



Connecting People, Science and Regulation®



# ICH Q7 Chapter 1: Introduction



PDA - PIC/S ICH Q7 Training

© PIC/S and Parenteral Drug Association (PDA), May 2015

Reproduction prohibited for commercial purposes. Reproduction for internal use is authorised, provided that the source is acknowledged.



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GOOD MANUFACTURING PRACTICE GUIDE FOR  
ACTIVE PHARMACEUTICAL INGREDIENTS

Q7

Current Step 4 version  
dated 10 November 2000

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*

[www.ich.org](http://www.ich.org)



**Q7 Implementation Working Group**  
**ICH Q7 Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients**  
**Questions and Answers**

**Current version**  
**dated 10 June 2015**

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH Secretariat, Chemin des Mines 9, P.O. Box 195, 1211 Geneva 20, Switzerland

Telephone: +41 (22) 338 32 06 - [admin@ich.org](mailto:admin@ich.org), <http://www.ich.org>

**www.ich.org**



# Content

- **Objective** (1.1)
- **Regulatory Applicability** (1.2)
- **Scope** (1.3)

## 1.3 Scope: ICH Q7 applies to...

- APIs manufactured for use in human drug (medicinal) products including sterile APIs, but only up to the point immediately before the API is rendered sterile
  - APIs manufactured by chemical synthesis, extraction, cell culture / fermentation, recovery from natural sources, or any combination of these processes
  - APIs used in production of medicinal / drug products for clinical trials
  - APIs produced using blood or plasma as raw materials
  - APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms (& Section 18)
- ◆ *Manufacturers **and** Agents, Brokers, Traders, Distributors, Repackers and Relabellers (ABTDRR) (Chapter 17)*



## 1.3 Scope: ICH Q7 applies to...

- ◆ **Thoughts on ‘Atypical’ Actives** *(see local requirements)*  
(e.g. alginate, Glucose, Iodine, honey, NaCl, KCl, Mg-salts)
  - *There is no expectation that atypical actives are manufactured according to the full requirements of ICH Q7*
  - *Alternative and appropriate controls must be implemented using principles of Quality Risk Management (ICH Q9) to ensure the controls are proportionate to the risk to the drug product*
  - *However in case of parenteral products consider conducting the final isolation/purification step according to ICH Q7*

## 1.3 Scope: ICH Q7 excludes

- **All vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation) and gene therapy APIs**
- **Medical gases**
- **Bulk packaged medicinal / drug products**
- **Radiopharmaceuticals**

# ICH Q7 does **not** address

- **Registration and filing requirements for APIs within the context of marketing / manufacturing authorisations or medicinal / drug product applications (see ICH Q11)**
- **Pharmacopoeial requirements**
- **APIs intended for use in veterinary medicinal / drug products**
  - ◆ *In some countries ICH Q7 is also applicable to API for veterinary medicines*



# Meaning of ‘should’

## ICH Version

In this guide the term **“should”** indicates **recommendations that are expected to apply** unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

## FDA Version

In this guide the term ***should*** identifies **recommendations that, when followed, will ensure compliance with cGMPs**. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes.

# ICH Q7 is well thought out

If ICH Q7 says you should do something, you probably should do it

If it doesn't say you have to do something, you probably don't have to do it

If it doesn't prohibit something, it's probably OK to do it

If ICH Q7 prohibits something, you probably shouldn't do it

# How are GMPs applied in API Manufacturing?

- The same GMP *concepts* apply to both finished product and API manufacture
- **HOWEVER application** of these concepts may differ
  - Receipt of materials
  - Production
  - Packaging and repacking
  - Labeling and relabeling
  - Quality control and release
  - Storage and distribution



# Application of ICH Q7 (Table 1) (1.3.)

- **Type of Manufacturing**
  - Chemical Manufacturing
  - API derived from animal sources
  - API extracted from plant sources
  - Herbal extracts used as API
  - API consisting of comminuted or powdered herbs
  - Biotechnology: fermentation / cell culture
  - “Classical” Fermentation to produce an API

# How are GMPs applied in API Manufacturing?

- ◆ *Areas/topics with specific requirements for APIs:*
  - *Recovery of solvent, mother liquor, catalyst*
  - *Lots of dangerous reagents or materials*
  - *Blending fractions of different lots is common practice*
  - *Blending subparts of the same lot is also common practice*
  - *Validity date vs retest period*

### Increasing GMP requirements

Application of ICH Q7 (Table 1) (1.3.)

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	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
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	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
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

◆ GMP according to ICH Q7 applies to steps in grey; for the steps in white follow 'good practices'



