Main Differences between GMP Part I and Part II (and ICH Q7)

Inspector’s point of view

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Regional Medicines Inspectorate of Eastern and Central Switzerland
Program

1. GMP Guide, History

2. GMP Guide, Structure Overview

3. Document Revisions

4. Applicability Annexes and Part III

5. GMP Guide, Structure Details and Comparability

6. Similarities and Differences in Parts I and II

7. Summary and Outlook
Scopes of Parts I & II

Part II

Manufacture of Active Pharmaceutical Ingredients

Part I

Manufacture of Intermediates and Finished Products
General Structure

EU-Guide
- Introduction
- Part I
- Part II
- Part III
- Part IV
- Annexes
- Glossary
- Other Doc

PIC/S-Guide
- Introduction
- Part I
- Part II
- Annexes
- Glossary
- SMF (3x)
- Other Doc

For Industry

For Inspectors

Kanton Zürich
Kantonale Heilmittelkontrolle
Part I Revisions

Chapters 1 – 8 of Part I have undergone recent revisions. Part I is a constantly living document.

Part I chapters: Revision status

<table>
<thead>
<tr>
<th>#</th>
<th>Scope</th>
<th>Revision</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Pharmaceutical Quality System</td>
<td>2013</td>
</tr>
<tr>
<td>2</td>
<td>Personnel</td>
<td>2014</td>
</tr>
<tr>
<td>3</td>
<td>Premises and Equipment</td>
<td>2015</td>
</tr>
<tr>
<td>4</td>
<td>Documentation</td>
<td>2011</td>
</tr>
<tr>
<td>5</td>
<td>Production</td>
<td>2015</td>
</tr>
<tr>
<td>6</td>
<td>Quality Control</td>
<td>2014</td>
</tr>
<tr>
<td>7</td>
<td>Outsourced Activities</td>
<td>2013</td>
</tr>
<tr>
<td>8</td>
<td>Complaints, Quality Defects and Product Recalls</td>
<td>2015</td>
</tr>
<tr>
<td>9</td>
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Part II Revisions

Part II is much more conservative and has undergone only two small amendments since the implementation of ICH Q7A (now ICH Q7) into the GMP guide.

The introduction in chapter 1 was changed in the course of the implementation of ICH Q7A as Annex 18.

In 2010 paragraphs 2.19, 2.20 and 2.21 on quality risk management were implemented in chapter 2 (including a change in numbering of sections 2.2 to 2.5).

In 2014 paragraph 1.2 was revised (clarification to applicability of the annexes and to the relationship between chapter 17 and the new GDP guidelines).
Annexes Revisions and Applicability

Some annexes of the GMP guidelines have undergone revision since the reorganisation in 2005.

Applicability to Parts I and II is not always clearly stated.
# Annexes Revisions and Applicability

<table>
<thead>
<tr>
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<th>Date</th>
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<th>Applicability</th>
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<td>Sampling of Starting and Packaging Materials</td>
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<td>I</td>
<td>not stated but clear</td>
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<tr>
<td>9</td>
<td>Manufacture of Liquids, Creams and Ointments</td>
<td>&lt; 2006</td>
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<td>Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation</td>
<td>&lt; 2006</td>
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<td>11</td>
<td>Computerised Systems</td>
<td>30 June 2011</td>
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<td>13</td>
<td>Investigational Medicinal Products</td>
<td>31 July 2010</td>
<td>I</td>
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<td>14</td>
<td>Manufacture of Medicinal Products Derived from Human Blood or Plasma</td>
<td>30 November 2011</td>
<td>I &amp; II</td>
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<td>Qualification and Validation</td>
<td>1 October 2015</td>
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<td>16</td>
<td>Certification by a Qualified Person and Batch Release</td>
<td>15 April 2016</td>
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<td>17</td>
<td>Real Time Release Testing and Parametric Release</td>
<td>26 December 2018</td>
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<td>Reference and Retention Samples (now Q9 in Part III)</td>
<td>1 June 2006</td>
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### Part III Applicability

