ICH Q12 (Pharmaceutical Product Lifecycle Management): Current Status and Future Perspectives

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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA and ICH Q12 EWG.
Presentation Outline

- Background
  - ICH Quality Guidelines
  - 2003 ICH Quality Vision

- ICH Q12
  - Scope and Objectives
  - Issues to be addressed
  - Current Proposed Outline
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“Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science”.

- ICH Quality EWG July 2003 (Brussels)

Product lifecycle;
Pharmaceutical development → Technology transfer → Commercial Manufacturing → Product discontinuation
ICH Quality Strategy Workshop

- Reflected on the progress since 2003
- Developed a future vision and strategy
- Five priorities were identified:
  - Lifecycle Management
  - API Starting Materials
  - Quality Overall Summary
  - Enhanced Approaches for Analytical Procedures
  - Continuous Manufacturing of Pharmaceuticals

Endorsed as ICH Q12 by ICH steering committee.
Statement of the Perceived Problems

- While the concepts in ICH Q8, Q9, Q10 and Q11 provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle, the envisioned post-approval ‘operational flexibility’ has not been achieved.

- There is currently a lack of a harmonized approach on technical and regulatory considerations for lifecycle management.

- Lack of alignment has led to confusion on the necessary information and level of detail in the dossier and its impact on change management and regulatory reporting.

- It has hindered the anticipated innovation and continual improvement.
Bringing a Global Change through Approval is often a multiple year endeavor even for the simplest of changes

- Core File Prep 2 m
- Core review cycle 4-10 m
- EM File Prep 1-2 m
- Non-ref EM reviews 6-20 m
- Ref EM reviews 6-24 m
- Wave 1 (core) 6-12 month approval cycle (post data)
- Wave 2 (non-ref countries) approval cycle 9-24 m
- Wave 3 (ref-countries) approval cycle 12-36 months (post data)

Example 1: Lyophilization Cycle Change

Pre-approval not required
No stability data required in submission

- Require 3 months stability data
- Require 6 months stability data
- Require US/EU approval or CPP (Certificate of Pharmaceutical Product) prior to submission or during review

Approved details differ from country to country after Q&A compared to the submitted dossier

From Richard Lit, 2013 APEC Harmonization Center Biotherapeutics Workshop

From Susanne Ausborn, CMC Strategy Forum Europe 2014

From Stefanie Pluschkell, WHO/MFDS Implementation Workshop: Evaluation of biotherapeutic products 2014
ICH Q12: Objectives and Scope

Objectives include:

- Provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle
- Optimization of industry and regulatory resources
- Support innovation and continual improvement and help to assure drug product supply

Scope

Pharmaceutical products, including currently marketed chemical, biotechnological and biological products. (However, each regulatory authority will decide whether generic medicines can be included in the scope of this guideline.)
Issues to be addressed

- Regulatory Dossier
- Pharmaceutical Quality System (PQS) aspect
- Post-Approval Change Management Plans and Protocols
Although CTD format has been defined for a marketing authorization application, there is not harmonized understanding/approaches to defining which information in the dossier is binding and therefore requires a post-approval regulatory action when it is changed.

Defining “Regulatory Commitments/Approved Matters/Established Conditions” to clarify binding information and supportive details in dossier

...are binding information or elements concerning the manufacture and control of a pharmaceutical product, including description of the product, elements of the manufacturing process, facilities and certain equipment, specifications [i.e., test, method and criteria] and other elements of the associated control strategy (e.g. storage conditions or shelf-life), found in a submission, that assure process performance and desired quality of an approved/licensed product.
Issues under Discussion

- How are “ECs” identified? What is and is not a “EC”? 
- How are the current state of “non-ECs ”reported?
- Application to already marketed products.
- Need to develop a list of “ECs”? 
- Location in the CTD.
Approved Matters = Established Conditions?

Japan

Module 3

Summarized

ICH

Module 3

Extracted

Module 2 (QOS)

Module 1(AF)

• Composition
• Mfg. process incl.
control of materials
• Specification
• Storage condition,
Shelf life
• Mfg. sites inf.
• Etc.

Established Conditions

?
Today’s ECs/AMs Session

- Presentation
  - New Drug Application of Biotechnology Products in Japan: Approval Contents / Legal Binding Related to CMC Part (Takao Kojima, JPMA)
  - J-Module 1 Preparation (CMC): Model Document for Manufacturing Process Description (Kei Nishimura, JPMA)
  - Japanese Application Form: PMDA’s Perspective on Manufacturing Process Description (Reiko Yanagihara, PMDA)

- Panel discussion
  - What is the Established Conditions?
  - How are established conditions chosen?
  - How should the company separate “Established Conditions” from supporting information in the regulatory dossier?
  - How can the Established Conditions facilitate the post-approval changes in each region/country?
  - What level of details is required in the Established Conditions?
  - What should we take into consideration to introduce Regulatory Commitments into regulatory procedure in each country?
ICH Q10 is a basis.

A robust/effective PQS is a prerequisite for Q12 as all changes are managed in a company’s PQS.

