ICH Q12 (Pharmaceutical Product Lifecycle Management): PMDA Perspective

Yasuhiro Kishioka, Ph.D.
Principal Reviewer
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency (PMDA)

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

- ICH Q12
  - Background
  - Scope and Objectives
  - Issues to be addressed
- PMDA Perspective
“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
Regional initiatives and ICH activities

- Revision of PAL
- Pharmaceutical cGMPs for the 21st Century
- GL on parametric release
- ICH Quality Vision 2003
- EMA-FDA Pilot Program for QbD (PMDA joined as an observer)
- Q8, 9, 10, 11, PtC, Q&As
- Q12
Mandatory to all products

Discussions in research groups

Guideline incl. mock for chemicals

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law in 2005

http://www.pmda.go.jp/files/000153677.pdf (in English)
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.
- The main emphasis to date has focused on early stages of the lifecycle (i.e., development through launch).
- There is currently a lack of a harmonized approach on technical and regulatory considerations for lifecycle management.
- It has hindered the anticipated innovation and continual improvement.
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**
  - Explore the development of a harmonised approach to “regulatory commitments” for inclusion in the guideline. Such approaches could enable post approval changes that facilitate continual improvement and encourage the adoption of innovative technologies.
  - Delineate the appropriate level of detail and information necessary for regulatory assessment and inspection in the dossier, in order to create a more enabling post approval change management system.

- **Pharmaceutical Quality System (PQS) aspect**
  - Establish criteria for a harmonised risk-based change management system based on product, process and/or clinical knowledge that effectively evaluates the impact of change on quality, and, as applicable to safety and efficacy.
  - Clarify expectations and reinforce the need to maintain a knowledge management system that ensures continuity of product and process information over the product lifecycle.

- **Post-Approval Change Management Plans and Protocols**
  - Introduce the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (Assessors and Inspectors).
  - Establish criteria for post-approval change management protocols that can be adopted by the ICH regions (enabling a harmonised proactive approach for lifecycle management).
  - Encourage enhanced product development and control strategy approaches (Quality by Design (QbD)) providing opportunities for scientific and risk based foundations for post-approval change management plans.
Presentation Outline

- ICH Q12
  - Background
  - Scope and Objectives
  - Issues to be addressed

- PMDA Perspective
Regulatory Commitments/Established Conditions/Approved Matters

Japan
Module 3
Summarized
Module 2 (QOS)
Extracted
Module 1(AF)

ICH
Module 3

Established Conditions

- Composition
- Mfg. process incl. control of materials
- Specification
- Storage condition, Shelf life
- Mfg. sites inf.
- Etc.
Review Process of MAA with document flow

- Focus on CMC -

Applicant

F2F meeting

Inquiry/Response

Manufacturing site

GMP audit

Review report

Consultation

Opinion (Positive/Negative)

Ministry of Health, Labour and Welfare

Pharmaceutical Affairs and Food Sanitation Council

AF, M2, M3

AF, M2

AF (M2, M3, if needed)

Review report

External experts

AF, M2, M3

AF, M2, M3

AF, M2, M3
Japanese Application Form (AF)

MHLW

MAHs

- Composition
- Mfg. process incld. control of materials
- Specification
- Storage condition, Shelf life
- Mfg. sites info
- Etc.
Japanese AF/Approved Matters

- AF, found in Module 1.2, is a legally binding document in Japan.

- Essential elements to ensure pharmaceutical quality should be described in AF.

- A post-approval regulatory action is required if a MAH changes the content in the AF (Approved Matters; AMs).
  - AMs (incl. PCA/MCN) are determined on a product-by-product basis.

- AF provides the transparency and flexibility in terms of post-approval changes.
AF and Review/Inspection

- Focus on post-approval change -

Scientific Knowledge / Knowledge Management

Stimulus
Driving to Change Request

Change Evaluation
- Science & Risk-based evaluation
- Evaluate the PAC against EC/ non-EC
- Determine the data needed
- Design & review PAC strategy

Change-Management Process

Implement PAC & Strategy

Change Approval

Regulatory notification (if required)
Regulatory approval (if required)

Internal Company Process

AF

review

Past Changes Implemented
CAPA

Development / Co-Development Report
Product/ Process Performance Review
Other...
Management review
PQR / APR

Pharmaceuticals and Medical Devices Agency

Modified from draft Q12 document
Japanese AF/Approved Matters

- AF, found in Module 1.2, is a legally binding document in Japan.

