F.4	Pure steam distribution system	5.F (10)
5.F.4.1	<i>Planning and layout</i>	5.F (10)
5.F.4.2	<i>Condensate drain</i>	5.F (15)
5.F.4.3	<i>Insulation</i>	5.F (19)
5.F.4.4	<i>Pressure reducing valve</i>	5.F (19)
5.F.4.5	<i>Safety valve</i>	5.F (20)
5.F.4.6	<i>Pipe connections</i>	5.F (21)
5.F.4.7	<i>Sampling cooler</i>	5.F (21)
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.5.1	<i>Integration of external capacities ("consultants") into the qualification process</i>	6.B (7)
6.B.5.2	<i>Transfer of parts of qualification activities to consulting engineers</i>	6.B (7)
6.B.5.3	<i>Transfer of qualification activities to suppliers, acquisition of qualification packages</i>	6.B (8)
6.B.6	Risk analysis	6.B (10)
6.B.6.1	<i>Risk analysis during the life cycle of a facility</i>	6.B (11)
6.B.6.2	<i>Organization of risk analysis</i>	6.B (12)
6.B.6.3	<i>Implementation of the risk analysis</i>	6.B (13)
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.1.1	<i>Example: Reaction vessel</i>	6.D (5)
6.D.1.2	<i>Example: Washer</i>	6.D (8)
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.1.1	<i>Materials and lubricants</i>	6.E (4)
6.E.1.2	<i>Supply of (energy and media) utilities</i>	6.E (7)
6.E.1.3	<i>Measuring and control technology points and initial calibration</i>	6.E (9)
6.E.1.4	<i>Calibration records</i>	6.E (11)
6.E.1.5	<i>P & I diagrams</i>	6.E (13)
6.E.1.6	<i>Pipes</i>	6.E (15)
6.E.1.7	<i>Technical documentation</i>	6.E (17)
6.E.1.8	<i>IQ report</i>	6.E (20)
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.1.1	<i>Safety devices</i>	6.F (4)
6.F.1.2	<i>Risk analysis operating functions</i>	6.F (6)
6.F.1.3	<i>Check for the presence of screw caps</i>	6.F (8)
6.F.1.4	<i>OQ report</i>	6.F (11)
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.1.1 *Legal requirements for drug products* 7.A (1)

7.A.1.2 *Responsibilities* 7.A (2)

7.A.1.3 *GMP Requirements* 7.A (3)

7.A.1.4 *Aspects regarding marketing authorization* 7.A (4)

7.A.2 Principles of process validation 7.A (9)

7.A.2.1 *Process understanding* 7.A (10)

7.A.2.2 *Type and scope of process validation* 7.A (10)

7.A.2.3 *Traceability of validation investigations* 7.A (13)

7.A.2.4 *Manufacturing under routine conditions* 7.A (13)

7.A.2.5 *Bracketing (product group formation)* 7.A (14)

7.A.2.6 *Challenge tests* 7.A (14)

7.A.2.7 *Deviations* 7.A (14)

7.A.3 Types of validation 7.A (15)

7.A.3.1 *Prospective validation* 7.A (15)

7.A.3.2 *Concurrent validation* 7.A (16)

7.A.3.3 *Retrospective validation* 7.A (18)

7.A.4 Revalidation 7.A (19)

7.A.4.1 *Validation master plan* 7.A (21)

7.A.4.2 *Validation protocol and report* 7.A (22)

7.A.4.3 *Archiving* 7.A (23)

7.A.5 Maintaining the validation status 7.A (24)

7.A.5.1 *General conditions and prerequisites* 7.A (24)

7.A.5.2 *Principles of statistical process control* 7.A (25)

7.A.5.3 *Quality control cards* 7.A (28)

7.A.5.4 *Process capability investigation* 7.A (32)

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.D.2.1 *Changes to the manufacturing instructions* 7.D (2)

7.D.2.2 *Extension of the ranges of critical process parameters* 7.D (5)