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<td>2015</td>
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### Document Structure

#### Part I

<table>
<thead>
<tr>
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#### Part II

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<td>3</td>
<td>Personnel</td>
<td>300</td>
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<td>4</td>
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<td>Documentation and Records</td>
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<td>7</td>
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<td>8</td>
<td>Production and In-Process Controls</td>
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<td>Packaging and Identification Labelling of APIs and Intermediates</td>
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<td>Storage and Distribution</td>
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<td>14</td>
<td>Rejection and Reuse of Materials</td>
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<tr>
<td>15</td>
<td>Complaints and Recalls</td>
<td>200</td>
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<tr>
<td>16</td>
<td>Contract Manufacturers (including Laboratories)</td>
<td>200</td>
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<tr>
<td>17</td>
<td>Agents, Brokers, Traders, Distributors, Repackers, and Relabellers</td>
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<td>Specific Guidance for APIs Manufactured by Cell Culture / Fermentation</td>
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<tr>
<td>19</td>
<td>APIs for Use in Clinical Trials</td>
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Total words 15800

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**Annexes**

Most of the chapters have one or more corresponding sections in the other guide or in an annex.
# Comparability

<table>
<thead>
<tr>
<th>Similar</th>
<th>Part I</th>
<th>Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration</td>
<td>In process controls</td>
<td>QC documentation</td>
</tr>
<tr>
<td>Change control</td>
<td>Intermediates</td>
<td>Quality control</td>
</tr>
<tr>
<td>Cleaning (rooms, Equipment)</td>
<td>Job descriptions</td>
<td>Quality risk management</td>
</tr>
<tr>
<td>Computerised Systems</td>
<td>Log-books</td>
<td>Reagents / standards QC</td>
</tr>
<tr>
<td>Consultants</td>
<td>Maintenance (rooms, Equipment)</td>
<td>Reference samples (Part I)</td>
</tr>
<tr>
<td>Dedicated facilities</td>
<td>Management</td>
<td>Retention samples (Part I)</td>
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<td>Deviations</td>
<td>Manufacturing documentation</td>
<td>Reserve/ retention samples (Part II)</td>
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<td>Organisation</td>
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<td>Packaging / Packaging materials</td>
<td>Reprocessing</td>
</tr>
<tr>
<td>GMP (general aspects)</td>
<td></td>
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</tr>
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<td>Head of quality control / units</td>
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<td>Training</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<td>CoA</td>
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<td>On-going stability</td>
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<td>(Cross) contamination</td>
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<td>Process validation</td>
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<td>Qualification</td>
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<td>Manufacturing</td>
<td>Raw materials</td>
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<tr>
<td>Analytical method transfer</td>
<td>Recalls</td>
</tr>
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<td>Out of trend results</td>
<td>Revalidation</td>
</tr>
<tr>
<td>Packaging validation</td>
<td>Sampling</td>
</tr>
<tr>
<td>Retention samples</td>
<td>Specifications</td>
</tr>
<tr>
<td>Shortage of MP</td>
<td>Supplier Qualification</td>
</tr>
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<td>Transport verification</td>
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<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents, brokers, traders</td>
<td>Process aids</td>
</tr>
<tr>
<td>APIs for Use in Clinical Trials</td>
<td>Recovery solvents &amp; materials</td>
</tr>
<tr>
<td>Blending of batches</td>
<td>Repackers</td>
</tr>
<tr>
<td>Cell Culture / Fermentation</td>
<td>Retrospective validation</td>
</tr>
<tr>
<td>Distribution</td>
<td>Returns</td>
</tr>
<tr>
<td>Expiry / Retest</td>
<td>Reworking</td>
</tr>
<tr>
<td>Impurity profile</td>
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</tbody>
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Similar Regulations

Some topics have a high similarity in Parts I and II of the GMP guide.