What should be included in Q12?
- Knowledge Management
- Change Management
- Outsourcing
- Interaction b/w reviewers and inspectors
Post-Approval Change Management Protocol

- **A regulatory tool** that enables prospective planning of future change(s) including the assessment of the impact of the proposed CMC change(s) to product quality.

- Describes specific change(s) a company would like to implement during lifecycle of a product and how these would be prepared and verified.

- May be submitted with the original marketing authorization or subsequently as a stand-alone submission.

- Companies may implement the change based on the established regional requirements without using a PACMP.
(EU) Principle of PACMP

Traditional
Evaluation of a proposed variation as a ‘whole’
(Strategy + Results)

Strategy
• Planned studies
• Acceptance criteria
• Methods

Results

Early Step 1:
Submission of a Change Management Protocol
Type II Variation

Fast Step 2:
Reporting of implementation of a change in accordance with an approved protocol
Type IA or IB Variation

Questions and answers on post approval change management protocols
(EMA/CHMP/CVMP/QWP/586330/2010)
Advantages of PACMP approach

- Predictability and transparency in terms of the requirements and studies needed to implement a change as the approved protocol provides an agreement between the MAH and the regulator.

- Reduced reporting category for future reporting of CMC changes covered by the approved protocol.

- Potential for faster review and/or inspection at step 2 of PACMP procedure due to familiarization with the change.

- Faster implementation, if the pre-determined criteria of the PACMP are met.
Issues under Discussion

- Multiple protocols across products
- Acceptability across ICH regions

Benefits of “Lifecycle Strategy”
- Summary of the knowledge of the product which determines the control strategy
- A list of the ECs for the products
- A proposal for regulatory reporting categories
- A description of any follow-up/post-marketing commitments
- (Optional) References to any PACMPs
- (Optional) Future planned CMC changes
Today’s PACMP Session

- Presentation
  - Past Experience and Current Perspective on the Use of Comparability Protocols in Biologics: An Effective Tool to Manage Post-Approval Changes (Ingrid Markovic, CBER, FDA)
  - Post-approval Change Management Protocols - Current Status and Next Steps on the Way towards a Global Tool (Markus Goese, F. Hoffmann-La Roche Ltd.)
  - Industry Perspective: Current Status of Global Change Control Management (Tetsuya Kawakami, Chugai Pharmaceutical Co., Ltd.)

- Panel discussion
  - What is the difference between post-approval change management protocols in EU and comparability protocols in US? Are there any challenges with the both systems?
  - What is the advantage of PACMP for regulators and industry?
  - What should be considered during development or post-approval to establish robust protocols?
  - What kinds of description and levels of detail are required for PACMP?
  - Is it acceptable to make one PACMP for multiple products/multiple facilities?
  - PACMP is not currently available in Japan. What should be considered to introduce PACMP in Japan?
Product Lifecycle Process

**Pharmaceuticals and Medical Devices Agency**

### PQS Enablers
- Knowledge Management
- Quality Risk Management

### Key Phases
- Pharmaceutical Development
- Technology Transfer
- Commercial Manufacturing
- Product Discontinuation

#### Pre-Approval Phase
- Approval Phase
- Post-Approval Phase

#### Industry

**Submission of MA (and Lifecycle Management Plan – LCMP), incl.:**
- Ref. to Regulatory Commitment/ Established cond.:  
  - What is in, what is out
  - What is for inspection
  - What needs regulatory review
  - Define do & tell and tell & do
  - Location in CTD
- Post-Approval Change Management Protocol(s) (PACMPs)
  - Broad & Specific protocol
  - Change Mgt for Regulatory
  - Future extrapolation

#### Regulation Influence
- Legislation
- Scientific advices
- Guidelines including Q&A and other relevant documentation

#### Assessment of the application
- Approval of
  - Regulatory Commitments/ Established Conditions
  - PACMPs

#### Regulators
- Assessment / Inspection

- Changes performed as agreed in the LCMP / PACMP(s)
- Further gain of knowledge based mainly on commercialisation
- Submission of an updated/new LCMP / PACMP according to gained knowledge
- Other changes

- Regulatory submission as per agreed procedure (incl. no regulatory submission but subject to inspection, if applicable)
- Not applicable
- Evaluation of a new LCMP / PACMP
- Evaluated according to regional legislation
Current Proposed Q12 Outline

- Introduction
- Scope
- Desired State
- Relationship to other ICH Guidelines
- Q12 Guiding Principles
- Overview of Product Lifecycle Management
- Pharmaceutical Quality System and Change Management
- Knowledge Management
- Established Conditions
- Post Approval Change Management Protocols
- Lifecycle Strategy – general considerations
- Relationship between Assessment and Inspection
- Examples of Changes
- Annex 1: Glossary
- Annex 2: References to Lifecycle Management in other ICH Guidelines
- Annex 3: Location and examples of Established Conditions
Desired Approach to Q12 Development

- Clear, comprehensive, self-contained without need for additional examples or annexes
- ICH harmonized guideline and useful globally in the future
- Forward-looking and pragmatic
- Appropriately balancing conceptual and practical aspects
- Supports innovation and continual improvement
Thank you for your attention!

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