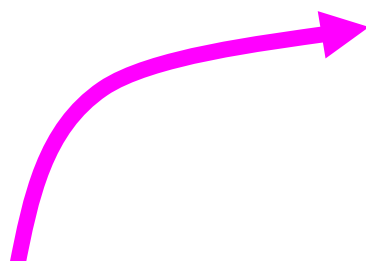
# Applying ICH Q7

## Chemical Manufacturing

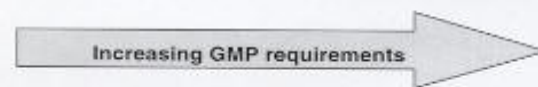
Outside scope



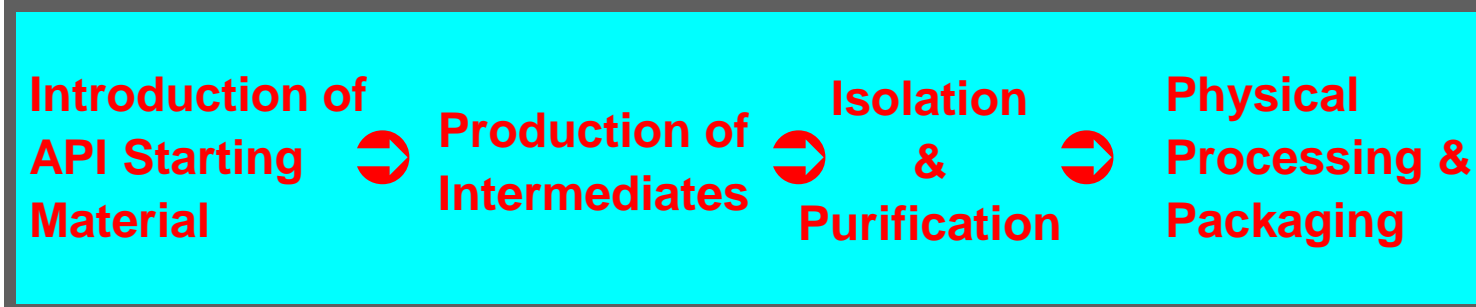
Covered by ICH Q7



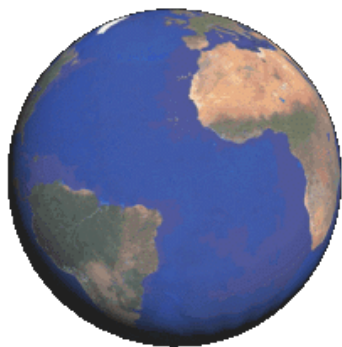
Type of Manufacturing	Application of this Guide to steps used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing and packaging
API derived from animal sources	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
Biotech/ Fermentation cell culture	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
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging



**Production of API Starting Material**



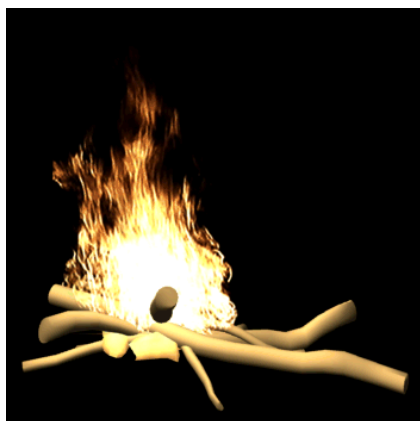
# Where does API Process begin?



**Earth**



**Wind**



**Fire**



**Water**

## Definition ‘API Starting Materials’ (Q7)

- A material used in the production of an API which is “incorporated as a ***significant structural fragment into the structure of the API***”
- May be “an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or may be ***produced in-house***”
- “Are normally of defined chemical properties and structure”

# Definition ‘API Starting Materials’ (Q11)

Part of the registration process see ICH Q11

- **Selection of Starting Materials and Source Materials (5.)**
  - Synthetic Drug Substance (5.1.1) e.g.
    - *Impact of changes in material attributes or operating conditions in 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
    - An API starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate API starting material
    - An API starting material is incorporated as a significant structural fragment into the structure of the drug substance.
  - Biotechnological / Biological Drug Substances (5.2.3)
    - Guidance is contained in ICH Q5A, Q5B and Q5D.

# Definition ‘API Starting Materials’

- **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. (1.3)**
- **From this point on appropriate GMP, as defined in the guidance, should be applied to these intermediate and / or API manufacturing steps. (1.3)**
- ◆ *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*





# Overview: GMP for APIs (ICH Q7)

## 1 Introduction

- 1.1 Objective
- 1.2 Regulatory Applicability
- 1.3 Scope

## 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

## 4 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

## 5 Process Equipment

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

## 6 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

## 7 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

## 8 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

## 9 Packaging and Identification Labelling of APIs and Intermediates

- 9.1 General
- 9.2 Packaging Materials
- 9.3 Label Issuance and Control
- 9.4 Packaging and Labelling Operations

## 10 Storage and Distribution

- 10.1 Warehousing Procedures
- 10.2 Distribution Procedures

## 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

## 14 Rejection and Reuse of Materials

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

## 15 Complaints and Recalls

## 16 Contract Manufacturers (including Laboratories)

## 17 Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

- 17.1 Applicability
- 17.2 Traceability of Distributed APIs and Intermediates
- 17.3 Quality Management
- 17.4 Repackaging, Relabelling and Holding of APIs and Intermediates
- 17.5 Stability
- 17.6 Transfer of Information
- 17.7 Handling of Complaints and Recalls
- 17.8 Handling of Returns

## 18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

- 18.1 General
- 18.2 Cell Bank Maintenance and Recordkeeping
- 18.3 Cell Culture/Fermentation
- 18.4 Harvesting, Isolation, and Purification
- 18.5 Viral Removal/Inactivation Steps

## 19 APIs for Use in Clinical Trials

- 19.1 General
- 19.2 Quality
- 19.3 Equipment and Facilities
- 19.4 Control of Raw Materials
- 19.5 Production
- 19.6 Validation
- 19.7 Changes
- 19.8 Laboratory Controls
- 19.9 Documentation

## 20 Glossary



# Key Messages

## GMP Controls in API Manufacturing

Controls increase as process proceeds to final isolation and purification steps

**‘Starting material’**  
(for Drug products)

Apply GMP controls beginning with the use of API starting materials

Degree of control depends on process and manufacturing stage

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

# ICH Q7 QaA *Clarification of Uncertainties*

1. Should GMP according to ICH Q7 be applied for manufacturing steps before the defined 'API starting material' i.e. steps not identified in grey in Table 1?
2. Does ICH Q7 apply to manufacturing steps for the addition of substance(s) to an API (e.g., to stabilize the API)?

## **20. Glossary**

1. *Are the terms 'deviation' and 'non-conformance' synonyms?*

