Regulation of Active Pharmaceutical Ingredients (API)

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Agenda

Regulations

Compliance

Development

Manufacturing

Summary
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Summary
Active Pharmaceutical Ingredients

Be aware of different (synonym) wordings

• Active Pharmaceutical Ingredient (API)
• Active ingredient
• Active substance
• Drug substance
• Starting material (& Excipient)

Understand the specific regulations in regards to API

• API to be manufactured according to GMP (ICH Q7)
• However no manufacturing license is needed (most countries)
• Companies perform audits according to the Quality System
• In general no authority inspections are/were usually conducted
The Regulation of APIs

- Harmonised Requirements
  - e.g. ICH, World Health Organization, PIC/S

- Regional / Local Regulations
  - e.g. MESGOU, EU, WHO

- Sharing Experience, Training and Support
  - e.g. PIC/S, fip, PDA
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH M4 Documents

• Common Technical Document (CTD)
ICH Q-Guidelines Work Together

Processes
- Development & Manuf. of APIs (ICH Q11)
- Pharmaceutical Development (ICH Q8)
- Biotechnological Products (ICH Q5A-E)

Systems
- Pharmaceutical Quality System (ICH Q10)
- GMP for APIs (ICH Q7)
- Analytical Validation (ICH Q2)

Product
- Specifications (ICH Q6A-B)
- Pharmacopoeias (ICH Q4)
- Impurities (ICH Q3A-D & ICH M7)
- Stability (ICH Q1A-F)

Enabler
Quality Risk Management (ICH Q9)

Common Technical Document (CTD)
(ICH M4Q, eCTD: ICH M8, Communication: ICH M2)
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Summary
Compliance

- Say, what you do
- Do, what you say
- Prove it
- Manufacture
- Unable to prove!
- Why?
- Be proactive
- Continuous improvement
- Improve it
- Do, what you say
- Approve
- Change Variation
- Say, what you do

- Reactive Risk Management
Verification of Compliance

• Marketed products must be manufactured according to
  – The information submitted and approved in each country or region (e.g. EEG, GCC; regulatory compliance)
  – Good Manufacturing Practice (GMP) regulations

• Changes need to be submitted to regulatory authorities
  – Country specific around the world
  – Implemented after approval - *timelines*

• Compliance oversight of a firm’s manufacturing
  – Auditing according to the companies Quality System
  – Inspections by health authorities, if applicable
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Regulations

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Summary
Traditionally most regulations focus on individual aspects:

- **API Starting Material**
- **API Production (up stream)**
- **API Purification (down stream)**
- **API Distribution**

Repeatability, Testing Quality

**A life Cycle Approach** (ICH Q8, Q9, Q10, Q11):

- **Pharmaceutical Development**
- **Technology Transfer**
- **Commercial Manufacturing**
- **Product Discontinuation**

Process understanding, Knowledge and Risk management, Continuous improvement
Development and Manufacturing of API

ICH Q11

• ICH Q11 define principles to justify the selection the ‘API starting material’

• ICH Q11 is just approved

• ICH Q11 can get the world wide accepted standard

• ICH Q11 Implementation just started

• We are on a learning curve – both industry and regulators
Process Development Points

• Risk based Development and Manufacturing (ICH Q11, ICH Q9)
  – The relative criticality of Quality Attributes will be assessed
  – These will be periodically as new information becomes available
  – Used to augment, but not replace, scientific and engineering judgment

• A different implementation of the Control Strategy
  – Evaluated through a formal risk assessment, factoring in product knowledge, process knowledge and the testing strategy
  – The rational supporting the control strategy will be used to support the filing and lifecycle management

• A different basis for Control Strategy: ‘Quality by Design’
  – Development and documentation of an understanding of the impact of the manufacturing process on Quality Attributes
Quality by Design (QbD) Activities

• **Focus 1: Product / Molecule**
  – Apply QbD principals to molecule /cell line selection and development
  – Identify, understand and justify PQAs / CQAs
  – Understand impact of molecule attributes on pharmacokinetics, potency and safety
  – Up-front investment in molecule selection can pay dividend

