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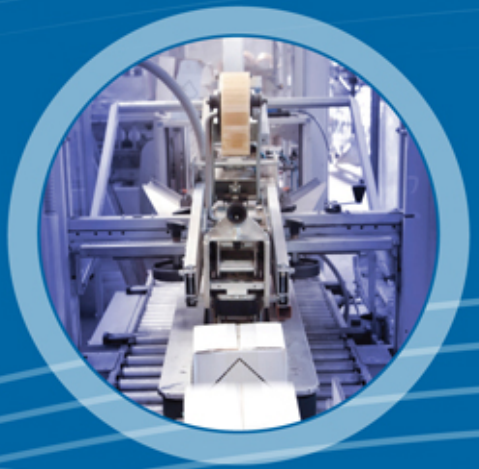
ICH Q7 Chapter 1:
Introduction



PDA - PIC/S ICH Q7 Training

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.

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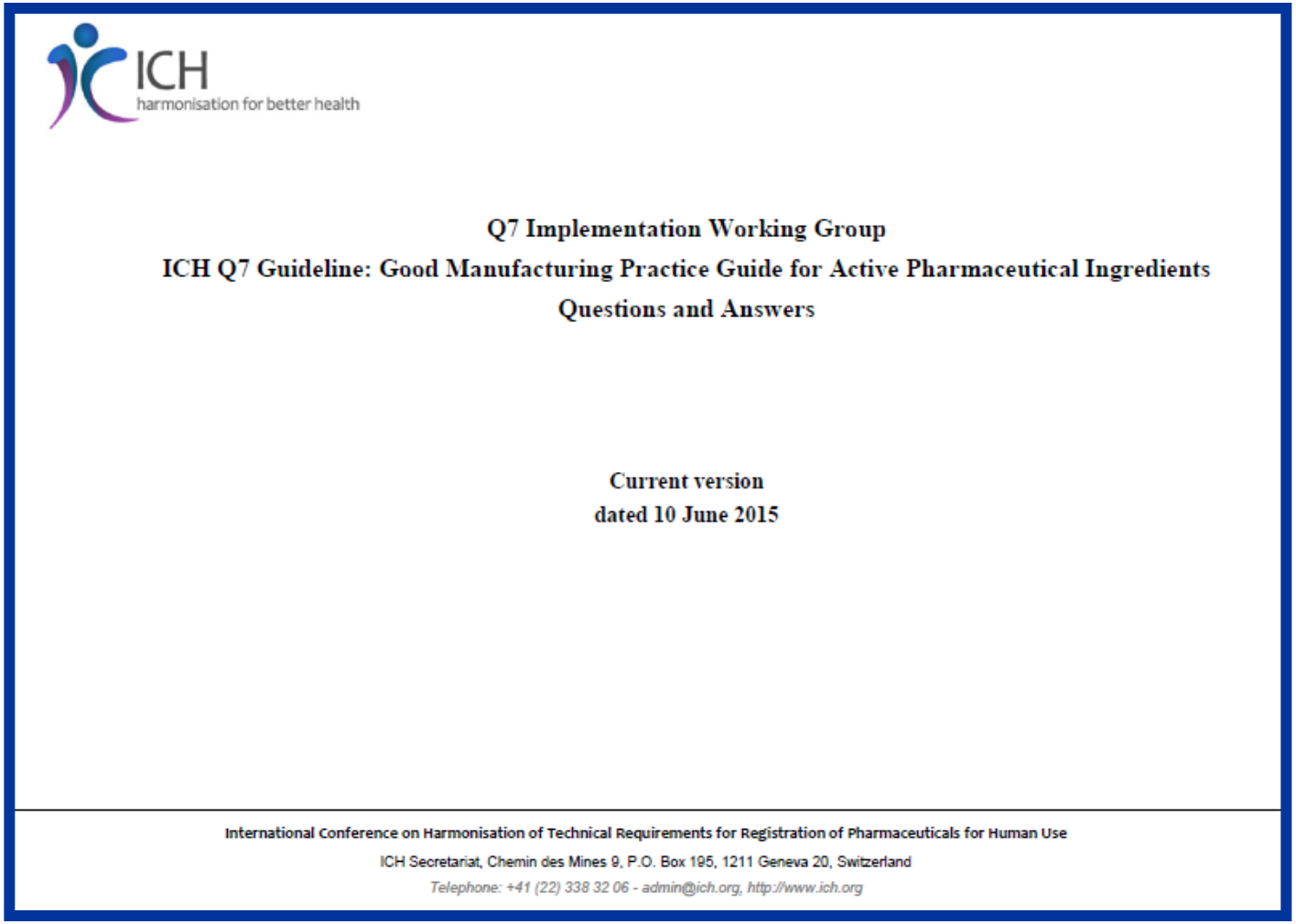

ICH
harmonisation for better health

Q7 Implementation Working Group

ICH Q7 Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Questions and Answers

Current version
dated 10 June 2015

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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