Although the wording may differ in their degree of detail and also in specific requirements, they may be looked at as comparable.
Example: Changes

Part I

1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:
   (xii) Arrangements are in place for the **prospective evaluation of planned changes** and their **approval** prior to implementation taking into account regulatory notification and approval where required
   (xiii) **After implementation** of any change, an **evaluation** is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality

1.8 Good Manufacturing Practice […]
   (ii) Critical steps of manufacturing processes and **significant changes** to the process are **validated**

4.29 There should be **written** policies, **procedures**, protocols, reports and the associated records of actions taken, or conclusions reached, where appropriate, for the following examples: […] **Change control** […]

5.25 Significant amendments to the manufacturing process, including **any change in equipment or materials**, which may affect product quality and/or the reproducibility of the process, **should be validated**.

6.33 In certain situations, additional batches should be included in the **on-going stability programme**. For example, an on-going stability study should be conducted after **any significant change** or significant deviation to the process or package. […]

7.2 All arrangements for the outsourced activities including any **proposed changes** in **technical or other arrangements** should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.
   7.12 The **Contract Acceptor should not make unauthorized changes**, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the **Contract Giver**.

A11.10. **Change** and Configuration Management
   Any changes to a **computerised system** including system configurations should only be made in a controlled manner in accordance with a defined procedure.

A15.11. **CHANGE CONTROL**
   A15.11.1. The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.
   A15.11.2. **Written procedures** should be in place to describe the actions to be taken if a planned change is **proposed** to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.
   A15.11.3. Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorisation and the **need for any regulatory actions assessed**.
   A15.11.4. **Quality risk management** should be used to evaluate planned changes to **determine** the potential **impact** on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and any other system to avoid unintended consequences and to plan for any necessary **process validation**, verification or requalification efforts.
   A15.11.5. Changes should be **authorised and approved** by the **responsible persons** or relevant functional personnel in accordance with the pharmaceutical quality system.
   A15.11.6. Supporting data, e.g. copies of documents, should be **reviewed** to confirm that the **impact of the change** has been demonstrated prior to final approval.
   A15.11.7. Following implementation, and, where appropriate, an evaluation of the **effectiveness of change** should be carried out to confirm that the change has been successful.
11.12 [...] Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

13 Change Control
13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.
13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit(s).
13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.
13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.
13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.
13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

A11.10. Change and Configuration Management
Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

Additional paragraphs for IMP API’s.
Example: Calibration

Part I

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:
[...] - Equipment assembly and calibration[...]

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department: [...] iii. Procedures for and records of the calibration/qualification of instruments and maintenance of equipment [...]
More Differences

In some areas there are more differences between Parts I and II of the GMP guide.

Some of them are specific to the inherent differences between the manufacture of active pharmaceutical ingredients and the manufacture of finished products.

Some topics cover more details in one or the other guide and some regulations also cover different quality assurance tools.
Part I

4. Certificates of Analysis: Provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification.

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department: [...] v. Testing reports and/or certificates of analysis [...]
Example: Complaints

Part I

Personnel and Organisation

8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Qualified Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects and for implementing any risk-reducing actions. Sufficient trained personnel and resources should also be available for the management of interactions with competent authorities.

8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.

8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.

8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.6 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.

8.7 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.8 There should be procedures in place to facilitate a request to investigate the quality defect of a medicinal product in order to support an investigation into a reported suspected adverse event.

8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

i. The description of the reported quality defect.

ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.

iii. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.

iv. The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.

v. The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.

vi. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.

vii. The internal and external communications that should be made in relation to a quality defect and its investigation.

viii. The identification of the potential root cause(s) of the quality defect.

9.10 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.