7.D.2.3	<i>Changes in manufacturing site</i>	7.D (5)
7.D.2.4	<i>Serious quality problems</i>	7.D (6)
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.E.4.1	<i>What action should be taken if not all prerequisites have yet been fulfilled?</i>	7.E (11)
7.E.4.2	<i>Manufacture of a development or pilot batch in the run-up to a validation</i>	7.E (12)
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.H.2.1	<i>How to deal with deviations from the requirements in the validation protocol</i>	7.H (11)
7.H.2.2	<i>Archiving of the validation documents</i>	7.H (11)
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 (7)
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	Validatability of cleaning procedures	
8.B.1	Optimisation 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 (7)
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 (9)
8.E.3	Determination of the microbial status	8.E (10)
8.F	Sampling procedures	
8.F.1	Swab test	8.F (1)
8.F.2	Rinse test	8.F (3)
8.F.3	Other procedures	8.F (5)
8.F.4	Selection of the appropriate procedure	8.F (7)
8.F.5	Microbiological testing of surfaces	8.F (8)
8.G	Analytical procedures	
8.G.1	Requirements for method validation	8.G (1)
8.G.2	Selection of the appropriate analytical method	8.G (6)
8.H	Documentation	
8.H.1	Validation protocol	8.H (1)
8.H.2	Validation report	8.H (3)
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 (2)
8.I.3	Revalidation	8.I (3)
8.I.3.1	<i>Change-related revalidation</i>	8.I (3)
8.I.3.2	<i>Periodic revalidation</i>	8.I (6)
8.I.4	New products and equipment	8.I (7)
8.I.4.1	<i>New products</i>	8.I (8)
8.I.4.2	<i>New equipment</i>	8.I (8)
8.I.5	Deviations	8.I (10)
8.J	Cleaning validation documentation (example)	
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.A.2.1	<i>Validation of computerised systems</i>	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 and electronic records	9.B (5)
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.1.1	<i>Class 1 – Operating system</i>	9.D (1)
9.D.1.2	<i>Class 2 – Firmware</i>	9.D (1)
9.D.1.3	<i>Class 3 – Standard software packages</i>	9.D (2)
9.D.1.4	<i>Class 4 – Configurable standard software packages</i>	9.D (2)
9.D.1.5	<i>Class 5 – Customer-specific software</i>	9.D (2)
9.D.1.6	<i>Validation tasks depending on classification</i>	9.D (2)
9.D.1.7	<i>Risk classification in accordance with GAMP</i>	9.D (5)
9.D.2	Risk indexes	9.D (5)
9.D.2.1	<i>Determining the risk index</i>	9.D (5)
9.D.2.2	<i>Measures that depend on the risk index</i>	9.D (9)
9.D.3	Risk management at the level of user requirements	9.D (13)
9.E	Validation of computerised systems	
9.E.1	Responsibility and organisation	9.E (1)
9.E.1.1	<i>Responsibilities</i>	9.E (1)
9.E.1.2	<i>Organisation</i>	9.E (1)
9.E.1.3	<i>Validation policy</i>	9.E (3)
9.E.1.4	<i>Inventory of systems</i>	9.E (3)
9.E.2	Validation plan	9.E (4)
9.E.2.1	<i>System description</i>	9.E (4)
9.E.2.2	<i>The validation process</i>	9.E (5)
9.E.2.3	<i>Acceptance criteria</i>	9.E (5)
9.E.2.4	<i>Planned deliverables</i>	9.E (5)
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.4.1	<i>Test stages in the V model</i>	9.E (12)
9.E.4.2	<i>Test method</i>	9.E (14)
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.7.1	<i>Example: Steam autoclave (low risk index)</i>	9.E (19)

9.E.7.2	<i>Example: spreadsheet</i>	9.E (21)
9.E.7.3	<i>Laboratory systems</i>	9.E (33)
9.E.8	Dealing with existing systems (legacy systems)	9.E (34)
9.E.8.1	<i>Analysis of the actual status</i>	9.E (34)
9.E.8.2	<i>Experience report</i>	9.E (36)

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.4.1	<i>Authorised access</i>	9.F (2)
9.F.4.2	<i>Security</i>	9.F (4)
9.F.5	Data backup and archiving	9.F (5)
9.F.5.1	<i>Data backup</i>	9.F (5)
9.F.5.2	<i>Archiving</i>	9.F (6)
9.F.6	Contingency plans and data recovery	9.F (7)
9.F.7	Change management and error reporting	9.F (8)
9.F.7.1	<i>Change management</i>	9.F (8)
9.F.7.2	<i>Error reporting</i>	9.F (9)
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.2.1	<i>Contents of a service level agreement</i>	9.G (3)
9.G.2.2	<i>Example of a service level agreement</i>	9.G (4)
9.G.3	Auditing of suppliers and service providers	9.G (8)

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.C.6.1	1st level: Quality Management System	10.C (6)
10.C.6.2	2nd level: local SOP	10.C (7)
10.C.6.3	3rd level: Application to a Specific Manufacturing Process	10.C (9)
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.1.1	Step 1: Prerequisites	10.F (2)
10.F.1.2	Step 2: Draw	10.F (2)
10.F.1.3	Step 3: Conclusions	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.2.1	Step 1: Preparation of the Necessary Process Information – Collect Basic Data	10.I (4)
10.I.2.2	Step 2: Preparation of the Necessary Process Information – Describe Process Conditions	10.I (4)
10.I.2.3	Step 3: Identification of Possible Failures, Consequences and Cause of Failure – Hazard Identification	10.I (4)

10.I.2.4	<i>Step 4: Identification of Possible Failures, Consequences and Cause of Failure: Hazard Assessment (Risk Analysis)</i>	10.I (6)
10.I.2.5	<i>Step 5: Evaluation of the Failures and Determination of the Risk Priority Number (RPN)</i>	10.I (8)
10.I.2.6	<i>Step 6: Definition of Reduction Measures</i>	10.I (15)
10.I.2.7	<i>Step 7: Awareness of the Residual Risks</i>	10.I (17)
10.I.2.8	<i>Step 8: Summary of the Results</i>	10.I (17)
10.I.2.9	<i>Step 9: Documentation of the Performed Process</i>	10.I (17)
10.I.2.10	<i>Step 10: Follow Up and the Implementation of Measures</i>	10.I (17)
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.1.1	<i>Step 1: Identification and Analysis of Potential Hazards (Hazard Analysis)</i>	10.J (3)
10.J.1.2	<i>Step 2: Determination of Critical Control Points (CCP) (Risk Evaluation)</i>	10.J (3)
10.J.1.3	<i>Step 3: Establish Target Limits and Critical Limits</i>	10.J (6)
10.J.1.4	<i>Step 4: Establish System to Monitor the Critical Control Points</i>	10.J (6)
10.J.1.5	<i>Step 5: Establish Corrective Actions to be Taken if the CCP is Out of Control</i>	10.J (7)
10.J.1.6	<i>Step 6: Establish Verification Procedures of the Operability of the System</i>	10.J (7)
10.J.1.7	<i>Step 7: Establish or Update Documentation of Processes</i>	10.J (8)
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.B	Personnel hygiene	
11.B.1	Clothing	11.B (1)
11.B.2	Personnel hygiene	11.B (11)
11.B.3	Code of conduct	11.B (11)
11.B.4	Hand disinfection	11.B (12)
11.B.5	Health requirements	11.B (13)
11.B.6	Training	11.B (13)
11.C	Production hygiene	
11.C.1	Sources of contamination	11.C (3)
11.C.2	Cleaning	11.C (6)
11.C.3	Disinfection	11.C (7)
11.D	Sanitation programme	
11.D.1	Cleaning procedure for rooms	11.D (1)
11.D.2	Documentation	11.D (6)