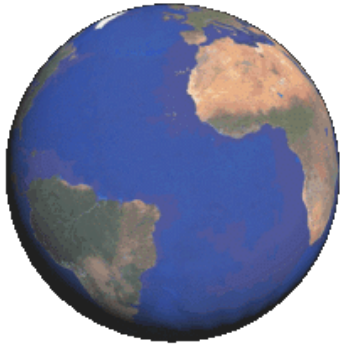
Type of Manufacturing	Application of this Guide to steps used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing and packaging
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

Increasing GMP requirements

Production of API Starting Material

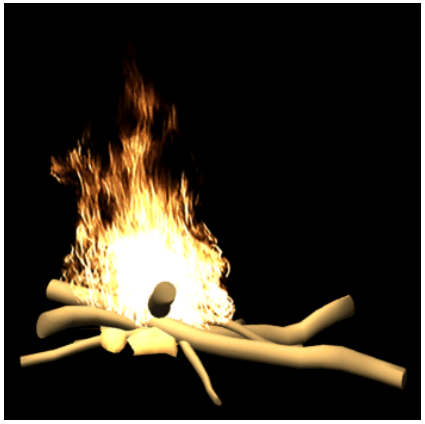
Introduction of API Starting Material ➲ **Production of Intermediates** ➲ **Isolation & Purification** ➲ **Physical Processing & Packaging**

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"**

See also ICH Q11

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.

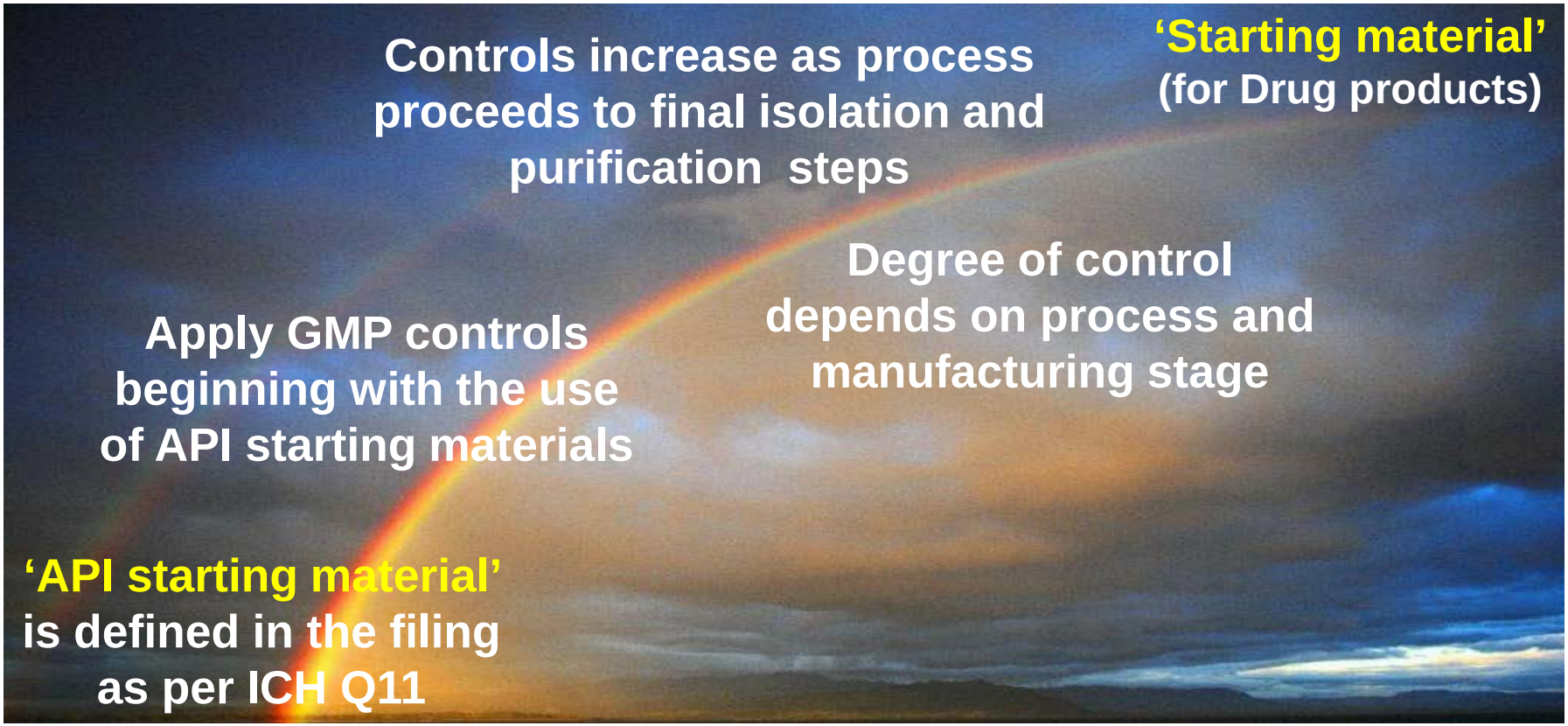
Definition ‘API Starting Materials’

- **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)

Key Messages
GMP Controls in API Manufacturing



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?

ICH Q7 Q&A, 2015


PDA
SM
Parenteral Drug Association


PIC/S