

Contents

GMP in Practice

| | | |
|------------|---|----------|
| 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.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.3.1 | <i>Critical Areas</i> | 3.C (4) |
| 3.C.3.2 | <i>Supporting Clean Areas</i> | 3.C (6) |
| 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.2.1 | <i>Conceptual features of pharmaceutical isolators</i> | 3.E (2) |
| 3.E.2.2 | <i>Isolator-specific regulatory and normative guidance</i> | 3.E (6) |
| 3.E.2.3 | <i>Biodecontamination of the isolator's internal surfaces</i> | 3.E (7) |
| 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.2.1 | <i>Pure (100%) external air conditioning system</i> | 3.G (4) |
| 3.G.2.2 | <i>Central recirculating air/mixed air conditioning system</i> | 3.G (5) |
| 3.G.2.3 | <i>Decentralized recirculating air/mixed air conditioning system with central external air preparation</i> | 3.G (6) |
| 3.G.2.4 | <i>Pure recirculating air conditioning system</i> | 3.G (7) |

| | | |
|---------|---|----------|
| 3.G.2.5 | <i>Systems for tempering and volume flow regulation</i> | 3.G (8) |
| 3.G.2.6 | <i>Control-systems of the air volume flows</i> | 3.G (10) |
| 3.G.2.7 | <i>Utilities for the operation of room ventilation systems</i> | 3.G (10) |
| 3.G.3 | Filters | 3.G (11) |
| 3.G.3.1 | <i>Particle air filter</i> | 3.G (13) |
| 3.G.3.2 | <i>Suspended matter filter – HEPA-Filter</i> | 3.G (16) |
| 3.G.3.3 | <i>Air Filtration in the FDA's Sterile Drug Products Produced by Aseptic Processing guideline</i> | 3.G (21) |
| 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 (28) |
| 3.G.5.1 | <i>Air technology design of a sterile room with negative pressure plenum</i> | 3.G (29) |
| 3.G.5.2 | <i>Pressure stages and design of the pressure differential measurement for a sterile area</i> | 3.G (30) |
| 3.G.5.3 | <i>Pressure Differentials in the FDA's Sterile Drug Products Produced by Aseptic Processing guideline</i> | 3.G (31) |
| 3.G.6 | Maintenance of air ventilation systems | 3.G (37) |
| 3.G.6.1 | <i>Time intervals for carrying out inspections or servicing</i> | 3.G (40) |
| 3.G.6.2 | <i>Tolerances for inspection and servicing deadlines</i> | 3.G (41) |
| 3.G.6.3 | <i>Maintenance plan</i> | 3.G (41) |
| 3.G.6.4 | <i>Forms for the inspection and servicing of ventilation systems</i> | 3.G (42) |
| 3.G.6.5 | <i>Log book for air technology systems</i> | 3.G (52) |
| 3.H | Process Gases | |
| 3.H.1 | Quality Requirements | 3.H (2) |
| 3.H.2 | Generation, Storage and Distribution | 3.H (4) |
| 3.H.2.1 | <i>Compressed Air</i> | 3.H (4) |
| 3.H.2.2 | <i>Other Pharmaceutical Gases</i> | 3.H (4) |
| 3.H.2.3 | <i>Sterile gases</i> | 3.H (5) |
| 3.H.3 | System design | 3.H (5) |
| 3.H.3.1 | <i>Installation of distribution systems</i> | 3.H (6) |
| 3.H.3.2 | <i>Materials of construction and finish</i> | 3.H (6) |
| 3.H.3.3 | <i>Selection of system components</i> | 3.H (6) |
| 3.H.3.4 | <i>Indication, controlling and recording of relevant parameters</i> | 3.H (7) |
| 3.H.3.5 | <i>Documentation and other requirements</i> | 3.H (7) |
| 3.H.3.6 | <i>Specific requirements for sterile gases</i> | 3.H (8) |
| 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.6.1 | <i>Design Qualification 1 and 2 (DQ 1 and 2)</i> | 3.I (7) |