11.E	Environmental monitoring	
11.E.1	Sampling plan	11.E (1)
11.E.2	Establishment of limits and frequencies	11.E (2)
11.E.2.1	<i>Methods</i>	11.E (4)
11.E.3	Investigation areas	11.E (6)
11.E.4	Evaluation	11.E (7)
11.F	GMP in the production process	
11.G	Weigh-in	
11.G.1	Legal principles	11.G (1)
11.G.2	Weigh-in principles	11.G (3)
11.G.3	Weigh-in procedure	11.G (4)
11.G.4	Weighing process sequence	11.G (6)
11.H	Identification	
11.H.1	Starting materials	11.H (2)
11.H.2	Labelling in the manufacturing process	11.H (3)
11.H.3	Labelling of rooms	11.H (6)
11.I	In-process control	
11.I.1	Objectives	11.I (1)
11.I.2	Organisation	11.I (3)
11.I.3	Carrying out	11.I (4)
11.I.4	Documentation	11.I (6)
11.I.5	Scope of tests and limits	11.I (7)
11.I.6	Responsibilities	11.I (7)
11.J	Prevention of cross-contamination	
11.J.1	Rooms and facilities	11.J (1)
11.J.2	Cleaning	11.J (2)
11.J.3	Labelling	11.J (3)
11.J.4	Personnel	11.J (3)
11.J.5	Reviewing the measures	11.J (4)
11.J.6	Manufacture of critical products	11.J (4)
11.K	Deviations	
11.K.1	Definition	11.K (1)
11.K.2	Sequence	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	11.K (7)
11.K.7	SOP "deviations" – (example)	11.K (8)
11.L	Reworking	
11.L.1	Reworking rejected products	11.L (1)
11.L.2	Reworking of products that have not been rejected	11.L (4)

11.M	Warehouse and logistics	
11.M.1	Stock management system	11.M (1)
	<i>11.M.1.1 Responsibilities</i>	<i>11.M (1)</i>
	<i>11.M.1.2 Personnel</i>	<i>11.M (2)</i>
	<i>11.M.1.3 Controlling the turnover of materials</i>	<i>11.M (2)</i>
	<i>11.M.1.4 Warehouse organisation</i>	<i>11.M (3)</i>
11.M.2	Storage areas	11.M (4)
	<i>11.M.2.1 Size</i>	<i>11.M (4)</i>
	<i>11.M.2.2 Illumination</i>	<i>11.M (4)</i>
	<i>11.M.2.3 Incoming goods and dispatch</i>	<i>11.M (5)</i>
	<i>11.M.2.4 Sampling</i>	<i>11.M (5)</i>
	<i>11.M.2.5 Quarantine</i>	<i>11.M (6)</i>
	<i>11.M.2.6 Other storage areas</i>	<i>11.M (7)</i>
11.M.3	Storage conditions	11.M (8)
	<i>11.M.3.1 Temperature and humidity</i>	<i>11.M (8)</i>
	<i>11.M.3.2 Sanitation</i>	<i>11.M (10)</i>
11.M.4	Receipt	11.M (11)
11.M.5	Identification using material and batch number	11.M (15)
11.M.6	Dispatch and transport	11.M (16)

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)
	<i>12.B.1.1 Air locks in cleanliness grade F/E</i>	<i>12.B (2)</i>
	<i>12.B.1.2 Air locks in cleanliness grade E/D</i>	<i>12.B (2)</i>
	<i>12.B.1.3 Air locks in cleanliness grade D/C</i>	<i>12.B (3)</i>
	<i>12.B.1.4 Air locks in cleanliness grade C/B</i>	<i>12.B (4)</i>
12.B.2	Material locks	12.B (7)
12.C	Manufacturing the solution	
12.C.1	Starting materials	12.C (1)
	<i>12.C.1.1 Rooms used for weighing</i>	<i>12.C (2)</i>
	<i>12.C.1.2 Processing instructions (manufacturing instructions)</i>	<i>12.C (2)</i>
	<i>12.C.1.3 Weighing of starting materials</i>	<i>12.C (3)</i>
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)
	<i>12.C.4.1 History</i>	<i>12.C (9)</i>
	<i>12.C.4.2 Mode of operation</i>	<i>12.C (10)</i>
	<i>12.C.4.3 Materials, designs and properties</i>	<i>12.C (10)</i>

