ICH Q11 – Development & manufacture of drug substances

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Disclaimer:

- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

Outline

- Background to ICH Q11
- Overview of Q11 at Step 3
- Next steps of ICH process

What is the purpose of ICH Q11 ?

A new tripartite high level technical guidance harmonising the scientific and technical principles relevant to design, development and manufacture of drug substances as part of a total control strategy designed to ensure product quality and consistency.

- **Harmonisation**
- **Facilitate innovative development over the product lifecycle in order to improve product and process understanding**
- **No new regulatory requirements**
- **Utility for regulators & industry**

Why is a new ICH guideline for active substances required ?

- **ICH Q Round-table – Washington 2007**
  - Region specific data packages and data presentation
  - Differences in data requirement between regions present administrative burden to industry
  - Inefficient use of industry & regulatory authority resources
- **Application of concepts of the new quality paradigm (ICH Q8, Q9 & Q10) to drug substance**
- **Facilitate innovation in approaches to development and control of drug substance manufacturing processes, enabled by application of on-, at- and in- line analytical technologies coupled with robust risk management strategies**

What is the scope of ICH Q11 ?

- **In scope: 3.2.S.2.2 – 2.6 of CTD**
  - New Chemical Entities – as defined in ICH Q6A
  - Biotechnological/Biological Products – as defined in ICH Q6B

- **Not in scope:**
  - Clinical trial materials
  - Regional post approval change requirements

Does Q11 impact other ICH guidance ?

- **Addresses principles & concepts of Q8, Q9 & Q10 in relation to drug substance**
- **Specific guidance applicable to substances of biotechnology provided in Q5 series**
- **Additional guidance to ICH Q series but does not create new regulatory requirements.**

What topics are covered in ICH Q11 ?

- Introduction & scope
- Manufacturing Process Development
- Description of the Manufacturing Process & Process Controls
- Selection of Starting Materials and Source Materials
- Control Strategy
- Process Validation/Evaluation
- Where to file information in CTD
- Lifecycle Management
- Illustrative Examples
- Glossary

Manufacturing Process Development

- **Identifying CQA for drug substance in relation to drug product target product profile**
- **Defining a suitable manufacturing process**
- **Defining a robust control strategy to ensure process performance and drug substance quality**
- **Systematic evaluation, understanding and refining of the manufacturing process**
  - **Use of risk assessment tools, prior knowledge and experimentation to identify the material attributes and process parameters that can have an effect on drug substance CQA**
  - **Determining the functional relationships that link material attributes and process parameters to drug substance CQA**

Manufacturing Process Development

- **What data/information to submit ?**
  - Summary overview
  - Level of detail – pivotal v non-pivotal studies
  - Relevance of development studies to the commercial process
  - Effect of scale
  - History of batches produced to date & linked to significant developments in the manufacturing process
  - An applicant may adopt either a traditional or enhanced approach to development of the process or a combination of both

Description of Manufacturing Process

- **Flow chart and sequential procedural narrative similar to M4Q**
- **Any proposed design space described here. Example 3.**

Starting / Source Materials

- **Different perspectives for NCE as compared to substances of biotechnology**
- **For biotech substances, advice concerning cell banks is given in Q5A, B & D**
- **For NCE –**
  - Considerations for selection of a given molecule in the synthetic sequence as the regulatory starting material
  - Reassurance that the defined process and control strategy, operating within GMP will consistently provide drug substance of the required quality
  - Example provided to illustrate application of considerations

Starting Materials

- **What information to provide in the regulatory submission ?**
  - NCE – synthetic
  - NCE – semi-synthetic
  - Biotech substance

Control Strategy - Considerations

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));
- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g., release testing).

Control strategy

- **Control strategy applies irrespective of development approach adopted (traditional or enhanced)**
- **Point of application of control may differ depending on the nature of the attribute requiring control and process knowledge as a result of development studies**
  - Sterility assurance
  - RTRT

Control strategy – what information to submit

- **Description of Manufacturing Process & Process Controls (3.2.S.2.2)**
- **Control of Materials (3.2.S.2.3)**
- **Control of Critical Steps & Intermediates (3.2.S.2.4)**
- **Container Closure System (3.2.S.6)**
- **Control of Drug Substance (3.2.S.4)**

Example of presentation of an overview of this information for NCE & biotech substances is provided

Process validation/Evaluation

- High level overview of approaches to PV
- Includes optionality for ‘traditional 3 batch’ approach and continuous process verification approach described in Q8.
- All manufacturing processes to be validated prior to product commercialisation
- Differences in data requirements at time of MA submission/approval depending on molecular complexity/characterisation (NCE v biotech) and depending on nature of process (e.g aseptic processing)

Process validation / Evaluation

- **Biotech specific aspects:**
  - PV studies include studies at commercial scale in addition to particular studies (e.g virus removal) conducted at small scale.
  - When platform manufacturing experience is utilised, the suitability of the control strategy should be demonstrated and the drug substance manufacturing process should be appropriately validated at the time of the marketing authorisation application. Full scale validation studies should include data derived from the final manufacturing process and site(s) used to produce the product to be commercialised.

Where to submit using CTD

- Quality risk management & process development
- Critical Quality Attributes
- Design Space
- Control Strategy

Lifecycle Management

- Continual improvement of the drug substance manufacturing process is facilitated via quality systems elements & management responsibilities described in Q10
- Periodic re-evaluation of control strategy including any design space within the product quality review
- Knowledge management across the product lifecycle – incl supply chain
- Science and risk based approach to evaluation of impact of process changes
- Specific guidance for changes to biotech processes – link to Q5E
- Proposals for management of specific future changes can be included in the original pre-approval dossier – Example 2
- Regional requirements for post approval changes apply

Examples

- **Linking Material Attributes & Process Parameters to Drug Substance CQAs – Chemical Entity**
- **Use of Quality Risk Management to Support Lifecycle Management of Process Parameters for Biotech Unit Operation**
- **Presentation of a Design Space for Biotechnological Product Unit Operation**
- **Selecting a Starting Material in an NCE Synthesis**
- **Presentation of the Elements of a Control Strategy for NCE and biotech substances**

Glossary

- **Platform Manufacturing**
  - The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g as in production of monoclonal antibodies using predefined host cell, cell culture and purification process, for which there exists considerable experience)

Next steps

- **Public Consultation Periods**
  - USA
  - Japan
  - EU
- **Timetable to Step 4**
- **Implementation**
  - See IWG Q&A
  - No new regulatory requirements
  - Optionality in approaches to manufacturing process development

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harmonisation for better health

Thank You!