| | | |
|------------|--|----------|
| 3.1.6.2 | <i>Installation Qualification (IQ)</i> | 3.1 (16) |
| 3.1.6.3 | <i>Operational Qualification (OQ)</i> | 3.1 (22) |
| 3.1.6.4 | <i>Performance Qualification (PQ)</i> | 3.1 (27) |
| 3.1.7 | Requirements for measurement and test reports | 3.1 (29) |
| 3.1.8 | Requalification | 3.1 (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.1.1 | <i>Definition</i> | 4.I (1) |
| 4.I.1.2 | <i>Cleaning mechanisms</i> | 4.I (2) |
| 4.I.2 | CIP systems | 4.I (3) |
| 4.I.2.1 | <i>CIP facility for stack cleaning</i> | 4.I (3) |
| 4.I.2.2 | <i>CIP facility for lost cleaning</i> | 4.I (4) |
| 4.I.3 | GMP-conforming design of CIP facilities | 4.I (6) |
| 4.I.3.1 | <i>Influences of the surfaces</i> | 4.I (6) |
| 4.I.3.2 | <i>Requirements for pipes and tanks</i> | 4.I (7) |
| 4.I.3.3 | <i>Requirements for bonding elements and seals</i> | 4.I (8) |
| 4.I.3.4 | <i>Requirements for pumps</i> | 4.I (9) |
| 4.I.3.5 | <i>Requirement for valves</i> | 4.I (10) |
| 4.I.3.6 | <i>Requirements for measuring instruments</i> | 4.I (10) |
| 4.I.4 | Nozzle heads for container cleaning | 4.I (11) |
| 4.I.4.1 | <i>Spray ball</i> | 4.I (12) |
| 4.I.4.2 | <i>Rotating nozzle head</i> | 4.I (12) |
| 4.I.4.3 | <i>Targeted jet/orbital cleaner</i> | 4.I (12) |
| 4.I.5 | Measuring technology | 4.I (13) |
| 4.I.5.1 | <i>Flow measurement</i> | 4.I (13) |
| 4.I.5.2 | <i>Pressure measurement</i> | 4.I (13) |
| 4.I.5.3 | <i>Temperature measurement</i> | 4.I (14) |
| 4.I.5.4 | <i>Conductivity measurement</i> | 4.I (14) |
| 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.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 | <i>System 1: Sampling via a withdrawal screw fitted in the production area</i> | 4.J (28) |
| 4.J.10.2 | <i>System 2: Sampling via a micro Powder Transfer System (MPTS)</i> | 4.J (29) |
| 4.J.11 | Containment on equipment | 4.J (30) |
| 4.J.11.1 | <i>Example 1: Shaft leadthroughs</i> | 4.J (30) |
| 4.J.11.2 | <i>Example 2: Filling and discharging cone dryers</i> | 4.J (31) |
| 4.J.11.3 | <i>Practical example of a containment API plant</i> | 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 | <i>Weaknesses in facility planning</i> | 4.L (2) |
| 4.L.2 | Surfaces | 4.L (3) |
| 4.L.2.1 | <i>Product-contact surfaces</i> | 4.L (3) |
| 4.L.2.2 | <i>Non-product-contact surfaces</i> | 4.L (4) |
| 4.L.3 | Material: stainless steel | 4.L (6) |
| 4.L.3.1 | <i>Coating of stainless steel surfaces</i> | 4.L (8) |
| 4.L.3.2 | <i>Welds</i> | 4.L (8) |
| 4.L.4 | Connections | 4.L (11) |
| 4.L.4.1 | <i>Flange and quick release connections</i> | 4.L (11) |
| 4.L.4.2 | <i>Flexible connections</i> | 4.L (17) |
| 4.L.4.3 | <i>Screw connections</i> | 4.L (19) |
| 4.L.5 | Hoists and roller conveyors | 4.L (22) |
| 4.L.5.1 | <i>Hoists</i> | 4.L (22) |
| 4.L.5.2 | <i>Roller conveyors</i> | 4.L (23) |
| 4.L.6 | Pneumatic conveyor system | 4.L (25) |
| 4.L.6.1 | <i>Vacuum conveyor with separator</i> | 4.L (25) |
| 4.L.6.2 | <i>Powder transport system (PTS)</i> | 4.L (26) |
| 4.L.7 | Dosing systems | 4.L (26) |
| 4.L.7.1 | <i>Vibration dosing device</i> | 4.L (27) |

| | | |
|------------|--|----------|
| 4.L.7.2 | <i>Dosing screw</i> | 4.L (27) |
| 4.L.7.3 | <i>Slide dosing gate (knife-gate)</i> | 4.L (27) |
| 4.L.7.4 | <i>Flexidos dosing system</i> | 4.L (28) |
| 4.L.7.5 | <i>Transbatch feeder</i> | 4.L (28) |
| 4.L.8 | Platforms and stands | 4.L (28) |
| 4.L.8.1 | <i>Platforms</i> | 4.L (28) |
| 4.L.8.2 | <i>Stands</i> | 4.L (30) |
| 4.L.9 | Clean room installations | 4.L (31) |
| 4.L.9.1 | <i>Rail design</i> | 4.L (31) |
| 4.L.9.2 | <i>Control panels</i> | 4.L (32) |
| 4.L.9.3 | <i>Cable ducts</i> | 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 | <i>Purified Water filled into containers (Packaged Purified Water)</i> | 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 | <i>Sterilized Water for Injection</i> | 5.A (8) |
| 5.A.4.2 | <i>Water for Injection: special USP monographs</i> | 5.A (10) |
| 5.B | Generation of pharmaceutical water | |
| 5.B.1 | Purified water (PW) | 5.B (3) |
| 5.B.1.1 | <i>Airbreak</i> | 5.B (3) |
| 5.B.1.2 | <i>Softener</i> | 5.B (3) |
| 5.B.1.3 | <i>Removal of chlorine</i> | 5.B (3) |
| 5.B.1.4 | <i>Reverse osmosis</i> | 5.B (5) |
| 5.B.1.5 | <i>Electrodeionization (EDI, CDI)</i> | 5.B (7) |
| 5.B.1.6 | <i>Ultra filtration</i> | 5.B (9) |
| 5.B.1.7 | <i>Ion exchanger</i> | 5.B (10) |
| 5.B.1.8 | <i>Purification plants</i> | 5.B (10) |
| 5.B.2 | Water for injection (WFI) | 5.B (12) |
| 5.B.2.1 | <i>Distillation technology</i> | 5.B (12) |
| 5.B.3 | Purification of pharmaceutical water treatment systems | 5.B (15) |
| 5.C | Distribution and storage of pharmaceutical water | |
| 5.C.1 | Loop | 5.C (1) |
| 5.C.1.1 | <i>Flow rate and turbulent flow</i> | 5.C (2) |
| 5.C.1.2 | <i>Pipes</i> | 5.C (3) |
| 5.C.1.3 | <i>Requirements of welds</i> | 5.C (4) |
| 5.C.1.4 | <i>Dead end piping</i> | 5.C (5) |
| 5.C.1.5 | <i>Use of plastics (PVDF)</i> | 5.C (6) |
| 5.C.2 | Fixtures | 5.C (6) |
| 5.C.2.1 | <i>Valves</i> | 5.C (6) |
| 5.C.2.2 | <i>Sensors</i> | 5.C (7) |