12.C.4.4	Filter integrity test	12.C (11)
12.C.4.5	Executing sterile filtration	12.C (12)
12.D	Washing processes	
12.D.1	Stoppers	12.D (1)
12.D.1.1	Material	12.D (1)
12.D.1.2	Manufacture	12.D (2)
12.D.2	Particulate impurities	12.D (3)
12.D.2.1	Stopper washing	12.D (4)
12.D.3	Glass containers (ampoules, bottles)	12.D (5)
12.D.3.1	Types of glass	12.D (5)
12.D.3.2	Manufacture	12.D (6)
12.D.3.3	Washing	12.D (6)
12.D.3.4	Ready to fill	12.D (8)
12.D.4	Transport	12.D (8)
12.E	Filling	
12.E.1	Filling equipment for solutions	12.E (1)
12.E.1.1	System structure	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.E.6.1	System layout of the filling equipment	12.E (13)
12.E.6.2	Practical process using a glass bottle as an example	12.E (14)
12.F	Steam sterilisation	
12.F.1	Sterilisers	12.F (1)
12.F.2	Description of the procedure	12.F (2)
12.F.2.1	Sterilisation	12.F (3)
12.F.2.2	Drying	12.F (4)
12.F.2.3	Sterilisation kinetics	12.F (4)
12.F.3	Qualification of a steam steriliser	12.F (6)
12.F.3.1	Installation qualification	12.F (7)
12.F.3.2	Operational qualification	12.F (9)
12.F.4	Validation of the steam sterilisation process	12.F (11)
12.F.4.1	Description of equipment and process	12.F (12)
12.F.4.2	Loading configurations	12.F (16)
12.F.4.3	Bioindicators	12.F (19)
12.F.4.4	Determining the sterilisation time	12.F (19)
12.F.4.5	Executing the validation	12.F (20)
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.3.1	<i>Limits (level)</i>	12.G (8)
12.G.3.2	<i>Methods and equipment</i>	12.G (10)
12.G.3.3	<i>Microbiological testing of surfaces and personnel</i>	12.G (12)
12.G.4	Sampling	12.G (17)
12.G.4.1	<i>Frequencies</i>	12.G (18)
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.2.1	<i>Environmental conditions</i>	12.H (6)
12.H.2.2	<i>Environmental monitoring</i>	12.H (6)
12.H.3	Method description	12.H (10)
12.H.3.1	<i>Incubation</i>	12.H (11)
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.1.1	<i>Testing for tightness using a dye bath</i>	12.I (1)
12.I.1.2	<i>Testing for tightness in the water bath (for freeze-dried drug products)</i>	12.I (3)
12.I.1.3	<i>Testing for tightness in steam</i>	12.I (3)
12.I.1.4	<i>High-frequency crack test</i>	12.I (3)
12.I.1.5	<i>Testing for tightness by weighing</i>	12.I (5)
12.I.2	Particle test	12.I (5)
12.I.2.1	<i>Visual inspection</i>	12.I (6)
12.I.2.2	<i>Visual control with semi-automated equipment</i>	12.I (8)
12.I.2.3	<i>Electronic control for visible particles</i>	12.I (9)
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.1.1	<i>System components</i>	12.J (4)
12.J.2	Qualification of a freeze dryer	12.J (6)
12.J.2.1	<i>Installation qualification (IQ)</i>	12.J (7)
12.J.2.2	<i>Operational qualification (OQ)</i>	12.J (8)
12.J.3	Validation of the freeze drying process	12.J (9)
12.J.3.1	<i>Description of equipment and process</i>	12.J (9)
12.J.3.2	<i>Executing the validation</i>	12.J (10)

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.3.1	<i>Installation qualification</i>	12.K (5)
12.K.3.2	<i>Operational qualification</i>	12.K (6)
12.K.4	Validation of the sterilisation process	12.K (8)
12.K.4.1	<i>Description of the device</i>	12.K (8)
12.K.4.2	<i>Preparation of the endotoxin test objects</i>	12.K (9)
12.K.4.3	<i>Description of the process</i>	12.K (10)
12.K.4.4	<i>Position of the heat sensors</i>	12.K (10)
12.K.4.5	<i>Determining the endotoxin reduction</i>	12.K (10)
12.K.4.6	<i>Executing the validation</i>	12.K (11)
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.A.5.1	<i>Control tests carried out at the supplier</i>	13.A (7)
13.A.5.2	<i>Examples</i>	13.A (8)
13.A.5.3	<i>Defect evaluation lists</i>	13.A (9)
13.A.5.4	<i>Storage</i>	13.A (11)
13.A.5.5	<i>Labelling</i>	13.A (12)
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.6.1	<i>Organisation</i>	13.B (15)
13.B.6.2	<i>Function inspections</i>	13.B (18)
13.B.6.3	<i>Checking (partially) packed goods</i>	13.B (20)
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.2.1	<i>Design qualification protocol</i>	13.C (8)
13.C.2.2	<i>Design qualification report</i>	13.C (10)
13.C.3	Installation qualification (IQ)	13.C (24)
13.C.3.1	<i>Installation qualification protocol</i>	13.C (24)
13.C.3.2	<i>Installation qualification report</i>	13.C (29)
13.C.4	Operational qualification (OQ)	13.C (34)
13.C.4.1	<i>Operational qualification protocol</i>	13.C (34)
13.C.4.2	<i>Operational qualification report</i>	13.C (39)
13.C.5	Performance qualification (PQ)	13.C (46)
13.C.5.1	<i>Performance qualification protocol</i>	13.C (46)
13.C.5.2	<i>Performance qualification report</i>	13.C (49)