9.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

9.12 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

9.13 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

9.14 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

9.15 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

Root Cause Analysis and Corrective and Preventative Actions

8.16 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.18 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.
15 Complaints and Recalls
15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:
- Name and address of complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Complaint nature (including name and batch number of the API);
- Date complaint is received;
- Action initially taken (including dates and identity of person taking the action); and
- Any follow-up action taken;
- Final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.
Example:
Qualification and Validation

Part I

Annex 15: Qualification and Validation

1. Organising and Planning
2. Documentation, VMP
3. Qualification stages
4. Re-Qualification
5. Process Validation
6. Verification of Transportation
7. Validation of Packaging
8. Qualification of utilities
9. Validation of Test Methods
10. Cleaning Validation
11. Change Control
12. Glossary

Part II

Chapter 12: Validation

12.1 Validation Policy
12.2 Validation Documentation
12.3 Qualification
12.4 Approaches to Process Validation
12.5 Process Validation Program
12.6 Periodic Review of Validated Systems
12.7 Cleaning Validation
12.8 Validation of Analytical Methods

Chapter 13: Change Control

2015:
VMP should be established
Retrospective validation not possible
Qualification stages more detailed
URS, FAT, SAT
Continuous process verification
PDE in cleaning validation
Transportation
Packaging

2000:
Less detailed instructions
No VMP required (only “policy” required)
Retrospective validation possible
General reference to toxicology
Utilities qualification in chapter 4
Other Differences

Contamination / Cross-Contamination
In Part II requirements may increase towards the finished API, in Part I contamination control has to be strictly respected throughout the whole process (usually no cleaning steps for the product possible).

Batch Production Record Review
In Part II one section describes the expectations for batch production record review (no details in Part I).

On-going Stability Monitoring
In Part I instructions for on-going stability programs are more detailed. In Part I an appropriate number of tests must allow statistical evaluation (trend analysis). In Part II test should be performed at least annually for one batch and the first three commercial batches should be monitored.
Other Differences

Product Quality Reviews
Requirements for PQRs are more detailed in Part I than in Part II (more aspects).

Sampling
Part I describes identity tests for starting materials on each container. Packaging materials have to be sampled statistically. According to Part II at least one test to verify the identity of each batch of material has to be performed but exceptions are possible (processing aids, hazardous or highly toxic raw materials, other special materials).
Other Differences

Specifications
In Part I detailed requirements for the structure of specifications for starting and packaging materials, intermediate, bulk and finished products are given. In Part II only general remarks for the need of specifications are implemented.

Supplier Qualification
In Part I detailed instructions for the qualification of suppliers were introduced during the revision of chapter 5 in 2015, covering aspects for the qualification of manufacturers of excipients (appropriate good manufacturing practice). In Part II only a very brief description of supplier qualification is implemented (paragraphs 7.11 and 7.31).
Other Differences

Water
In Part I there are no specific instructions for water systems and water quality (paragraphs 3.43 and 6.7vi) but pharmacopoeial requirements apply. In Part II there is a section about water quality and water systems (section 4.3).
Specific Requirements

In some areas there specific requirements in Part I or II.

Some of these regulations are ultimately connected to the characteristics of APIs or finished products. Some regulations are described in additional documents (e.g. GDP guide).
Specific to Part I

Analytical Method Transfer
In Part I (paragraphs 6.37 – 6.41) specific regulations on technical transfers of testing methods were introduced.

Results out of Trend
According to paragraph 6.7iv in addition to a procedure for the investigation of out of specification results a procedure for out of trend results should also be established.

Retention Samples
In annex 19 retention sample are described as “a sample of a fully packaged unit from a batch of finished product”, which is not relevant for APIs.
Specific to Part I

Shortage of Medicinal Products
In Part I (paragraph 5.71) there is a regulation on product shortage due to manufacturing constraints. This should be reported to the marketing authorization holder.
Specific to Part II

Distribution, Agents, Brokers, Traders, Distributors, Repackers, and Relabellers
Distribution guidance is given in chapter 10 of Part II. In chapter 17 of Part II there are specific regulations for agents, brokers, traders, distributors, repackers, and relabellers of API’s. In the EU they are complemented with the GDP Guide for APIs (2015/C 95/01).