| | | |
|---------|--|----------|
| 5.C.2.3 | <i>Sterile filter</i> | 5.C (7) |
| 5.C.2.4 | <i>Sampling points</i> | 5.C (7) |
| 5.C.3 | Measuring technique | 5.C (7) |
| 5.C.3.1 | <i>Level measurement</i> | 5.C (8) |
| 5.C.3.2 | <i>Flow measurement</i> | 5.C (12) |
| 5.C.3.3 | <i>Conductivity measurement</i> | 5.C (15) |
| 5.C.3.4 | <i>Pressure measurement</i> | 5.C (16) |
| 5.C.3.5 | <i>Temperature measurement</i> | 5.C (18) |
| 5.C.3.6 | <i>Ozone measurement (online)</i> | 5.C (19) |
| 5.C.3.7 | <i>TOC measurement (online)</i> | 5.C (19) |
| 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 (28) |
| 5.C.7 | Loop with subloops | 5.C (30) |
| 5.C.7.1 | <i>Cleanability of the loop for purified water</i> | 5.C (30) |
| 5.C.7.2 | <i>Valve groupings</i> | 5.C (31) |
| 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 | <i>Legal requirements for drug products</i> | 7.A (1) |
| 7.A.1.2 | <i>Responsibilities</i> | 7.A (2) |
| 7.A.1.3 | <i>GMP Requirements</i> | 7.A (3) |
| 7.A.1.4 | <i>Aspects regarding marketing authorization</i> | 7.A (4) |
| 7.A.2 | Principles of process validation | 7.A (9) |
| 7.A.2.1 | <i>Process understanding</i> | 7.A (10) |
| 7.A.2.2 | <i>Type and scope of process validation</i> | 7.A (10) |
| 7.A.2.3 | <i>Traceability of validation investigations</i> | 7.A (13) |
| 7.A.2.4 | <i>Manufacturing under routine conditions</i> | 7.A (13) |
| 7.A.2.5 | <i>Bracketing (product group formation)</i> | 7.A (14) |
| 7.A.2.6 | <i>Challenge tests</i> | 7.A (14) |
| 7.A.2.7 | <i>Deviations</i> | 7.A (14) |
| 7.A.3 | Types of validation | 7.A (15) |
| 7.A.3.1 | <i>Prospective validation</i> | 7.A (15) |
| 7.A.3.2 | <i>Concurrent validation</i> | 7.A (16) |
| 7.A.3.3 | <i>Retrospective validation</i> | 7.A (18) |
| 7.A.4 | Revalidation | 7.A (19) |
| 7.A.4.1 | <i>Validation master plan</i> | 7.A (21) |
| 7.A.4.2 | <i>Validation protocol and report</i> | 7.A (22) |
| 7.A.4.3 | <i>Archiving</i> | 7.A (23) |
| 7.A.5 | Maintaining the validation status | 7.A (24) |
| 7.A.5.1 | <i>General conditions and prerequisites</i> | 7.A (24) |
| 7.A.5.2 | <i>Principles of statistical process control</i> | 7.A (25) |
| 7.A.5.3 | <i>Quality control cards</i> | 7.A (28) |
| 7.A.5.4 | <i>Process capability investigation</i> | 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 | <i>Changes to the manufacturing instructions</i> | 7.D (2) |
| 7.D.2.2 | <i>Extension of the ranges of critical process parameters</i> | 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 (10) |
| 7.H.2.1 | <i>How to deal with deviations from the requirements in the validation protocol</i> | 7.H (12) |
| 7.H.2.2 | <i>Archiving of the validation documents</i> | 7.H (12) |
| 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.B.3.1 | <i>Standardization and reproducibility of the process parameters</i> | 8.B (8) |
| 8.B.3.2 | <i>Compliance with process parameters</i> | 8.B (8) |
| 8.B.3.3 | <i>Training and qualification</i> | 8.B (9) |
| 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.1.1 | <i>Risk assessment – first step</i> | 8.D (2) |
| 8.D.1.2 | <i>Risk assessment – second step</i> | 8.D (3) |
| 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.1.1 | <i>Dose criterion</i> | 8.E (2) |
| 8.E.1.2 | <i>ppm criterion</i> | 8.E (3) |
| 8.E.1.3 | <i>Selection of the appropriate acceptance criteria</i> | 8.E (4) |
| 8.E.1.4 | <i>Calculation of the acceptable residue in a sample</i> | 8.E (5) |
| 8.E.1.5 | <i>Visual criterion (visually clean)</i> | 8.E (7) |
| 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.2.1 | <i>Final Rinse</i> | 8.F (5) |
| 8.F.2.2 | <i>Solvent rinse</i> | 8.F (5) |
| 8.F.3 | Other procedures | 8.F (6) |
| 8.F.3.1 | <i>Steam condensate method</i> | 8.F (6) |
| 8.F.3.2 | <i>Placebo method</i> | 8.F (7) |