14 Laboratory and Analytical Controls

14.A	Sampling	
14.A.1	Requirements	14.A (2)
14.A.1.1	<i>Personnel</i>	14.A (2)
14.A.1.2	<i>Equipment</i>	14.A (2)
14.A.1.3	<i>Containers</i>	14.A (3)
14.A.1.4	<i>Premises</i>	14.A (3)
14.A.2	Sampling plan (instructions)	14.A (3)
14.A.3	Notes for the sampling process	14.A (8)
14.A.3.1	<i>Containers and identification labeling</i>	14.A (8)
14.A.3.2	<i>Sampling report</i>	14.A (8)
14.A.3.3	<i>Reference samples</i>	14.A (9)
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.1.1	<i>Design qualification (DQ)</i>	14.D (2)
14.D.1.2	<i>Installation qualification (IQ)</i>	14.D (4)
14.D.1.3	<i>Operational qualification (OQ)</i>	14.D (4)
14.D.1.4	<i>Performance qualification (PQ)</i>	14.D (5)
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.1.1	<i>Persons</i>	14.E (1)
14.E.1.2	<i>Instruments</i>	14.E (2)
14.E.1.3	<i>Working</i>	14.E (2)
14.E.1.4	<i>Laboratory Equipment Inventory List</i>	14.E (3)
14.E.2	Calibration instructions and record	14.E (4)
14.E.2.1	<i>Test intervals, test points, test instructions</i>	14.E (4)
14.E.3	Examples	14.E (5)
14.E.3.1	<i>Balance</i>	14.E (5)
14.E.3.2	<i>Volume measuring instruments</i>	14.E (7)
14.E.3.3	<i>Photometer</i>	14.E (9)
14.E.3.4	<i>HPLC system</i>	14.E (11)
14.E.4	Decision	14.E (20)
14.E.4.1	<i>Requirements, tolerances, specifications</i>	14.E (20)
14.E.4.2	<i>Equipment release</i>	14.E (20)
14.E.4.3	<i>Out of calibration</i>	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.2.1	<i>Precision</i>	14.F (3)
14.F.2.2	<i>Accuracy</i>	14.F (3)
14.F.2.3	<i>LOD = Limit of Detection</i>	14.F (4)
14.F.2.4	<i>LOQ = Limit of Quantitation</i>	14.F (4)
14.F.2.5	<i>Selectivity</i>	14.F (5)
14.F.2.6	<i>Linearity, Range</i>	14.F (5)
14.F.2.7	<i>Robustness</i>	14.F (5)
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.2.1	<i>Standard storage conditions</i>	14.G (4)
14.G.2.2	<i>Packaging</i>	14.G (7)
14.G.2.3	<i>Sample quantities</i>	14.G (8)
14.G.2.4	<i>Stress test</i>	14.G (8)
14.G.2.5	<i>Freeze test</i>	14.G (8)
14.G.2.6	<i>Temperature cycling test</i>	14.G (10)
14.G.2.7	<i>Special storage conditions for drug products</i>	14.G (10)
14.G.2.8	<i>Labeling</i>	14.G (12)
14.G.3	Analyses	14.G (13)
14.G.3.1	<i>Test parameters</i>	14.G (14)
14.G.3.2	<i>Reference samples</i>	14.G (15)
14.G.3.3	<i>Consumption test</i>	14.G (15)
14.G.3.4	<i>Compatibility test for injection solutions for infusions</i>	14.G (15)
14.G.3.5	<i>Analysis of compatibility of rubber stoppers and plastic components</i>	14.G (15)

14.G.3.6	Photostability (ICH Q1B)	14.G (16)
14.G.3.7	Microbiological analyses	14.G (18)
14.G.3.8	Analysis of standing times	14.G (19)
14.G.3.9	Analysis of transport conditions	14.G (19)
14.G.4	Reduction of the study design	14.G (20)
14.G.4.1	Bracketing	14.G (21)
14.G.4.2	Matrixing	14.G (21)
14.G.5	Stability testing in the marketing phase	14.G (24)
14.G.5.1	Follow-up stability testing (FuST)	14.G (24)
14.G.5.2	Stability commitment (SC)	14.G (25)
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.6.1	Data evaluation for the retest period for APIs and shelf life for drug products that are intended for storage at room temperature	14.G (37)
14.G.6.2	Data evaluation for retest period for APIs and shelf life for drug products intended for storage in refrigerator (2–8 °C)	14.G (39)
14.G.6.3	Data evaluation for retest period for APIs and shelf life for drug products for intended storage in a freezer (–20 °C)	14.G (40)
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.G.9.1	Data analysis for a single batch	14.G (42)
14.G.9.2	Data analysis of one attribute in each batch for several batches of the same product (known as One-Factor, Full-Design Studies)	14.G (43)
14.G.9.3	Data analysis of all attributes for several batches (Multi-Factor, Full-Design Studies)	14.G (44)
14.H	Out-of-specification results	
14.H.1	Significance	14.H (1)
14.H.1.1	The BARR Laboratories case	14.H (1)
14.H.1.2	The consequences	14.H (3)
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.I.2.1	Cover sheet	14.I (3)
14.I.2.2	Data sheet	14.I (3)
14.I.2.3	Index sheet	14.I (7)

