Post-Approval CMC Changes in Japan: How We Envision the Future

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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.
Outline

- Past, Present
- ...and Future
Regulatory Framework in Japan

- Focus on biologics CMC -

- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law
- Etc.

- MHLW: Minister of Health Labour and Welfare
- PSEHB: Pharmaceutical Safety and Environmental Health Bureau
- ELD: Evaluation and Licensing Division
Article 14 Persons intending to market a drug ...... must obtain approval of the Minister for marketing of each item.

When persons who have received an approval as specified in Paragraph 1 wish to make a partial change of approval items (excluding cases where such changes are minor changes as specified by MHLW Ordinance), approval of the Minister must be obtained for such cases. In such cases, the provisions of the preceding paragraphs shall apply mutatis mutandis.

A person who has obtained approval as specified in Paragraph 1 shall submit a notification of minor changes specified by MHLW Ordinance in the preceding paragraph to the Minister as specified by MHLW Ordinance.
Article 47  The minor changes specified by MHLW Ordinance pursuant to the provisions of Article 14, Paragraph 10 of the Act shall be changes other than those specified below.

1. Changes in the manufacturing methods, etc. that will affect the nature, properties, performance, or safety of a product
2. Deletion of items from the specifications and changes in the specifications
3. Changes concerning methods for the inactivation or elimination of pathogenic factors
4. Addition, changes or deletions concerning the dosage and administration, or the indications
5. In addition to those specified in the preceding items, any changes that could potentially affect the quality, efficacy, or safety of a product
Relationship between Application Form and ICH CTD

Approved Matters

Application Form

Extracted

Module 2 (QOS)

Summarized

Main review document

Module 3
Section of Application Form

- General name (JAN)
- Brand name
- Composition
- Manufacturing process, incl. control of materials
- Specifications
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information
Revision of PAL* in 2002 (enforced in 2005)

*: Pharmaceutical Affairs Law
currently Pharmaceuticals and Medical Devices Act (PMD. Act)

Revision of the Quality Regulation and Needs for Practice Development

1. MAH’s responsibility for the Quality management
   New Ministerial Ordinance (GQP), Guidance- ICH Q10

2. Manufacturing process commitment
   Policy Notification, Guidance- Case study, Mock

3. Drug Master File system
   Policy Notification

4. Consolidation of the Legal Positioning of GMP
   Revise GMP Ministerial Ordinance,
   Policy Notification: Pre-approval and Foreign inspections

5. Revision and Consolidation of GMP standards
   Revise GMP Ministerial Ordinance,
   Guidance: Product GMP, Change Control

Dr. Yukio Hiyama
EDQM Conference Quality of Medicines in a Globalised World: Dreams and Reality
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Pharmaceuticals and Medical Devices Agency

Regulatory change in Application Form (1)

- **Chemicals**
  - Specifications
  - Mfg. process
  - **Mandatory for all products**

- **Biologics**
  - Specifications
  - Mfg. process
  - **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)
Minors Change Notification in mfg. process section was introduced.

Harmonization among ICH regions was considered.
- CBE30/Type1B, Annual Report/Type1A, Comparability Protocol were NOT introduced.
- Information/elements classified as Annual Report/Type1A were considered as non-Approved Matters.
## 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><strong>Partial change Application</strong> (prior approval for change)</td>
<td>Major change (Prior approval supplement)</td>
<td>Type II variation (Application for approval of variation)</td>
</tr>
<tr>
<td>Moderate</td>
<td><strong>Minor change Notification</strong> (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>2) Supplement- changes being effected (CBE)</td>
<td></td>
<td>Type IA&lt;sub&gt;IN&lt;/sub&gt; variation (Immediate notification)</td>
</tr>
<tr>
<td>Low</td>
<td><strong>(Non-approved matters)</strong></td>
<td>Minor change (Annual report)</td>
<td>Type IA variation (Notification within 12 months after implementation)</td>
</tr>
</tbody>
</table>
Our 2005 GL has provided the basic principle of AMs in the Mfg. process and helped both regulators and the industry.

However, there still remain some challenges, including:

- **Adverse effects of mock**
  - Some just followed the mock described in the guideline to meet deadline.
  - Both regulators and the industry tend to follow the mock (?), although the description in the AF is on a product-by-product basis.

- **Document management**
  - The discrepancy between the actual situation (e.g. MBR) and AF is caused by multiple factors.

- **Others**
  - Some tend to lose sight of the original purpose of the AF.
  - Some tend to think MAHs manufacture and control their products only according to the AF.
  - There had been no detailed discussion on Specification.
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)
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)
Outline

- Past, Present
- ...and Future

Reminder!

Some of the content are currently under discussion. 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.
Issues to be addressed in ICH Q12

- **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.
Approved Matters ≈ Established Conditions

Japan

ICH

Module 1(AF)

Module 2 (QOS)

Module 3

Summarized

Extracted

Approved Matters

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

Application

F2F meeting

Inquiry/Response

Manufacturing site

AF, M2, M3

AF, M2, M3, if needed

(AF, M2, M3, if needed)

AF (Approval Letter)

PMDA

GMP audit

Review report

Consultation

Opinion (Positive/Negative)

Ministry of Health, Labour and Welfare

Pharmaceutical Affairs and Food Sanitation Council

External experts

Expert discussion

AF, M2, M3

Review report

Review report

AF, M2

AF, M2, M3

Approval
Japanese Application Form

MHLW

MAHs

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

Pharmaceuticals and Medical Devices Agency
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

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

Stimulus
Driving to Change Request

Implement PAC & Strategy

Change Approval

Past Changes Implemented
CAPA

Development/Co-Development Report
Product/Process Performance Review
Other...

Management review
PQR/APR

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

Modified from draft Q12 document
Japanese Application Form/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.
Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8 (R2))

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8 (R2))
How to determine AMs of PPs in Mfg. process? *(before MAA)*

**Process Parameters**
- Prior knowledge
- Process characterization studies

**Criticality Assessment**
- Impact on defined CQAs?
  - Yes or Unknown
  - No

**CPP (incl. pCPP)**
- Control Strategy
  - Severe harm if the control is failed?
    - Yes
    - No
    - Risk is well controlled?
      - Yes
      - No

**Non-CPP**
- AM (PCA)
- AM (MCN)
- Non-AM

**Quality Risk Management**

- Development
- Submission
- Approval

Under discussion
How to determine AMs of PPs in Mfg. process? (after MAA)

Quality Risk Management

Criticality Assessment
- Impact on defined CQAs?

Yes (or Unknown)
- CPP (incl. pCPP)
- AM (PCA)

No
- AM (MCN)
- Non-AM

Continuous Monitoring
Product Quality Review /Annual Product Review
New knowledge on CQAs

Control Strategy
- Severe harm if the control is failed?
- Remained as high risk?

Yes
- Risk is well controlled?
- AM (PCA)
- Non-AM

No
- AM (MCN)
- Non-AM
My Expectations...

Current

Development

Post-Approval

Future

Development

Post-Approval
Regional initiatives and ICH activities

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

ICH Quality Vision 2003

Pharmaceuticals and Medical Devices Agency
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- JPMA General Regulation Subcommittee Regulatory Affairs Committee
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Thank you for your attention!

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