| | | |
|------------|--|----------|
| 8.F.4 | Selection of the appropriate sampling procedure | 8.F (7) |
| 8.F.4.1 | <i>Design of the production equipment</i> | 8.F (7) |
| 8.F.4.2 | <i>Solubility of the residue to be detected</i> | 8.F (8) |
| 8.F.4.3 | <i>Analytical method</i> | 8.F (8) |
| 8.F.5 | Microbiological testing of surfaces | 8.F (9) |
| 8.F.5.1 | <i>Sampling material</i> | 8.F (9) |
| 8.F.5.2 | <i>Sampling locations</i> | 8.F (9) |
| 8.F.5.3 | <i>Implementation of the direct contact test</i> | 8.F (9) |
| 8.F.5.4 | <i>Other test methods</i> | 8.F (10) |
| 8.G | Analytical procedures | |
| 8.G.1 | Requirements for method validation | 8.G (1) |
| 8.G.1.1 | <i>Specificity</i> | 8.G (2) |
| 8.G.1.2 | <i>Sensitivity</i> | 8.G (3) |
| 8.G.1.3 | <i>Recovery</i> | 8.G (3) |
| 8.G.2 | Selection of the appropriate analytical procedure | 8.G (6) |
| 8.G.2.1 | <i>Active pharmaceutical ingredient residues</i> | 8.G (6) |
| 8.G.2.2 | <i>Cleansing agent residues</i> | 8.G (7) |
| 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.3.1 | <i>Change-related revalidation</i> | 8.I (4) |
| 8.I.3.2 | <i>Periodic revalidation</i> | 8.I (7) |
| 8.I.4 | New products and equipment | 8.I (9) |
| 8.I.4.1 | <i>New products</i> | 8.I (9) |
| 8.I.4.2 | <i>New equipment</i> | 8.I (10) |
| 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.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 / 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 ^r classification | 9.D (1) |
| 9.D.1.1 | <i>Class 1 – Infrastructure</i> | 9.D (2) |
| 9.D.1.2 | <i>Class 2 – Firmware</i> | 9.D (2) |
| 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 (3) |
| 9.D.1.5 | <i>Class 5 – Customer-specific software</i> | 9.D (3) |
| 9.D.1.6 | <i>Validation tasks depending on classification</i> | 9.D (3) |
| 9.D.1.7 | <i>Risk classification in accordance with GAMP</i> | 9.D (6) |
| 9.D.2 | Risk indexes | 9.D (6) |
| 9.D.2.1 | <i>Determining the risk index</i> | 9.D (6) |
| 9.D.2.2 | <i>Measures that depend on the risk index</i> | 9.D (10) |
| 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.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) |
| 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.C.6.1 | <i>1st level: Quality Management System</i> | 10.C (6) |
| 10.C.6.2 | <i>2nd level: local SOP</i> | 10.C (7) |
| 10.C.6.3 | <i>3rd level: Application to a Specific Manufacturing Process</i> | 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 | <i>Step 1: Prerequisites</i> | 10.F (2) |
| 10.F.1.2 | <i>Step 2: Draw</i> | 10.F (2) |
| 10.F.1.3 | <i>Step 3: Conclusions</i> | 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 | <i>Step 1: Preparation of the Necessary Process Information – Collect Basic Data</i> | 10.I (4) |
| 10.I.2.2 | <i>Step 2: Preparation of the Necessary Process Information – Describe Process Conditions</i> | 10.I (4) |
| 10.I.2.3 | <i>Step 3: Identification of Possible Failures, Consequences and Cause of Failure – Hazard Identification</i> | 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.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.1.1 | <i>Clothing material</i> | 11.B (4) |
| 11.B.1.2 | <i>Design of the clothing</i> | 11.B (5) |
| 11.B.1.3 | <i>Preparation/Cleaning</i> | 11.B (10) |
| 11.B.1.4 | <i>Gowning procedure</i> | 11.B (11) |
| 11.B.2 | Code of Conduct | 11.B (11) |
| 11.B.2.1 | <i>Personal hygiene</i> | 11.B (12) |
| 11.B.2.2 | <i>General requirements</i> | 11.B (12) |
| 11.B.2.3 | <i>Special requirements for clean rooms</i> | 11.B (13) |
| 11.B.2.4 | <i>Policies to be established</i> | 11.B (13) |