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.1.1	<i>Regulations contained in Directive 2001/83/EC</i>	14.J (4)
14.J.1.2	<i>Objectives of appendix 16</i>	14.J (5)
14.J.1.3	<i>Cases of application</i>	14.J (6)
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.1.1	<i>Determination of the total microbial count</i>	14.K (10)
14.K.1.2	<i>Product testing</i>	14.K (16)
14.K.1.3	<i>Culture media and culture media checks</i>	14.K (18)
14.K.1.4	<i>Incubation</i>	14.K (21)
14.K.1.5	<i>Evaluation</i>	14.K (21)
14.K.1.6	<i>Validation of the method</i>	14.K (23)
14.K.2	Specified microorganisms	14.K (24)
14.K.2.1	<i>Detection of specified microorganisms</i>	14.K (30)
14.K.2.2	<i>Detection method for the specified microorganisms</i>	14.K (32)
14.K.2.3	<i>Evaluation</i>	14.K (41)
14.K.2.4	<i>Culture media and culture media tests</i>	14.K (42)
14.K.2.5	<i>Suitability test of the method (validation of the methods)</i>	14.K (47)
14.K.3	Testing frequencies	14.K (48)
14.K.3.1	<i>Preparations</i>	14.K (48)
14.K.3.2	<i>Raw materials</i>	14.K (49)
14.K.4	Miscellaneous tests	14.K (52)
14.K.4.1	<i>Monitoring of the hygiene status</i>	14.K (52)
14.K.4.2	<i>Aseptic working conditions</i>	14.K (55)
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.1.1	<i>Manufacturing instructions</i>	15.C (3)
15.C.1.2	<i>Batch processing record</i>	15.C (4)
15.C.1.3	<i>Master of manufacturing instructions/batch processing record</i>	15.C (6)
15.C.2	Packaging instruction and batch packaging record	15.C (26)
15.C.2.1	<i>Packaging instruction</i>	15.C (26)
15.C.2.2	<i>Batch packaging record</i>	15.C (27)
15.C.3	Electronic batch recording	15.C (28)
15.C.3.1	<i>Strategic objectives of an Electronic Batch Recording System (EBRS)</i>	15.C (29)
15.C.3.2	<i>GMP aspects</i>	15.C (29)
15.C.4	Testing procedures and test protocol	15.C (31)
15.C.4.1	<i>Testing procedures</i>	15.C (31)
15.C.4.2	<i>Test protocol</i>	15.C (33)
15.C.5	Batch record review	15.C (36)
15.C.5.1	<i>Regulatory requirements</i>	15.C (36)
15.C.5.2	<i>Benefits of an independent batch record review</i>	15.C (36)
15.C.5.3	<i>Responsibility and competencies</i>	15.C (37)
15.C.5.4	<i>Scope of a batch record review</i>	15.C (37)
15.C.5.5	<i>Deviations, changes relevant to marketing authorization, recording errors</i>	15.C (38)
15.D	Standard operating procedures (SOPs)	
15.D.1	Compilation	15.D (2)
15.D.1.1	<i>Design and format</i>	15.D (4)
15.D.1.2	<i>Identification</i>	15.D (6)
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.8.1	<i>Status identification</i>	15.D (10)
15.D.8.2	<i>Distribution</i>	15.D (10)
15.D.8.3	<i>Integration</i>	15.D (11)
15.D.8.4	<i>Use of computerized systems</i>	15.D (11)
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.E.2.1	<i>General information</i>	15.E (2)
15.E.2.2	<i>Personnel</i>	15.E (3)
15.E.2.3	<i>Premises and equipment</i>	15.E (4)

15.E.2.4	Documentation	15.E (7)
15.E.2.5	Production	15.E (9)
15.E.2.6	Quality control	15.E (10)
15.E.2.7	Contract manufacturing and analysis	15.E (10)
15.E.2.8	Distribution, complaints and product recall	15.E (11)
15.E.2.9	Self-inspection	15.E (12)
15.E.2.10	Appendix	15.E (13)
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.1.1	<i>Comparison of GLP – GMP</i>	16.C (2)
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.3.1	<i>Blinding and randomization</i>	16.D (10)
16.D.4	Control and release of investigational medicinal products	16.D (11)
16.D.4.1	<i>Product release of investigational drugs is often performed in several stages</i>	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 Contract Manufacturing and Analysis

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 (8)

17.A.3.1 Selection of one or more contract acceptors 17.A (9)

17.A.3.2 Handover of the necessary documents to the contract acceptor 17.A (10)

17.A.3.3 Secrecy agreement 17.A (11)

17.A.3.4 Carrying out an audit and approval of the contract acceptor 17.A (11)

17.A.3.5 Approval of manufacturing instructions 17.A (11)

17.A.4 Duties of the contract acceptor 17.A (11)

17.A.4.1 Flexibility of a contract acceptor 17.A (12)

17.A.4.2 Full-service contract acceptor 17.A (12)

17.A.4.3 Procurement and testing of starting materials 17.A (12)

17.A.4.4 Analysis of products manufactured under contract 17.A (13)

17.A.4.5 Implementation of the contract giver's requirements 17.A (15)

17.A.4.6 Manufacture and analysis in accordance with the relevant instructions from the contract giver 17.A (15)

17.A.4.7 Existence of quality assurance activities 17.A (16)

17.A.5 Contract manufacturer agreement 17.A (16)