• **Focus 2: Manufacturing Process**
  – Utilize QbD concepts to design processes which control quality targets
  – Risk assessments, process understanding, design space, control strategy, Design of Experiments

• **Focus 3: Regulation**
  – Understanding potential value of QbD lifecycle regulatory strategies
  – Guidance for filings: All files will include some QbD elements
  – Information and documentation requirements, integration of QbD elements
Development is Managed

Marketing Application Elements (CTD)

- Raw Materials
- Process Controls
  - Procedural Controls
  - Operating Ranges
  - Process Qualification
- Testing
  - In process
  - Specifications
  - Characterization and Comparability
  - Stability

Continuous Process Verification (Commercial Scale)

Process - Product Risk Matrix

- Overall Quality Attribute Risk
- Risk Priority Number
- Criticality Assessment
  - Severity
- Process Capability
  - Occurrence
- Testing Strategy
  - Detection

Severity: The impact of quality attribute on product efficacy and patient safety

Occurrence: The probability of quality attributes failing outside the acceptable ranges due to a deviation in the unit operation (e.g., out of operating ranges)
  - High score reflects low process capability: Parameter excursions; Operation likely to impact QA; No redundancy in subsequent step

Detection: The probability a QA excursion going undetected
  - High likelihood of detecting an excursion results in a low detection score
Where Does GMP Begin?

‘API Starting Material’ is where GMP starts

<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, Introduction of the API Starting Material into process, Production of Intermediate(s)</td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid, or tissue, Cutting, mixing, and/or initial processing, Introduction of the API Starting Material into process, Isolation and purification, Physical processing, and packaging</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plant, Cutting and initial extraction(s), Introduction of the API Starting Material into, Isolation and purification, Physical processing, and packaging</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants, Cutting and initial extraction, Further extraction, Physical processing, and packaging</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting, Cutting/comminuting, Physical processing, and packaging</td>
</tr>
<tr>
<td>Biotechnology: fermentation/cell culture</td>
<td>Establishment of master cell bank and working cell bank, Maintenance of working cell bank, Cell culture and/or fermentation, Isolation and purification, Physical processing, and packaging</td>
</tr>
<tr>
<td>“Classical” Fermentation to produce an API</td>
<td>Establishment of cell bank, Maintenance of the cell bank, Introduction of the cells into fermentation, Isolation and purification, Physical processing, and packaging</td>
</tr>
</tbody>
</table>

Material data needs to be provided for a dossier

(CTD Section 3.2.S.2.3 Control of Materials)
- Source
- History
- Generation of cell substrate
- Cell banking system, ...

Table: ICH Q7
Definition of the ‘API Starting Material’

API Starting Material
(for the production of drug substance)

Starting Material
(for the manufacturing of Drug Product)
= API & Excipient

Prior to API Production

API/Drug Substance Manufacturing

Drug Product Manufacturing

Batch Release Drug Product

GMP for API’s$_{IC\text{~}Q7}$

GMP for DP
Definition of the ‘API Starting Material’

Selection of Starting Materials and Source Materials
PIC/S-GMP Part II = ICH Q7 Chapter 1.3, 2001

- The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which “API Starting Materials” are entered into the process.

- From this point on appropriate GMP, as defined in the guidance, should be applied to these intermediate and/or API manufacturing steps.

- The ‘API starting material’ is defined in the regulatory filing and defined in ICH Q11. For existing filings companies should ensure current expectations on ‘API starting materials’ are met.