| | | |
|-------------|---|-----------|
| 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.1.1 | <i>Premises and facilities</i> | 11.C (4) |
| 11.C.1.2 | <i>Starting materials</i> | 11.C (6) |
| 11.C.1.3 | <i>Packaging materials</i> | 11.C (6) |
| 11.C.1.4 | <i>Cleansing agents, disinfectants and aids</i> | 11.C (7) |
| 11.C.1.5 | <i>Equipment and utensils</i> | 11.C (8) |
| 11.C.1.6 | <i>Process gases</i> | 11.C (9) |
| 11.C.1.7 | <i>Ambient air</i> | 11.C (9) |
| 11.C.1.8 | <i>Processes</i> | 11.C (10) |
| 11.C.2 | Cleaning | 11.C (11) |
| 11.C.2.1 | <i>Cleaning procedure for equipment</i> | 11.C (11) |
| 11.C.2.2 | <i>Cleaning procedure for rooms</i> | 11.C (12) |
| 11.C.3 | Disinfection | 11.C (13) |
| 11.C.3.1 | <i>General procedure</i> | 11.C (13) |
| 11.D | Sanitation programme | |
| 11.D.1 | Organisation of room cleaning | 11.D (1) |
| 11.D.1.1 | <i>Hygienic areas</i> | 11.D (1) |
| 11.D.1.2 | <i>General room cleaning</i> | 11.D (1) |
| 11.D.1.3 | <i>Cleansing agents and disinfectants</i> | 11.D (2) |
| 11.D.1.4 | <i>Cleaning process and aids</i> | 11.D (4) |
| 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.3.1 | <i>European requirements</i> | 11.E (4) |
| 11.E.3.2 | <i>US requirements</i> | 11.E (7) |
| 11.E.3.3 | <i>ISO standards</i> | 11.E (8) |
| 11.E.4 | Methods | 11.E (9) |
| 11.E.4.1 | <i>Direct contact test</i> | 11.E (9) |
| 11.E.4.2 | <i>Measurement of airborne microbes</i> | 11.E (9) |
| 11.E.5 | Investigation areas | 11.E (11) |
| 11.E.5.1 | <i>Surfaces</i> | 11.E (11) |
| 11.E.5.2 | <i>Air</i> | 11.E (12) |
| 11.E.5.3 | <i>Cleansing agents and disinfectants</i> | 11.E (14) |
| 11.E.5.4 | <i>Personnel</i> | 11.E (15) |
| 11.E.5.5 | <i>Utilities</i> | 11.E (16) |

| | | |
|-------------|--|-----------|
| 11.E.6 | Evaluation | 11.E (16) |
| 11.E.6.1 | <i>Report</i> | 11.E (16) |
| 11.E.6.2 | <i>Trend analyses</i> | 11.E (16) |
| 11.E.6.3 | <i>Measures when limit is exceeded</i> | 11.E (17) |
| 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.2.1 | <i>Product-specific weigh-in</i> | 11.G (4) |
| 11.G.2.2 | <i>Raw material-specific weigh-in</i> | 11.G (4) |
| 11.G.2.3 | <i>Central/local weigh-in systems</i> | 11.G (5) |
| 11.G.2.4 | <i>Manual weigh-in</i> | 11.G (6) |
| 11.G.2.5 | <i>Automatic weigh-in</i> | 11.G (6) |
| 11.G.3 | Weigh-in procedure | 11.G (7) |
| 11.G.3.1 | <i>Allocation of raw materials</i> | 11.G (8) |
| 11.G.3.2 | <i>Weigh-in</i> | 11.G (8) |
| 11.G.3.3 | <i>Return</i> | 11.G (10) |
| 11.G.3.4 | <i>Allocation for production</i> | 11.G (10) |
| 11.G.3.5 | <i>Cleaning</i> | 11.G (10) |
| 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.3.1 | <i>General</i> | 11.H (3) |
| 11.H.3.2 | <i>Rejection / Quarantine</i> | 11.H (4) |
| 11.H.3.3 | <i>Cleaning status</i> | 11.H (5) |
| 11.H.4 | Labelling of rooms | 11.H (7) |
| 11.I | In-process control | |
| 11.I.1 | Objectives | 11.I (2) |
| 11.I.1.1 | <i>Quality control</i> | 11.I (2) |
| 11.I.1.2 | <i>Process control</i> | 11.I (2) |
| 11.I.2 | Organisation and responsibilities | 11.I (3) |
| 11.I.3 | Carrying out | 11.I (4) |
| 11.I.3.1 | <i>Scope and kind of tests</i> | 11.I (4) |
| 11.I.3.2 | <i>Location</i> | 11.I (7) |
| 11.I.3.3 | <i>Sampling</i> | 11.I (7) |
| 11.I.3.4 | <i>Testing</i> | 11.I (8) |
| 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.1.1 | <i>Rooms</i> | 11.J (2) |
| 11.J.1.2 | <i>Equipment</i> | 11.J (2) |

| | | |
|-------------|--|-----------|
| 11.J.1.3 | <i>Processes</i> | 11.J (4) |
| 11.J.1.4 | <i>Personnel</i> | 11.J (4) |
| 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.1.1 | <i>Rework</i> | 11.L (1) |
| 11.L.1.2 | <i>Reprocessing</i> | 11.L (1) |
| 11.L.1.3 | <i>Recovery</i> | 11.L (2) |
| 11.L.2 | Procedure | 11.L (2) |
| 11.L.2.1 | <i>Reasons for rework / reprocessing</i> | 11.L (2) |
| 11.L.2.2 | <i>Request for rework / reprocessing</i> | 11.L (2) |
| 11.L.2.3 | <i>Risk assessment</i> | 11.L (3) |
| 11.L.2.4 | <i>Responsibilities</i> | 11.L (3) |
| 11.L.2.5 | <i>Documentation requirements</i> | 11.L (3) |
| 11.L.2.6 | <i>Regulatory submission requirements</i> | 11.L (4) |
| 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.5.1 | <i>Size</i> | 11.M (7) |
| 11.M.5.2 | <i>Illumination</i> | 11.M (7) |
| 11.M.5.3 | <i>Incoming goods and dispatch</i> | 11.M (7) |
| 11.M.5.4 | <i>Sampling</i> | 11.M (8) |
| 11.M.5.5 | <i>Quarantine</i> | 11.M (9) |
| 11.M.5.6 | <i>Special storage areas</i> | 11.M (12) |
| 11.M.6 | Storage conditions | 11.M (13) |
| 11.M.6.1 | <i>Temperature and humidity</i> | 11.M (13) |
| 11.M.6.2 | <i>Monitoring</i> | 11.M (13) |
| 11.M.6.3 | <i>Deviation handling</i> | 11.M (16) |