17.A.5.1 Legal principles 17.A (17)

17.A.5.2 Minimum requirements 17.A (17)

17.A.5.3 Compilation of a secrecy agreement 17.A (19)

17.A.5.4 Time needed 17.A (19)

17.A.5.5 Contract manufacturer agreements for audits 17.A (19)

17.A.6 Audits of contract manufacturers 17.A (20)

17.A.6.1 Frequency of audits 17.A (20)

17.A.6.2 Types of audits 17.A (21)

17.A.6.3 Main audit priorities 17.A (22)

17.A.6.4 Result of an audit 17.A (22)

17.A.6.5 How does a contract acceptor prepare for an audit? 17.A (27)

17.A.6.6 Carrying out follow-up audits 17.A (27)

17.A.6.7 Positive spin offs of audits 17.A (27)

17.A.7 SOP for assigning manufacturing contracts 17.A (28)

17.A.8 Framework contract for contract manufacture and quality control 17.A (34)

17.B Contract Analysis

17.B.1 Introduction 17.B (1)

17.B.2 Legal basis 17.B (1)

17.B.3 Selection of a suitable external testing laboratory 17.B (3)

17.B.4 Sequence of external contracting 17.B (3)

17.B.5	Liability limitation contract	17.B (4)
17.B.5.1	<i>Sample contract for contract analysis</i>	17.B (6)
17.B.6	Questions that emerge in practise	17.B (9)
17.B.6.1	<i>Test procedure – who is responsible for what?</i>	17.B (9)
17.B.6.2	<i>Questions of liability</i>	17.B (9)
17.B.6.3	<i>Test certificates containing evaluations</i>	17.B (10)
17.B.6.4	<i>Typical errors</i>	17.B (11)
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.3.1	<i>Opening discussion</i>	18.D (4)
18.D.3.2	<i>Site inspection</i>	18.D (5)
18.D.3.3	<i>Documentation check</i>	18.D (6)
18.D.3.4	<i>Concluding discussion</i>	18.D (7)
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	Supplier qualification	
18.I.1	Suppliers (traders) and manufacturers of raw materials	18.I (1)
18.I.2	Selection of manufacturer or supplier	18.I (3)
18.I.3	Audit of active pharmaceutical ingredient manufacturers	18.I (4)
18.I.3.1	<i>Preparation</i>	18.I (5)
18.I.3.2	<i>Type of inspection</i>	18.I (6)
18.I.3.3	<i>Questions for opening discussion</i>	18.I (7)
18.I.3.4	<i>Inspection sequence: Documents versus site visit</i>	18.I (7)
18.I.3.5	<i>Inspection questionnaire</i>	18.I (8)
18.I.3.6	<i>Change of supplier</i>	18.I (59)
18.I.3.7	<i>Suppliers of packaging materials</i>	18.I (59)
19	Tools for Quality Assurance	
19.A	Project management	
19.A.1	Definition of project and project management	19.A (1)
19.A.2	Project sequence	19.A (2)
19.A.2.1	<i>Project planning</i>	19.A (2)
19.A.2.2	<i>Project controlling</i>	19.A (2)
19.A.2.3	<i>Project conclusion</i>	19.A (2)
19.A.3	Project organisational structure	19.A (3)
19.A.3.1	<i>Project manager</i>	19.A (4)
19.A.3.2	<i>Project team</i>	19.A (4)
19.A.3.3	<i>Steering team</i>	19.A (5)
19.A.4	Project phases	19.A (5)
19.A.4.1	<i>Project start</i>	19.A (5)
19.A.4.2	<i>Project implementation</i>	19.A (5)
19.A.4.3	<i>Project conclusion</i>	19.A (6)
19.A.5	Aids	19.A (6)
19.A.6	Multi-project organisation	19.A (9)
19.A.6.1	<i>Project classes</i>	19.A (9)
19.A.6.2	<i>Project priorities</i>	19.A (9)
19.A.6.3	<i>Management information</i>	19.A (9)
19.A.7	Frequently occurring problems in the context of project management	19.A (10)
19.B	Risk analysis	
19.B.1	Development of the risk analysis	19.B (1)
19.B.2	FMEA – Failure Mode and Effects Analysis	19.B (4)
19.B.2.1	<i>Development</i>	19.B (4)
19.B.2.2	<i>Procedure during FMEA</i>	19.B (4)
19.B.2.3	<i>Failure finding</i>	19.B (5)
19.B.2.4	<i>Failure evaluation</i>	19.B (9)
19.B.2.5	<i>Measures to eliminate failures</i>	19.B (11)
19.B.3	Introduction of a GMP risk analysis according to FMEA method	19.B (13)