- **Essential elements to ensure pharmaceutical quality should be described in AF.**

- A post-approval regulatory action is required if a MAH changes the content in the AF (Approved Matters; AMs).
  - AMs (incl. PCA/MCN) are determined on a product-by-product basis.

- AF provides the transparency and flexibility in terms of post-approval changes.
Japan’s Effective/Efficient/Flexible Quality Regulation

Module 1
(Application Form)

Module 2 (QOS)

Module 3

Legally binding

Not-Changeable without regulatory procedures (PCA/MCN)

Changeable without regulatory procedures (PCA/MCN)
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

Traditionally, evaluation of a proposed variation as a ‘whole’ (Strategy + Results)

- **Strategy**
  - Planned studies
  - Acceptance criteria
  - Methods

- **Results**

**Steps**

**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

- Expedited review and/or inspection at step 2 of PACMP procedure.
- Reduced reporting category for future reporting of CMC changes covered by the approved protocol.
- Predictability and transparency in terms of the requirements and studies needed to implement a change.
- Faster implementation, if the pre-determined criteria of the PACMP are met.

PMDA considers the implementation of the concept of PACMP.
The content, value and benefits are still under discussion.

- Product Development summary
- Control Strategy summary
- Established Conditions
- Planned changes and regulatory reporting category of change(s)
- Justification for ECs and regulatory reporting category of change(s)
- Plan to verify that initial set of ECs are appropriate
- Post-Approval Change Management Protocols (PACMPs)
- Post-approval commitments (PACs), if applicable
- Etc.

PMDA continues to seek the value and benefits.
For better post-approval changes

- Review Current Requirements/Guidelines
  - Application Form

- Discuss New Concepts/Guidelines
  - ICH Q12
  - Post-approval change management protocol
For better post-approval changes

Review Current Requirements/Guidelines
- Application Form

Discuss New Concepts/Guidelines
- ICH Q12
- Post-approval change management protocol
Acknowledgements

- ICH Q12 EWG members
- AMED* research group members (*: Japan Agency for Medical Research and Development) special thanks to Dr. Haruhiro Okuda and Dr. Akiko Ishii-Watabe
- Colleagues in the Office of Cellular and Tissue-based Products, PMDA
Thank you for your attention!

Yasuhiro Kishioka, PhD.
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency
kishioka-yasuhiro@pmda.go.jp
Back-up
Relationship between Application Form and CTD Documents in Japan

Approved Matters

Application Form

Extracted

Major review document

Module 2 (QOS)

Summarized

Module 3

Relationship between Application Form and CTD Documents in Japan

Approved Matters

Application Form

Extracted

Major review document

Module 2 (QOS)

Summarized

Module 3
Japan’s Performance on NDA Review

Reference: The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013. CIRS (Centre for Innovation in Regulatory Science) R&D 55

http://cirsci.org/node/73
### Post-Approval Change Reporting Categories

<table>
<thead>
<tr>
<th>Impact on quality</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Partial change Application (approval of variation)</td>
<td>Major change (Prior approval supplement)</td>
<td>Type II variation (Application for approval of variation)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Minor change Notification (within 30 days after implementation or shipping)</td>
<td>Moderate change 1) Supplement- changes being effected (CBE) in 30 days</td>
<td>Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Supplement- changes being effected (CBE)</td>
<td>Type IA&lt;sub&gt;IN&lt;/sub&gt; variation (Immediate notification)</td>
</tr>
<tr>
<td>Low</td>
<td>SOP (Under GMP change control)</td>
<td>Minor change (Annual report)</td>
<td>Type IA variation (Notification within 12 months after implementation)</td>
</tr>
</tbody>
</table>