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

Industry’s point of view

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Swissmedic Training, Locarno
22 May 2019
Disclaimer

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For the purpose of this presentation the terms ‘medicinal product’ and ‘drug product’ are equivalent.
01 the evolution of guidelines
02 Selected topics to compare part I and part II
03 discussion of differences - industry perspective
04 conclusions
The Evolution of DP and API Guidelines
The Evolution of Guidelines and current challenges
the evolution of guidelines

Similarities, differences and implications...

- Harmonization between Regulatory Agencies and sharing of information
- Authorizations in EU: MIA (and GMP Certificate) vs Registration
- Surveillance in EU: Inspections, Audits, QP Declaration, Written Confirmation, CEP etc.
- Variety of Materials/Products - starting materials, potency, toxicity, biotech
- Complex supply chain – added source of non-compliance investigations and recall
Selected topics to compare part I and part II

1. Structural Differences and Relationship with other Guidelines
2. Quality Control/Quality Unit
3. Facilities and Materials
4. Control over Processes
5. Rejected and Reused Materials
6. Certificate of Analysis and Retention of Samples and Documents
1. Structural Differences and Relationship with other Guidelines

**DP**

**PE 009-14 Part I - 54 pages, 9 Chapters**
- **Authorized Person**: EudraLex vol.4 Ch.I, Annex 16
- **Sampling of Starting and Packaging Materials**: PE 009-14, Annex 8
- **Computerized Systems**: PE 009-14, Annex 11 and many other guidelines
- **Qualification and Validation**: PE 009-14, Annex 15 including **Change Control** in sec. 11 of the Annex.
- **Technical Transfer of Analytical Methods** – Ch 6 Quality Control

**API**

**PE 009-14 Part II - 50 pages, 19 Chapters**
- **Authorized Person**: N/A
- **Sampling of Starting and Packaging Materials**: Ch 7 Production, Materials Management
- **Computerized Systems**: Ch 4 Process Equipment, Computerized Systems
- **Qualification and Validation**: Ch 12 Validation including **Change Control**

Main Differences between GMP/PIC/S Part 1 and 2 (ICH Q7)
### Table 1: Application of this Guide to API Manufacturing

<table>
<thead>
<tr>
<th>Type of Manufacturing</th>
<th>Application of this Guide to steps (shown in grey) used in this type of manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Manufacturing</td>
<td>Production of the API Starting Material</td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid, or tissue</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting</td>
</tr>
<tr>
<td>Biotechnology/fermentation / cell culture</td>
<td>Establishment of master cell bank and working cell bank</td>
</tr>
<tr>
<td>&quot;Classical&quot; Fermentation to produce an API</td>
<td>Establishment of cell bank</td>
</tr>
</tbody>
</table>

**Increasing GMP requirements**
2. **Quality Control/Quality Unit**

**DP**

**Quality Control** (*QA not mentioned throughout*)
- to have control over issuance of batch records and batch numbers (hybrid documentation environment!)
- to do independent review of mfg and **test** records (*as in part II section 2.32/3*)
- to have defined and implemented collaboration between MAH and CMO (*regarding PQRs sec. 1.11*)

**Authorized Person- must have**
- access to information in the Quality System
- authority and realistic workload to exercise it

**Authorized Person- nice to have**
- delegation of duties well established
- participation in the design of the quality system

**API**

**Quality Unit**
- control over issuance of batch records and batch numbers- **may be assigned to production** (*sec. 2.4.1*); Master production records to be verified by quality (*sec. 6.40*)
- record of batches that failed specifications for the market that they were originally intended for - *(incomplete statement in PQR sec. 2.60)*
- PQRs that demonstrate continuous improvement (or not!), by comparing **current** performance with **previous** years- *(incomplete PQR sec. 2.60)*
3. Facilities and Materials

DP

Facilities
• **Maximum protection** against entry of insects or animals *(sec. 3.4)*
• **Controlled access in production, storage and QC** *(sec. 3.5)* - reliance on IT, internal job changes not followed through.