19.B.3.1	<i>Advantages</i>	19.B (13)
19.B.3.2	<i>Disadvantages</i>	19.B (16)
19.B.4	Company-specific risk analysis	19.B (26)
19.B.4.1	<i>Advantages</i>	19.B (26)
19.B.4.2	<i>Disadvantages</i>	19.B (27)
19.B.4.3	<i>Procedure</i>	19.B (28)
19.B.4.4	<i>Example</i>	19.B (28)
19.B.5	Hazard Analysis of Critical Control Points	19.B (37)
19.B.5.1	<i>Failure finding</i>	19.B (39)
19.B.5.2	<i>Evaluation of problem points</i>	19.B (40)
19.B.5.3	<i>Definition of measures</i>	19.B (40)
19.B.5.4	<i>Documentation</i>	19.B (41)
19.B.5.5	<i>HACCP summary</i>	19.B (42)
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)
20	Quality Tools	
	will be published in one of the following updates.	
21	GMPs for APIs	
21.A	Introduction	
21.A.1	Objective	21.A (1)
21.A.2	Scope	21.A (2)
21.A.2.1	<i>API Starting Materials</i>	21.A (2)
21.A.2.2	<i>Guidance on how to define API Starting Materials</i>	21.A (3)
21.B	Quality management	
21.B.1	Principles	21.B (1)
21.B.2	Responsibilities of the Quality Unit(s) – QU	21.B (2)
21.B.3	Responsibility for Production Activities	21.B (4)
21.B.4	Internal Audits (Self-Inspections)	21.B (4)
21.B.5	Product Quality Review	21.B (6)
21.C	Personnel	
21.C.1	Personnel hygiene	21.C (2)
21.D	Buildings and Facilities	
21.D.1	Design and Construction	21.D (1)
21.D.2	Utilities	21.D (3)
21.D.3	Water	21.D (4)
21.D.4	Containment	21.D (6)
21.D.5	Sanitation and Maintenance	21.D (6)

21.E	Process Equipment	
21.E.1	Design and Construction	21.E (1)
21.E.2	Equipment Maintenance and Cleaning	21.E (2)
21.E.3	Calibration	21.E (2)
21.E.4	Computerized Systems	21.E (3)
21.F	Documentation and Records	
21.F.1	Documentation System and Specification	21.F (1)
21.F.2	Equipment Cleaning and Use Record	21.F (3)
21.F.3	Records of Raw Materials, Intermediates, API	
	Labelling and Packaging Materials	21.F (4)
21.F.4	Master Production Instructions (Master Production and Control Records)	21.F (4)
21.F.5	Batch Production Records (Batch Production and Control Records)	21.F (4)
21.F.6	Laboratory Control Records	21.F (6)
21.F.7	Batch Production Record Review	21.F (6)
21.G	Materials Management	
21.G.1	General Controls	21.G (1)
21.G.2	Receipt and Quarantine	21.G (1)
21.G.3	Sampling and Testing of Materials	21.G (2)
21.G.4	Storage	21.G (2)
21.H	Production and In-Process Controls	
21.H.1	Production Operations	21.H (1)
21.H.2	Time Limits	21.H (4)
21.H.3	In-process Sampling and Controls	21.H (5)
21.H.4	Blending Batches of Intermediates or APIs	21.H (6)
21.H.5	Contamination Control	21.H (6)
21.I	Packaging and Identification Labelling of APIs and Intermediates	
21.I.1	General	21.I (1)
21.I.2	Packaging Materials	21.I (1)
21.I.3	Label Issuance and Control	21.I (2)
21.I.4	Packaging and Labelling Operations	21.I (3)
21.J	Storage and Distribution	
21.J.1	Warehousing procedures	21.J (1)
21.J.2	Distribution procedures	21.J (2)
21.K	Laboratory Controls	
21.K.1	General Control	21.K (1)
21.K.2	Testing of Intermediates and APIs	21.K (4)
21.K.3	Validation of Analytical Procedures	21.K (4)
21.K.4	Certificates of Analysis	21.K (4)
21.K.5	Stability Monitoring of APIs	21.K (4)
21.K.6	Expiry and Retest Dating	21.K (6)
21.K.7	Reserve/Retention Samples	21.K (6)

21.L	Validation	
21.L.1	Validation Policy	21.L (1)
21.L.2	Validation Documentation	21.L (1)
21.L.3	Qualification	21.L (2)
21.L.4	Approaches to Process Validation	21.L (2)
21.L.5	Process Validation Program	21.L (3)
21.L.6	Periodic Review of Validated Systems	21.L (3)
21.L.7	Cleaning Validation	21.L (3)
21.L.8	Validation of Analytical Methods	21.L (4)
21.M	Change Control	
21.N	Rejection and Re-use of Materials	
21.N.1	Rejection	21.N (1)
21.N.2	Reprocessing	21.N (2)
21.N.3	Reworking	21.N (4)
21.N.4	Recovery of Materials and Solvents	21.N (5)
21.N.5	Returns	21.N (6)
21.O	Complaints and Recalls	
21.P	Contract Manufacturers, including laboratories	
21.Q	Agents, Brokers, Traders, Distributors, Repackers, and Relabelers	
21.Q.1	Applicability	21.Q (1)
21.Q.2	Traceability of Distributed APIs and Intermediates	21.Q (1)
21.Q.3	Quality Management	21.Q (1)
21.Q.4	Repackaging, Relabeling and Holding of APIs and Intermediates	21.Q (2)
21.Q.5	Stability	21.Q (2)
21.Q.6	Transfer of Information	21.Q (2)
21.R	Specific Guidance for APIs Manufactured by Cell Culture/Fermentation	
21.S	APIs for Use in Clinical Trials	
21.S.1	General	21.S (1)
21.S.2	Quality	21.S (1)
21.S.3	Equipment and Facilities	21.S (1)
21.S.4	Control of Raw Materials	21.S (2)
21.S.5	Production	21.S (2)
21.S.6	Validationon	21.S (2)
21.S.7	Changes	21.S (2)
21.S.8	Laboratory Controls	21.S (3)
21.S.9	Documentation	21.S (3)