PMDA Updates:
Approach to Making much Further Progress

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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

- PMDA International Strategic Plan 2015
- SAKIGAKE Designation System
- Biosimilars
- Post-Approval Changes in Japan
PMDA International Strategic Plan 2015

International Pharmaceutical Regulatory Harmonization Strategy

Pharmaceuticals and Medical Devices Agency
Overview of the Strategic Plan

Structure of the Strategic Plan

VISION

STRATEGY

ROADMAPS

VISION 1:
To contribute to the world through regulatory innovation

VISION 2:
To maximize the common health benefits to other countries/regions

VISION 3:
To share the wisdom with other countries/regions
Key International Actions

- Establish the “Regulatory Science Center” for conducting first-in-the-world product reviews, implementing safety measures, and undertaking other activities, as well as publishing the outcomes.

- Launch the “Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs” to share PMDA’s accumulated knowledge and experience in product reviews, implementation of safety measures, and provision of relief services with Asian and overseas regulatory authorities.

- Cooperate with overseas regulatory authorities for expansion of harmonization activities (e.g., ICH, IMDRF) and work-sharing (e.g., GMP/QMS inspections).
Asian Training Center

Expand training courses in Japan

Conduct training courses in partner countries
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SAKIGAKE Designation System

- The MHLW drew up the “Strategy of SAKIGAKE” to lead the world in the practical application of innovative medical products in 2014.

- SAKIGAKE designation system
- Scheme for rapid authorization of unapproved drugs

- Designation criteria for SAKIGAKE designation system
  - Medical products for diseases in dire need of innovative therapy
  - Development & NDA in Japan being world’s first or simultaneous with other countries
  - Prominent effectiveness expected on non-clinical and early phase clinical trials

General Timeframe for SAKIGAKE Designation System

**[Standard]**

- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies → Clinical trials I/II → Consultation on Clinical trials → phase III study → Review → Reimbursement → Post-Marketing

**【SAKIGAKE】**

- Priority Consultations
- Prior review (rolling submission)
- Fore-runner review assignment
- Non clinical studies, Clinical studies → Clinical trials I/II → Consultation on Clinical trials → phase III study → Review → Reimbursement → Post-Marketing

- ※ In some cases, may accept phase III data during review

**Practical application of Innovative medical products**

- ① Priority Consultations
- ② Prior-review
- ③ Priority Review
- ④ Review Partner System
- ⑤ Strengthening Post-Marketing Safety
<table>
<thead>
<tr>
<th>Product name</th>
<th>Expected indication</th>
<th>company</th>
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<tr>
<td>Sirolimus</td>
<td>Vascular fibroma associated with tuberous sclerosis</td>
<td>Nobelpharma</td>
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<td>NS-065 / NCNP-01</td>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>NihonShinyaku</td>
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<td>Influenza A or B virus infection</td>
<td>Shionogi</td>
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<td>Management of angioedema attacks in patients with hereditary angioedema (HAE)</td>
<td>Integrated Development Associates</td>
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<td>ASP2215</td>
<td>First-relapse or treatment-resistant FLT3 gene mutation-positive acute myeloid leukemia</td>
<td>Astellas Pharma</td>
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<td>Pembrolizumab</td>
<td>Unresectable, advanced and recurrent gastric cancer</td>
<td>MSD</td>
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<td>Titanium Bridge (Hinge-type plate with Titanium)</td>
<td>Adduction-type spasmodic dysphonia</td>
<td>Nobelpharma</td>
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<td>Bioresorbable adhesion barrier (THN-01: Trehalose solution)</td>
<td>Postoperative adhesion prevention</td>
<td>Otsuka Pharmaceutical Factory</td>
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<td>STR01 (Autologous bone marrow-derived mesenchymal stem cell)</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO</td>
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<td>G47Δ (Growth-controlled oncolyticherpes simplexvirustype 1)</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo</td>
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<td>The University of Tokyo, Institute of Medical Sciences</td>
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<tr>
<td>Autologous cardiac progenitor/stem cells</td>
<td>Pediatric congenital heart disease</td>
<td>Japan Regenerative Medicine</td>
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<tr>
<td></td>
<td>(single ventricle physiology)</td>
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CMC Considerations for Accelerated Programs

- Where is the *acceptable* Minimum Requirement?
- Flexibility in Post-Approval changes
Outline

- PMDA International Strategic Plan 2015
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Regulatory History and Status of Biosimilars

- Application Category for biosimilars
- Guideline
- Nomenclature rules

Q&A

Revision of Nomenclature rules

2009
Somatropin BS [Sandoz]

2010
Epoetin alfa BS [JCR]

2011
Filgrastim BS [F], [MOCHIDA]

2012
Filgrastim BS [NK], [TEVA]

2013

2014
Filgrastim BS [Sandoz]

2015
Infliximab BS [NK], [CTH]

2016
Insulin glargine BS [FFP]

Q&A
Overview of new Q&As

- Multidisciplinary
  - Non-Japan approved reference product
  - Data required when submitting first notification for clinical trials

- Quality
  - Comparative bioassays for mAbs
  - Reference standard

- Non-clinical
  - Need for toxicity studies

- Clinical
  - Japanese population data
  - Comparative PK studies
    - Route
    - Equivalence margin
  - Comparative efficacy studies
    - 95% CI
    - Population
  - Indication extrapolation for mAbs

- Post-marketing surveillance
  - Reporting procedure
Is toxicity study (repeat-dose toxicity study) required for biosimilar development?

- Basically, a company should evaluate the non-clinical safety of biosimilar candidate itself prior to entering into clinical studies, in accordance with ICH S6 (R1).

- However, in cases where there is no concern on non-clinical safety based on characterization studies and comparative comparison of the physicochemical and pharmacological properties, *in vivo* toxicity studies may be not required.

- This approach should be on a case-by-case basis. PMDA recommends to use our consultations
Consultation for Biosimilars

Fiscal year (from April 1 to March 31)

Based on date of application

No. of consultations

<Number>

<Product type>

- mAbs & Fc-fusion proteins, 37 (65%)
- ESAs, 6
- Insulins (incl. analogues), 5
- G-CSFs, 4
- FSHs, 2
- Enzymes, 1

Pharmaceuticals and Medical Devices Agency
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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

Module 3

Summarized

Module 2 (QOS)

Extracted

ICH

Module 3

Module 1(AF)

Approved Matters

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

Established Conditions
Review Process of MAA with document flow

**Applicant**
- Application
- F2F meeting
- Inquiry/Response
- Manufacturing site
- Approval

**PMDA**
- GMP audit
- Review report
- Consultation

**External experts**
- Expert discussion

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

**Pharmaceutical Affairs and Food Sanitation Council**
- Consultation

**Focus on CMC**
- AF, M2, M3
- Review report
- AF
- (Approval Letter)
- AF, M2, M3
- Review report
- AF, M2, M3, if needed
- Review report
Japanese Application Form

MHLW

MAHs

- Composition
- Mfg. process incl. control of materials
- Specification
- Storage condition, Shelf life
- Mfg. sites info.
- Etc.
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))
My Expectations...

Current

Future

Development

Post-Approval
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 Approval

Implement PAC & Strategy

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
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)  
Legally binding

Module 2 (QOS)

Module 3

MAH’s Compliance and Responsibility
Thank you for your attention!

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