Starting Materials (API, Excipients)
• Audits *(sec. 5.29)*
• Identity of the contents of each container *(sec. 5.33)*
• QRM control of excipients and suppliers *(PI 04-1)*

API

**Delineation of GMP activities**
• Production of the API Starting Material
• Introduction of the API Starting Material into process

**Facilities**
• Some equipment (closed systems) - may be located outdoors *(sec. 4.2)*
When necessary insecticides, fungicides etc. used to protect equipment, materials and API. *(sec. 4.72)*
• Only **access to cell banks** is limited to authorized personnel *(sec. 18.20)*

**Incoming materials**
• Incoming materials to be tested before mixed with existing stock *(sec. 7.22)*
• Non-dedicated tankers - cross contamination prevention *(sec. 7.23)*
4a. Control over Processes

DP

Prevention of Cross-contamination

• QRM to include potency and toxicological evaluation

Processing Operation (Intermediate and Bulk)

• Validations and Holding times

API

Production and In-process controls

• Critical process controls e.g. measuring, subdividing, yields, time limits

• Blending batches of intermediates: OOS batches should not be blended with other batches for the purpose of meeting specifications (sec. 8.41)

• Critical physical attributes (particle size!)- blending must be validated, stability and expiry dating considerations (sec. 8.45-8.47)

• Contamination control (handling after purification!)

• Dedicated equipment records not necessary if batches follow traceable sequence (sec. 6.21)

• For continuous production, product code with date and time can serve as unique identifier until the final number is allocated (sec. 6.51)
4b. Control over Processes

**DP**

**Process Validation:** Concurrent validation as an exception, justified and approved by authorized personnel *(Annex 15)*

**API**

**Validation**

**Process Validation:**
- Specific conditions for concurrent and retrospective validation. *(Sec. 12.43-12.45)*
- Periodic quality review of validated systems, processes determines the need for revalidation *(sec. 12.60)*

**Cleaning Validation**
- **Cleaning validation:** shared equipment cleaned by the same cleaning process. Selection of representative API based on potency, toxicity, stability. *(sec. 12.71)*

**Analytical Methods Validation** *(cleaning)*
- **Analytical methods:** limits to be practical, achievable, verifiable, based on most harmful component. *(sec. 12.74)*
5. **Rejected and Reused Materials**

**DP**

**Packaging Materials and Operations**

- Samples taken away from the line should not be returned except after detailed record of inspection. *(sec. 5.60)*

**API**

**Rejection and re-use of materials** - note section no.!

- Recovery of solvents *(sec. 14.4)*
6. Certificate of Analysis and Retention of Samples and Documents

DP

Certificate of Analysis (CoA)
• No specific requirement for the content of certificate of analysis (most detail in the **definition** - not comprehensive)

Retention of documents
• 1 y after expiry / 5 y after batch certification - the longer applies;
• IMPs 5 y after discontinuation of the last CT (sec. 4.11)

Retention samples (**PE 009-14, Annex 19**)
• Product: 1 year after expiry of product,
• Starting materials: 2 years after the release of the product

API

Certificate of Analysis
• CoA – to list each test performed according to requirements (method number and version!), limits and numerical results for quantitative tests
• CoA - to list contact and address of manufacturer, if tests performed by re-packer/re-processor or if certificates were re-issued the original manufacturer, tester should be shown. (sec. 11.4)

Retention of Batch Production Records
• retention period: 1 y after expiry date of the batch; if retest dates apply: 3 y after the batch is completely distributed (sec. 6.13)- same for retention samples! (IMPs: appropriate length of time after discontinuation or termination of the study (sec. 19.92)
conclusions

- Know the guidelines and be aware of differences during audits and inspections
- Similarities are just as important as differences: demonstrate DI and use QRM!

- Guidelines are not perfect and not all-inclusive, they need to be complemented with each other and with **quality culture**!
- Guidelines are based on experience. Industry is innovative... only companies with forward looking GMP compliance are **Successful**!
Thank you for your Attention!