ICH Q7 Training by PIC/S - PDA
Definition of the ‘API Starting Material’

Selection of Starting Materials and Source Materials

ICH Q11 Chapter 5, 2012

- Six General Principles for justification of Starting Material
  - Changes in material attributes or operating conditions have lower potential to impact the quality of the drug substance
  - The relationship between risk and number of steps from the end of the manufacturing process
  - Manufacturing steps that impact the impurity profile of the drug substance
  - A substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials
  - A starting material is incorporated as a significant structural fragment into the structure of the drug substance
Definition of the ‘API Starting Material’

Selection of Starting Materials and Source Materials

ICH Q11 Chapter 5, 2012

ICH Q11 differs between the selection of starting materials for different kind of drug substances

• Synthetic Drug Substances
  – A substance of defined chemical properties and structure
  – Incorporated as a significant structural fragment into the structure of the drug substance

• Semi-Synthetic Drug Substances
  – Manufacturing process is a combination of chemical synthesis and elements of biological origin (e.g. by fermentation)

• Biotechnological / Biological Drug Substances
  – For further guidance see ICH Q5A, Q5B, Q5D
Definition of the ‘API Starting Material’

Regulatory Submission on Quality Drug Substance

ICH M4-CTD Module 3.2.S

- Level of detail expected depends from the nature of the respective substances

A: ‘API starting material’
   (for API manufacturing)

B: ‘Starting material’
   (for the drug product manufacturing)
To Keep in Mind

Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation for human and veterinary Medicinal Products (Rev1)

Background
The Directives 2001/83/EC, 2001/82/EC and 2001/20/EC. require the Qualified Person (OP) to certify provided in marketing authorisation applications or clinical trial applications should be put in place to minimise future occurrence of deviations that are caused by unnecessary detail. It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions. Updates to detail in the dossier, including removal of unnecessary detail, may be provided as variations.

... It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions...
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ICH Q7 was approved 2001

ICH Q7 is the world wide accepted standard

ICH Q7 training available with PIC/S and PDA

ANVISAs support was very appreciated

ICH Q7 Implementation Working Group is currently working on a Q&A jointly with PIC/S, DRA and WHO

ICH Q7 ‘GMP start with the manufacturing step using the ‘API starting material”
### ICH Q7 and Quality System Framework

#### General GMP Principles

**2 Quality Management**
- 2.1 Principles
- 2.2 Responsibilities of the Quality Unit(s)
- 2.3 Responsibility for Production Activities
- 2.4 Internal Audits (Self-Inspection)
- 2.5 Product Quality Review

**3 Personnel**
- 3.1 Personnel Qualifications
- 3.2 Personnel Hygiene
- 3.3 Consultants

**11 Laboratory Controls**
- 11.1 General Controls
- 11.2 Testing of Intermediates and APIs
- 11.3 Validation of Analytical Procedures
- 11.4 Certificates of Analysis
- 11.5 Stability Monitoring of APIs
- 11.6 Expiry and Retest Dating
- 11.7 Reserve/Retention Samples

**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

**13 Change Control**

**15 Complaints and Recalls**

**16 Contract Manufacturers (including Laboratories)**

PIC/S - PDA Training on Q7
ICH Q7 along End-to-End Quality

API Starting Material

Manufacturing

Supply Chain

API Starting Material

ICH Q7 Definition
API Starting Material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

ICH Q11
5 Selection of Starting Materials and Source Materials
5.1 General Principles
5.1.1 Selection of Starting Materials for Synthetic Drug Substances
5.1.2 Selection of Starting Materials for Semi-synthetic Drug Substances
5.1.3 Selection of Source Materials for Biotechnological/Biological Products

PIC/S - PDA Training on Q7
ICH Q7 along End-to-End Quality

API Starting Material → Manufacturing → Supply Chain

- API starting material
- API Production & Purification (upstream / downstream)
- API Distribution

API Starting Material:
- Buildings and Facilities
  - 4.1 Design and Construction
  - 4.2 Utilities
  - 4.3 Water
  - 4.4 Containment
  - 4.5 Lighting
  - 4.6 Sewage and Refuse
  - 4.7 Sanitation and Maintenance

- Process Equipment
  - 5.1 Design and Construction
  - 5.2 Equipment Maintenance and Cleaning
  - 5.3 Calibration
  - 5.4 Computerized Systems

- Documentation and Records
  - 6.1 Documentation System and Specifications
  - 6.2 Equipment Cleaning and Use Record
  - 6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials
  - 6.4 Master Production Instructions (Master Production and Control Records)
  - 6.5 Batch Production Records (Batch Production and Control Records)
  - 6.6 Laboratory Control Records
  - 6.7 Batch Production Record Review

