Update of Q12 Implementation in Japan

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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.
Please keep in mind

- Detailed regulations for implementation of ICH Q12 are still under discussion.

- Today I will introduce the **DRAFT** version of PACMP in Japan and this is subject to change.
Agenda

- Toward implementation of ICH Q12
- PACMP pilot program in Japan
- PACMP based on updated act
Agenda

- Toward implementation of ICH Q12
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Toward implementation of ICH Q12

- **PMDA ICH Q12 WG**
  - Members: Associate Center Director, Office Director, Reviewers (chemical, biologic, generic), Inspectors
  - Discuss regulatory, technical and practical issues to implement Q12 within PMDA

- **AMED Research Group**
  - Members: NIHS, Industries, PMDA
  - Discuss technical and practical issues
  - Report the outcome and proposal to MHLW

- **MHLW/PMDA-FPMAJ Task Force**
  - Members: MHLW, PMDA, FPMAJ
  - Driven by “domestic problems” (not by ICH Q12)
  - Rationalize the regulatory procedures for post-approval CMC changes

NIHS: The National Institute of Health Sciences
MHLW: Minister of Health Labor and Welfare
FPMAJ: The Federation of Pharmaceutical Manufacturers' Associations of JAPAN
Toward implementation of ICH Q12

- To Understand Q12 guideline in Japan
  - Will hold briefing session

- Established Conditions (ECs)
  - What is EC/not EC?
  - What is categorized as Partial Change Application/Minor Change Notification?
  - How to describe ECs and their reporting categories (Table/Flow chart/Description)

- PACMP
  - Discuss about detailed regulations of PACMP
  - Update our software for new PACMP application
  - Create PACMP mock-up

Q12 J-IWG (JAPAN sub-team)

TF (Task force); consist of MHLW, PMDA and industry

AMED (Japan Agency for Medical Research and Development) Research Group; consist of NIH, PMDA, academia and industry

Q12 J-IWG (JAPAN sub-team); JPMA and PMDA member of ICH Q12 IWG
Agenda

- Toward implementation of ICH Q12
- PACMP pilot program in Japan
- PACMP based on updated act
Post-Approval Change Management Protocol (PACMP)

- Regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a CMC change as the approved protocol provides an agreement between the MAH and the regulatory authority.
- Already implemented in US (2003-) and EU (2010-)
- PMDA started PACMP pilot program* since April 2018

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*(EU) Principle of PACMP

- Strategy
  - Planned studies
  - Acceptance criteria
  - Methods

- Results

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* “Handling of Changes to Approved Product Information Pertaining to the Quality of Drugs” (PSEHB/PED Notification No. 0309-1 and PSEHB/CND Notification No. 0309-1 dated March 9, 2018, jointly issued by the Director of the Pharmaceutical Evaluation Division and the Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW).
Overview of PACMP pilot program in Japan

1. **Pre-meeting**
   - Share draft PACMP document and schedule between PMDA and MAH

2. **Step 1**
   - **PACMP CMC Consultation**
     - Confirm PACMP
     - Agree PACMP between PMDA and MAH
   - **PACMP GMP Consultation**

   **Follow-up Meeting (Optional)**
   - If PACMP is changed, a follow-up meeting is used to confirm revised PACMP and agree between PMDA and MAH

3. **Step 2**
   - **MCN**
   - **PCA Application**
     - 3 months (Median Value)

   **Approval**

**Notes:**
- **PCA:** Partial Change Approval
- **MCN:** Minor Change Notification

Pharmaceuticals and Medical Devices Agency
Experiences in PACMP Pilot Program

- From April 2018 to Nov 2020...
  - Number of consultations?
    - more than 10
  - Biotechnological/Biological or small molecule?
    - Biotechnological/Biological: approx. 80%
    - Small molecule: approx. 20%
  - Details of the change?
    - The most common cases are as follows;
      - Addition of new manufacturing site
      - Extension of shelf life
Toward implementation of ICH Q12

PACMP pilot program in Japan

PACMP based on updated act
Updated act will come!

- We have introduced the PAMCP into our regulation, ‘Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices’.
- The updated act will come into effect next year.
- Now, PMDA/MHLW are working on detailed regulations of PACMP for the implementation of the updated Act.
Step 1

- For changes to approval items related to quality of pharmaceuticals, MAH submit PACMP to MHLW.
- The protocol is reviewed and approved by PMDA/MHLW.

Step 2

- The tests and studies outlined in the protocol are performed.
- If the results/data generated meet the acceptance criteria in the protocol and any other conditions are met, the MAH submits “Notification based on the approved PACMP” to MHLW.
- The change based on PACMP may be implemented if no inquiries are received within 40 or 20 business* days after submitting “Notification based on the approved PACMP”.

*: still under discussion
At PACMP review process, if a proposed change may significantly affect the quality, it will not be endorsed. In addition, if it is found that a proposed change was out of scope of the system after PACMP review, retraction may occur.

In case a change does not follow PACMP, suspension of a change may be ordered.

Use of PMDA consultation (Optional)

- Preliminary consultation
- F2F consultation
- Post-meeting consultation

*: still under discussion
## Major Differences

### PACMP Pilot Program vs PACMP based on updated act

<table>
<thead>
<tr>
<th></th>
<th>PACMP Pilot Program</th>
<th>PACMP based on updated act</th>
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</thead>
<tbody>
<tr>
<td>Review of PACMP</td>
<td>As PMDA consultation</td>
<td>As application to MHLW</td>
</tr>
<tr>
<td><strong>Scope</strong></td>
<td>Prescription drugs (New drugs and marketed products, Biological and chemicals)</td>
<td>Prescription drugs, Cellular and tissue-based products, OTC drugs, Quasi-drugs, and Cosmetics that require approval by MHLW (Pharmaceuticals approved by the governor are excluded)</td>
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<tr>
<td>GMP inspection</td>
<td>By PMDA</td>
<td>By PMDA and prefectural governments</td>
</tr>
<tr>
<td>PACMP in original submission</td>
<td>Not available</td>
<td>Will be available</td>
</tr>
<tr>
<td>Step2 period</td>
<td>About 3 months</td>
<td>In principle 40 business days (a special case: 20 business days)</td>
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<tr>
<td>Reporting category(step2)</td>
<td>PCA(prior approval) or MCN(notification)</td>
<td>Notification (Prior notification before implementation of the change)</td>
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</table>

This is a current plan and subject to change

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Summary

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Thank you for your attention!

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- ICH Q12 EWG/IWG
- PMDA Q12 EWG/IWG (Shinichi Okudaira, Yasuhiro Kishioka, Kentaro Hara)
- AMED Research group
- MHLW/PMDA-FPMAJ Task Force
- PMDA Q12 Working Group