Cell Culture/Fermentation and APIs for Use in Clinical Trials
In chapters 18 and 19 of Part II regulations for APIs manufactured by cell culture/fermentation and APIs for use in clinical trials are described (cf. annexes 2 and 13).
Specific to Part II

Blending of Batches (Intermediates and API’s)
In chapter 8.4 of Part II there are instructions for blending batches. It describes the cases, in which blending is possible or not and how it should be performed (validation, stability, expiry). Blending of OOS batches is not allowed (no blending into compliance).

Impurity Profiles
An impurity profile should be established (with exceptions), because impurities are always relevant in API production and they need to be controlled. Impurity profiles of manufactured batches should be compared to the profiles in the regulatory submission or to historical data. (paragraphs 11.21, 11.22, 12.52).
Specific to Part II

Expiry and Retest Dates

Retest or expiry dates should be based on stability characteristics of APIs. Normally the first three commercial production batches should be used to confirm the retest or expiry date (but pilot batches may be possible). A retest or expiry date should be established if an intermediate is intended to be transferred outside the control of the manufacturer’s material management system. (paragraphs 11.50, 11.53 and chapter 11.6).

If the API or intermediate is repackaged into a different type of container than used by the API or intermediate manufacturer, stability studies to justify assigned expiration or retest dates should be conducted, as described in paragraph 17.50.
Specific to Part II

Recovery of Materials and Solvents
Recovery of reactants, intermediates, or the API is considered acceptable using approved procedures and if recovered materials meet their specifications. The use of recovered materials should be adequately documented (chapter 14.4).

Processing Aids / Toxic Materials
Processing aids, hazardous, highly toxic raw materials or other special materials do not need to be tested if the manufacturer’s certificate shows compliance to established specifications (identity checks by visual examination of labels) (paragraph 7.32).
Specific to Part II

Glossary Part II

**Reprocessing**: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

**Reworking**: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).
Glossary Part I

**Reprocessing**: The *reworking* of all or part of a batch of product of an *unacceptable quality* from a defined stage of production, so that its quality may be rendered acceptable by *one or more additional operations*.

Reprocessing and reworking are combined in one definition. The definition is not as clear as in Part II and in effect reworking is not defined.
Specific to Part II

Reworking and Reprocessing
In chapter 14.2 some specific rules for reprocessing and in chapter 14.3 for reworking are described. There is a clear separation between the two approaches and the rules are clear.

In Part I reprocessing is described in paragraphs 5.66 to 5.70 and 8.28 (recall) (and in annexes A3.44, A14.6.12). There is no clear separation between reprocessing and reworking.
Reworking is also not explicitly prohibited (but not acceptable due to marketing authorizations anyway).
Conclusion

- Main sections in Parts I and II of the GMP Guide are comparable.

- There is still some potential for harmonisation between the two Parts.

- Amendments to Part II can be introduced via annexes of the GMP Guide, if required.

- Some topics in Part I and II are specific to finished products or APIs and are covered in the corresponding Part of the GMP Guide.
Current Development

Upcoming Revisions of the GMP Guide (EU):

– Annex 1 (sterile products)

– Annex 21 (GMP for importers of medicinal products) new
Future

- Parts I, II, III, IV and the annexes are living documents, new technologies and developments will be introduced if necessary (c.f. Real Time Release in Annex 17).

- A broader consolidation of the whole GMP guideline system might be required one day to remove redundancies and conflicts in the texts.

- A merge of the today separated Parts I and II might be possible, but seems unlikely because of the framework of international regulations they are embedded in.

- If international harmonisation is progressing, EU and PIC/S GMP guidelines might merge with other regulatory requirements to form a new, truly harmonised international GMP Guide.
Thank you for your attention!

Questions