| | | |
|--------|---------------------------------|-----------|
| 11.M.7 | Sanitation and pest control | 11.M (16) |
| 11.M.8 | Material Flow | 11.M (18) |
| | 11.M.8.1 Stock rotation | 11.M (18) |
| | 11.M.8.2 Reconciliation | 11.M (19) |
| | 11.M.8.3 Storage systems | 11.M (19) |
| 11.M.9 | Process Flow | 11.M (22) |
| | 11.M.9.1 Receipt | 11.M (22) |
| | 11.M.9.2 Identification | 11.M (25) |
| | 11.M.9.3 Dispatch and transport | 11.M (27) |

11.N 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.1.1 Air locks in cleanliness grade F/E | 12.B (2) |
| | 12.B.1.2 Air locks in cleanliness grade E/D | 12.B (2) |
| | 12.B.1.3 Air locks in cleanliness grade D/C | 12.B (3) |
| | 12.B.1.4 Air locks in cleanliness grade C/B | 12.B (4) |
| 12.B.2 | Material locks | 12.B (7) |

12.C Manufacturing the solution

| | | |
|--------|---|-----------|
| 12.C.1 | Starting materials | 12.C (1) |
| | 12.C.1.1 Rooms used for weighing | 12.C (2) |
| | 12.C.1.2 Processing instructions (manufacturing instructions) | 12.C (2) |
| | 12.C.1.3 Weighing of starting materials | 12.C (3) |
| 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.C.4.1 History | 12.C (9) |
| | 12.C.4.2 Mode of operation | 12.C (10) |
| | 12.C.4.3 Materials, designs and properties | 12.C (10) |
| | 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 | <i>Types of glass</i> | 12.D (5) |
| 12.D.3.2 | <i>Manufacture</i> | 12.D (6) |
| 12.D.3.3 | <i>Washing</i> | 12.D (6) |
| 12.D.3.4 | <i>Ready to fill</i> | 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 | <i>System structure</i> | 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 | <i>System layout of the filling equipment</i> | 12.E (13) |
| 12.E.6.2 | <i>Practical process using a glass bottle as an example</i> | 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 | <i>Sterilisation</i> | 12.F (3) |
| 12.F.2.2 | <i>Drying</i> | 12.F (4) |
| 12.F.2.3 | <i>Sterilisation kinetics</i> | 12.F (4) |
| 12.F.3 | Qualification of a steam steriliser | 12.F (6) |
| 12.F.3.1 | <i>Installation qualification</i> | 12.F (7) |
| 12.F.3.2 | <i>Operational qualification</i> | 12.F (9) |
| 12.F.4 | Validation of the steam sterilisation process | 12.F (11) |
| 12.F.4.1 | <i>Description of equipment and process</i> | 12.F (12) |
| 12.F.4.2 | <i>Loading configurations</i> | 12.F (16) |
| 12.F.4.3 | <i>Bioindicators</i> | 12.F (19) |
| 12.F.4.4 | <i>Determining the sterilisation time</i> | 12.F (19) |
| 12.F.4.5 | <i>Executing the validation</i> | 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 (4) |
| 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 | HPLC system | 14.E (11) |
| 14.E.4 | Decision | 14.E (20) |
| 14.E.4.1 | Requirements, tolerances, specifications | 14.E (20) |
| 14.E.4.2 | Equipment release | 14.E (20) |
| 14.E.4.3 | Out of calibration | 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 | Precision | 14.F (3) |
| 14.F.2.2 | Accuracy | 14.F (3) |
| 14.F.2.3 | LOD = Limit of Detection | 14.F (4) |
| 14.F.2.4 | LOQ = Limit of Quantitation | 14.F (4) |
| 14.F.2.5 | Selectivity | 14.F (5) |
| 14.F.2.6 | Linearity, Range | 14.F (5) |
| 14.F.2.7 | Robustness | 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 | Standard storage conditions | 14.G (4) |
| 14.G.2.2 | Packaging | 14.G (7) |
| 14.G.2.3 | Sample quantities | 14.G (8) |
| 14.G.2.4 | Stress test | 14.G (8) |
| 14.G.2.5 | Freeze test | 14.G (8) |
| 14.G.2.6 | Temperature cycling test | 14.G (10) |
| 14.G.2.7 | Special storage conditions for drug products | 14.G (10) |
| 14.G.2.8 | Labeling | 14.G (12) |
| 14.G.3 | Analyses | 14.G (13) |
| 14.G.3.1 | Test parameters | 14.G (14) |
| 14.G.3.2 | Reference samples | 14.G (15) |
| 14.G.3.3 | Consumption test | 14.G (15) |
| 14.G.3.4 | Compatibility test for injection solutions for infusions | 14.G (15) |
| 14.G.3.5 | Analysis of compatibility of rubber stoppers and plastic components | 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 | <i>Data evaluation for the retest period for APIs and shelf life for drug products that are intended for storage at room temperature</i> | 14.G (37) |
| 14.G.6.2 | <i>Data evaluation for retest period for APIs and shelf life for drug products intended for storage in refrigerator (2–8 °C)</i> | 14.G (39) |
| 14.G.6.3 | <i>Data evaluation for retest period for APIs and shelf life for drug products for intended storage in a freezer (–20 °C)</i> | 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 | <i>Data analysis for a single batch</i> | 14.G (42) |
| 14.G.9.2 | <i>Data analysis of one attribute in each batch for several batches of the same product (known as One-Factor, Full-Design Studies)</i> | 14.G (43) |
| 14.G.9.3 | <i>Data analysis of all attributes for several batches (Multi-Factor, Full-Design Studies)</i> | 14.G (44) |
| 14.H | Out-of-specification results | |
| 14.H.1 | Significance | 14.H (1) |
| 14.H.1.1 | <i>The BARR Laboratories case</i> | 14.H (1) |
| 14.H.1.2 | <i>The consequences</i> | 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 (13) |
| 14.H.5 | Trend tracking | 14.H (14) |
| 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 | <i>Cover sheet</i> | 14.I (3) |
| 14.I.2.2 | <i>Data sheet</i> | 14.I (3) |
| 14.I.2.3 | <i>Index sheet</i> | 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) |
| 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.4.1 | <i>Legal status and relationship to regulatory agencies</i> | 14.L (4) |
| 14.L.4.2 | <i>Structure</i> | 14.L (5) |
| 14.L.4.3 | <i>Publication</i> | 14.L (6) |
| 14.L.4.4 | <i>Particularities</i> | 14.L (6) |
| 14.L.5 | British Pharmacopoeia (BP) | 14.L (7) |
| 14.L.5.1 | <i>Legal status and relationship to regulatory agencies</i> | 14.L (7) |
| 14.L.5.2 | <i>Structure</i> | 14.L (7) |
| 14.L.5.3 | <i>Publication</i> | 14.L (8) |
| 14.L.5.4 | <i>Particularities</i> | 14.L (8) |
| 14.L.6 | United States Pharmacopoeia (USP) | 14.L (9) |
| 14.L.6.1 | <i>Legal status and relationship to regulatory agencies</i> | 14.L (9) |
| 14.L.6.2 | <i>Structure</i> | 14.L (10) |
| 14.L.6.3 | <i>Publication</i> | 14.L (10) |
| 14.L.6.4 | <i>Particularities</i> | 14.L (10) |
| 14.L.7 | Japanese Pharmacopoeia (JP) | 14.L (11) |
| 14.L.7.1 | <i>Legal status and relationship to regulatory agencies</i> | 14.L (11) |
| 14.L.7.2 | <i>Structure</i> | 14.L (12) |
| 14.L.7.3 | <i>Publication</i> | 14.L (12) |
| 14.L.8 | International Pharmacopoeia (Ph Int) | 14.L (13) |
| 14.L.8.1 | <i>Legal status and relationship to regulatory agencies</i> | 14.L (13) |