- Materials Management
  - 7.1 General Controls
  - 7.2 Receipt and Quarantine
  - 7.3 Sampling and Testing of Incoming Production Materials
  - 7.4 Storage
  - 7.5 Re-evaluation

- Production and In-Process Controls
  - 8.1 Production Operations
  - 8.2 Time Limits
  - 8.3 In-process Sampling and Controls
  - 8.4 Blending Batches of Intermediates or APIs
  - 8.5 Contamination Control

- Rejection and Reuse of Materials
  - 14.1 Rejection
  - 14.2 Reprocessing
  - 14.3 Reworking
  - 14.4 Recovery of Materials and Solvents
  - 14.5 Returns

PIC/S - PDA Training on Q7
ICH Q7 along End-to-End Quality

API Starting Material -> Manufacturing -> Supply Chain

Supply Chain requirements are adequately covered by ICHQ7

PIC/S - PDA Training on Q7
ICH Q7 along End-to-End Quality

Equipment: Multi Product versus Dedicated Facilities

• Approach: To ensure that our manufacturing sites can safely be operated as multi product facility with appropriate scientific justification

• How to do?
  – Follow an approach to assess and control risks
    (ICH Q9 based; e.g. Risk-Based Manufacture of Pharmaceutical Products, ISPE baseline guide ‘Risk MaPP’, 2010; ‘Quality Risk Management’, PDA Technical Report 54, 2012)
  – Define an acceptable level of carry-over of one product into another product: scientifically sound, health-based
  – Ensure that this acceptable level of carry-over is not exceeded by implementing necessary controls
GMP Controls in API Manufacturing

Implement ICH Q7 (= PIC/S GMP Part II)

Controls increase as process proceeds to final isolation and purification steps

Apply GMP controls beginning with the use of API starting materials

‘API starting material’ is justified in the filing as per ICH Q11

‘Starting material’ (for Drug products)

Degree of control depends on process and manufacturing stage

Training on Q7
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ICH Guidelines Provides Foundation

- Development, registration and filing requirements
  - ICH M4 established & ICH Q11 (ICH Q8) gets considered
  - ICH Implementation Working Group (Q-IWG):
    Questions & Answers, Points to Consider and Training material

- GMP for APIs
  - ICH Q7 is linked to the new ICH paradigm (ICH Q8, Q9, Q10, Q11)
  - Pharmaceutical Quality System (ICH Q10) has ICH Q7 as foundation
  - PIC/S - PDA training material available

- Quality Risk Management
  - The enabler for processes and systems
  - ICH Q9 guideline & the ICH Q9 briefing pack for training
Evaluate the Overall Risk to Patient

Quality Risk Management (ICH Q9)

• An enabler included in all manufacturing and quality related processes controls
  – Product Risk - Process Risk - System Risk

• Typical Risk Spectrum

  Critical to quality controls implemented
  Contributors to consistency descriptions in documentation
  Low risk parameters/attributes well controlled or assessed prior to use
Ready for Sustainable Manufacturing!

Efficiently & Reliably Deliver High Quality of APIs

**Production Process**

*with process understanding and continual improvement*

**Input controls**
(raw materials and components)

**Procedural controls**
(process design, facility, equipment and operational controls)

**In-process testing**
(IPCs, process monitoring, validation)

**End product testing**
(specifications, comparability, stability)
Conclusion

Efficiently & Reliably Deliver High Quality of APIs

• A consistent framework provided by
  – Product knowledge
  – Manufacturing process understanding
  – Established systems are continuously improved

• Efficient resource utilization and consistent approaches and tools required for
  – Development and Commercial Manufacturing of quality products
  – High reliability processes
Acknowledgement

- Duane Bonam, Amgen
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- Steve Mendivil, Amgen
Regulation and Oversight of API’s

• Current regulation is fit for the purpose (e.g. PIC/S GMPs)

• Understand the difference to Drug Products