How Will ICH Q12 Fly in Japan?

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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.
Expectation to ICH Q12

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

Pharmaceuticals and Medical Devices Agency
ICH Q12 Regulatory Tools & Enablers

Provide a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle

- Categorization of Post-approval CMC Changes
- Established Conditions (ECs)
- Post-Approval Change Management Protocol (PACMP)
- Product Lifecycle Management (PLCM)
- Pharmaceutical Quality System (PQS) and Change Management (CM)
- Relationship between Regulatory Assessment and Inspection
- Post-approval Changes for Marketed Products
Major Challenges for Q12 Implementation in Japan

- PQS and CM
- ECs and PLCM
  - Streamline AF (i.e. appropriate level of detail of Mfg. process and Specification sections)
  - Location of PLCM document
- PACMP
  - Introduce new system (e.g. PMDA consultation)
Responsibility of MAH based on GQP* in Japan

Total responsibility!

MAH

- Supervise and manage the manufacturers
- Ensure proper release to market

Manufacturer A (drug substance) → Manufacturer B (drug product) → Manufacturer C (packaging, label) → Market Release

External Testing laboratory

*: Good Quality Practice

https://www.pmda.go.jp/files/000153579.pdf (in English)
Major Challenges for Q12 Implementation in Japan

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- PACMP
  - Introduce new system (*e.g.* PMDA consultation)
How We Address These Challenges?

- **ICH Q12**: November 2014 – December 2017
- **PMDA ICH Q12 WG**: May 2015
- **AMED Research Group**: December 2014
- **MHLW/PMDA-FPMAJ Task Force**: September 2016

AMED: Japan Agency for Medical Research and Development
MHLW: Minister of Health Labour and Welfare
FPMAJ: The Federation of Pharmaceutical Manufacturers' Associations of JAPAN
Overview of Three Main Activities

- **PMDA ICH Q12 WG** (established in May 2015)
  - Members: Associate Center Directors, Office Director, Reviewers (chemical, biologic, generic), Inspectors
  - Discuss regulatory, technical and practical issues within PMDA

- **AMED Research Group** (joined since December 2014)
  - Members: Academia, Industry, PMDA
  - Discuss technical and practical issues
  - Report the outcome and proposal to MHLW

- **MHLW/PMDA-FPMAJ Task Force** (Established in September 2016)
  - Members: MHLW, PMDA, FPMAJ
  - Driven by “domestic problems” (not by ICH Q12)
  - Streamline the regulatory procedures for post-approval CMC changes
Rational Regulatory Oversight in Japan

Module 1 (Application Form)

Module 2 (QOS)

Module 3

Legally binding

Not-Changeable without regulatory procedures (PCA/MCN)

Changeable without regulatory procedures (PCA/MCN)

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Miscommunication b/w manufacturer and MAH (inappropriate CM) → Discrepancies b/w AF and actual mfg. and control

- tend to think company’s CM should be regulated by AF??
- tend to think MAHs manufacture and control their products only according to the AF??
→ AF has become enlarged

Administrative disposition primarily according to AF
Miscommunication b/w manufacturer and MAH (inappropriate CM)
→ Discrepancies b/w AF and actual mfg. and control

- Manufacturer tends to think company’s CM should be regulated by AF??
- Manufacturer tends to think MAHs manufacture and control their products only according to the AF??
→ AF has become enlarged

My personal observation

Measure to Break the Vicious Circle

MHLW

- Administrative disposition primarily according to AF
  - Enhance implementation of robust CM
  - Take administrative disposition against inappropriate CM

PMDA(reviewer)

- Review the aim/positioning of AF
- Clarify the criteria for identification of AMs incl. PCA/MCN

Application Form
Module 2
Module 3

【Ideal】

【Status quo】

- Implement robust CM
- Measures of industry organizations to support each company’s robust CM
Review Process of MAA with document flow

- Focus on CMC -

**Applicant**
- Application
- F2F meeting
- Inquiry/Response
  - AF, M2, M3
- Manufacturing site
- Application
  - Approval
  - AF
  - (Approval Letter)

**PMDA**
- AF, M2, M3
- Review report
- GMP audit
  - AF
  - (M2, M3, if needed)

**External experts**
- AF, M2, M3
- Expert discussion

**Ministry of Health, Labour and Welfare**
- Consultation
  - Opinion (Positive/Negative)

**Pharmaceutical Affairs and Food Sanitation Council**
- Review report

[Diagram showing the process flow with various stakeholders and decision points]
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).
AF and Review/Inspection

-Focus on post-approval change-

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)

Past Changes Implemented
CAPA

Development/Co-Development Report
Product/Process Performance Review

Other...
Management review

PQR / APR

Scientific Knowledge / Knowledge Management

AF

review

inspection

Modified from draft Q12 document
Mfg. Process Section in AF

For more detailed information: Dr. Sakurai, CMC Strategy Forum Japan 2016

- Current Issues
  - Unclear criteria for Partial Change Application, Minor Change Notification and Not Approved Matter
  - Risk-based approach has not been fully achieved yet

- Future perspective
  - Revise the existing guideline published in 2005
    http://www.pmda.go.jp/files/000153677.pdf (in English)
Specification Section in AF

For more detailed information: Dr. Fujita, CMC Strategy Forum Japan 2016

- Current Issues
  - No distinction b/t JP monograph and product specific Application Form
  - All Changes in Spec. section are in principle the Partial Change Applications

- Future perspective
  - Publish new guideline
  - Discuss the introduction of Minor Change Notification for changes in Spec. section
Rational Regulatory Oversight in Japan

Module 1 (Application Form) - Legally binding
Module 2 (QOS)
Module 3

MAH’s Compliance and Responsibility
Product Lifecycle Management document in Japan

Module 1 (Application Form) +α
Approved Matters

- Summary of Product Control Strategy
- PACMPs
- Post-approval CMC commitments
PACMP in Japan

- PACMP in EU

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

Traditional
Evaluation of a proposed variation as a ‘whole’ (Strategy + 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
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- JPMA General Regulation Subcommittee Regulatory Affairs Committee
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Thank you for your attention!

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