| | | |
|----------|---------------|-----------|
| 14.L.8.2 | Structure | 14.L (13) |
| 14.L.8.3 | Publication | 14.L (14) |
| 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.1.1 | Manufacturing instructions | 15.C (3) |
| 15.C.1.2 | Batch processing record | 15.C (4) |
| 15.C.1.3 | Master of manufacturing instructions/batch processing record | 15.C (6) |
| 15.C.2 | Packaging instruction and batch packaging record | 15.C (26) |
| 15.C.2.1 | Packaging instruction | 15.C (26) |
| 15.C.2.2 | Batch packaging record | 15.C (27) |
| 15.C.3 | Electronic batch recording | 15.C (28) |
| 15.C.3.1 | Strategic objectives of an Electronic Batch Recording System (EBRS) | 15.C (29) |
| 15.C.3.2 | GMP aspects | 15.C (29) |
| 15.C.4 | Testing procedures and test protocol | 15.C (31) |
| 15.C.4.1 | Testing procedures | 15.C (31) |
| 15.C.4.2 | Test protocol | 15.C (33) |
| 15.C.5 | Batch record review | 15.C (36) |
| 15.C.5.1 | Regulatory requirements | 15.C (36) |
| 15.C.5.2 | Benefits of an independent batch record review | 15.C (36) |
| 15.C.5.3 | Responsibility and competencies | 15.C (37) |
| 15.C.5.4 | Scope of a batch record review | 15.C (37) |
| 15.C.5.5 | Deviations, changes relevant to marketing authorization, recording errors | 15.C (38) |

15.D Standard operating procedures (SOPs)

| | | |
|----------|-----------------------------|----------|
| 15.D.1 | Compilation | 15.D (2) |
| 15.D.1.1 | Design and format | 15.D (4) |
| 15.D.1.2 | Identification | 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 <i>Documentation</i> | 15.E (7) |
| | 15.E.2.5 <i>Production</i> | 15.E (9) |
| | 15.E.2.6 <i>Quality control</i> | 15.E (10) |
| | 15.E.2.7 <i>Contract manufacturing and analysis</i> | 15.E (10) |
| | 15.E.2.8 <i>Distribution, complaints and product recall</i> | 15.E (11) |
| | 15.E.2.9 <i>Self-inspection</i> | 15.E (12) |
| | 15.E.2.10 <i>Appendix</i> | 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 | <i>Selection of one or more contract acceptors</i> | 17.A (9) |
| 17.A.3.2 | <i>Handover of the necessary documents to the contract acceptor</i> | 17.A (10) |
| 17.A.3.3 | <i>Secrecy agreement</i> | 17.A (11) |
| 17.A.3.4 | <i>Carrying out an audit and approval of the contract acceptor</i> | 17.A (11) |
| 17.A.3.5 | <i>Approval of manufacturing instructions</i> | 17.A (11) |
| 17.A.4 | Duties of the contract acceptor | 17.A (11) |
| 17.A.4.1 | <i>Flexibility of a contract acceptor</i> | 17.A (12) |
| 17.A.4.2 | <i>Full-service contract acceptor</i> | 17.A (12) |
| 17.A.4.3 | <i>Procurement and testing of starting materials</i> | 17.A (12) |
| 17.A.4.4 | <i>Analysis of products manufactured under contract</i> | 17.A (13) |
| 17.A.4.5 | <i>Implementation of the contract giver's requirements</i> | 17.A (15) |
| 17.A.4.6 | <i>Manufacture and analysis in accordance with the relevant instructions from the contract giver</i> | 17.A (15) |
| 17.A.4.7 | <i>Existence of quality assurance activities</i> | 17.A (16) |

| | | |
|---------------|--|------------------|
| 17.A.5 | Contract manufacturer agreement | 17.A (16) |
| 17.A.5.1 | <i>Legal principles</i> | 17.A (17) |
| 17.A.5.2 | <i>Minimum requirements</i> | 17.A (17) |
| 17.A.5.3 | <i>Compilation of a secrecy agreement</i> | 17.A (19) |
| 17.A.5.4 | <i>Time needed</i> | 17.A (19) |
| 17.A.5.5 | <i>Contract manufacturer agreements for audits</i> | 17.A (19) |
| 17.A.6 | Audits of contract manufacturers | 17.A (20) |
| 17.A.6.1 | <i>Frequency of audits</i> | 17.A (20) |
| 17.A.6.2 | <i>Types of audits</i> | 17.A (21) |
| 17.A.6.3 | <i>Main audit priorities</i> | 17.A (22) |
| 17.A.6.4 | <i>Result of an audit</i> | 17.A (22) |
| 17.A.6.5 | <i>How does a contract acceptor prepare for an audit?</i> | 17.A (27) |
| 17.A.6.6 | <i>Carrying out follow-up audits</i> | 17.A (27) |
| 17.A.6.7 | <i>Positive spin offs of audits</i> | 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 | 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.4.1 | <i>Legal responsibilities</i> | 19.B (8) |
| 19.B.4.2 | <i>Responsibilities according to the EU GMP-Guide, Part 1</i> | 19.B (8) |
| 19.B.4.3 | <i>Responsibilities according to Annex 16 of the EU GMP Guide</i> | 19.B (12) |
| 19.B.4.4 | <i>Responsibilities according to Annex 13 of the EU GMP Guide</i> | 19.B (15) |
| 19.B.4.5 | <i>Additional Responsibilities</i> | 19.B (19) |
| 19.B.4.6 | <i>Deviations from Market Authorization – the Qualified Person’s “Discretion”</i> | 19.B (19) |
| 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 Methods | |
| 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.2.1 | <i>The concept</i> | 20.B (2) |
| 20.B.2.2 | <i>Six Sigma Expert, the Black Belt</i> | 20.B (3) |
| 20.B.2.3 | <i>Six Sigma organization</i> | 20.B (4) |
| 20.B.2.4 | <i>Six Sigma roles and responsibilities</i> | 20.B (5) |
| 20.B.2.5 | <i>Six Sigma approach</i> | 20.B (7) |
| 20.B.2.6 | <i>The DMAIC Cycle</i> | 20.B (9) |
| 20.B.2.7 | <i>Six Sigma Training</i> | 20.B (18) |
| 20.B.3 | Goals/Objectives/Benefits | 20.B (19) |
| 20.B.4 | Implementation | 20.B (21) |
| 20.B.4.1 | <i>Pre-requisites for successful implementation</i> | 20.B (21) |
| 20.B.4.2 | <i>When to apply / when not to apply</i> | 20.B (22) |
| 20.B.4.3 | <i>How to implement</i> | 20.B (23) |
| 20.B.5 | Tools | 20.B (24) |
| 20.B.6 | Variations | 20.B (25) |
| 20.B.7 | Examples | 20.B (26) |
| 20.B.7.1 | <i>API Synthetis</i> | 20.B (26) |
| 20.B.7.2 | <i>Reducing cycle time</i> | 20.B (27) |
| 20.B.7.3 | <i>Improving the yield of a drug product</i> | 20.B (27) |
| 20.B.7.4 | <i>Improving the laboratory process</i> | 20.B (27) |
| 20.C | References | |

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 (5) |
| 21.F.6 | Laboratory Control Records | 21.F (5) |
| 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) |