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Perspectives on Trends in the Regulation of Biopharmaceutical Products in Europe and Asia (Japan)

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Contents

• Review Topics (Early Access Schemes)
• Biosimilars in Japan
• CMC, product lifecycle
• International Cooperation
MHLW drew up a new strategy to lead the world in the practical application of innovative medical products in 2014.

**SAKIGAKE Designation System**

– To put innovative products into practice in Japan first in the world –

**Designation Criteria**
- Medical products for **diseases in dire need** of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

**Designation Advantage**

<table>
<thead>
<tr>
<th>1. Prioritized Consultation [Waiting time: 2 months → 1 month]</th>
<th>2. Substantialized Pre-application Consultation [de facto review before application]</th>
<th>3. Prioritized Review [12 months → 6 months]</th>
</tr>
</thead>
</table>

**Designation Procedure**

1. Initiation by applicant  
2. Initiation by the MHLW
General Timeframe of Forerunner Review Assignment

【Standard】
Pharmaceutical affairs consultation for R&D strategy
Non clinical studies, Clinical studies
Clinical trials I/II Consultation on Clinical trials phase III study

① Priority Consultations

【Forerunner】
Pharmaceutical affairs consultation for R&D strategy
Non clinical studies, Clinical studies
Clinical trials I/II Consultation on Clinical trials phase III study Prior review (rolling submission)

② Prior-review

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

③ Priority Review
④ Review Partner System

⑤ Strengthening Post-Marketing Safety

Practical application of Innovative medical products

Pharmaceuticals and Medical Devices Agency
# Assignment on 27 October 2015

<table>
<thead>
<tr>
<th>Product name</th>
<th>Expected indication</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>sirolimus</td>
<td>Vascular fibroma associated with <a href="#">tuberous sclerosis</a></td>
<td>Novel Pharma (JP)</td>
</tr>
<tr>
<td>NS-065 / NCNP-01</td>
<td><a href="#">Duchenne muscular dystrophy (DMD)</a></td>
<td>Nihon-Shinyaku (JP)</td>
</tr>
<tr>
<td>S-033188</td>
<td>Type A or B <a href="#">Influenza</a></td>
<td>Shionogi Pharmaceuticals (JP)</td>
</tr>
<tr>
<td>BCX7353</td>
<td>Management of angioedema attacks of <a href="#">hereditary angioedema (HAE)</a></td>
<td>Integrated Development Associates (JP)</td>
</tr>
<tr>
<td>ASP2215</td>
<td>First relapse or treatment-resistant <a href="#">FLT3 gene mutation-positive myeloid leukemia</a></td>
<td>Astellas Pharmaceuticals (JP)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Unresectable advanced or recurrent <a href="#">Gastric cancer</a></td>
<td>MSD (US)</td>
</tr>
</tbody>
</table>

* [tuberous sclerosis](#): This term refers to a genetic condition characterized by the formation of fibrous tissue and muscle growth.  
* [Duchenne muscular dystrophy (DMD)](#): A progressive muscle disorder that affects boys.  
* [Influenza](#): The flu, a highly contagious respiratory infection.  
* [hereditary angioedema (HAE)](#): A genetic disorder that causes inflammation and swelling.  
* [Gastric cancer](#): Cancer that begins in the lining or lining cells of the stomach.
Regenerative Medical Products in the PMD Act

Former Pharmaceutical Affairs Law (PAL)

PMD Act (Revised PAL)

◆ Additions for Regenerative Medical Products
  • Definition and independent chapter for Regenerative Medical Products
  • Introduction of conditional/time limited approval system
How to expedite R&D and review for cellular and tissue based product

- Designed for unmet needs under the present treatment: **limited number of patients** available for CT
- Difficult to conduct **controlled study** to demonstrate clinical benefit
- **Heterogeneity** of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug guidelines too much?
Expedited approval system under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, such as non-uniform quality reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]

- Clinical study
- Phased clinical trials (confirmation of efficacy and safety)
- Marketing authorization
- Marketing

[New scheme for regenerative medical products]

- Clinical study
- Clinical trials (likely to predict efficacy, confirming safety)
- Conditional/term-limited authorization
- Marketing (Further confirmation of efficacy and safety)
- Re-application within a period (max. 7 yrs)
- Marketing authorization or Revocation
- Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
Two of the new product approvals under the new regulation (Update)

- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD (normal approval)
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease (conditional and time-limited authorization – 5 years, conducting post-marketing efficacy studies)

Note: Figures quoted from the company press release docs
Quality concept of hCTPs

Bio-pharmaceuticals

*hCTPs*

- Source materials, process variability
- In-process control
- Characterization
- Specification

- Difficult to cover every aspect of quality by specification
- Limited information can be obtained from characterization and specification
- Much more rely on in-process control to control quality
Challenges of Accelerated Process in general

- **Clinical study in post-marketing**: RCT may be difficult for confirmation in some cases (single arm study with pre-agreed threshold or observational case / control study) in the postmarketing settings
  - monitoring, collection and use of real-world data, post-authorisation, as a complement to RCT data (like Adaptive pathway of EU)

- **Reimbursement**: Question on consistency with regulatory approval and on acceptance of clinical data for HTA payers

- **CMC and quality assurance**: limited qualification in early stage and quality control under GMP/GCTP (validation, scalability, comparability)
CMC Considerations for Accelerated Programs

- Residual Risk
- Control Strategy

Knowledge

Product Lifecycle

Approval

Approval

Standard program (QbD approach)

Post-Approval

Pharmaceuticals and Medical Devices Agency
Biosimilars in Japan
Regulatory History and Status of Biosimilars

- Application Category for biosimilars
- Guideline
- Nomenclature rules

Revision of Nomenclature rules


- Somatropin BS [Sandoz]
- Epoetin alfa BS [JCR]
- Filgrastim BS [F], [MOCHIDA]
- Filgrastim BS [NK], [TEVA]
- Filgrastim BS [Sandoz]
- Infliximab BS [NK], [CTH]
- Insulin glargine BS [Lilly]
Regulations for Biosimilars in Japan

- Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics (FOBs)*
  
  (PFSB/ELD Notification No. 0304007 / March 4, 2009)
  
  
  *: “Follow-on Biologics” in this guideline is a synonym for “Biosimilars”.

- Marketing Approval Application for FOBs
  
  (PFSB Notification 0304004 / March 4, 2009)

- Nonproprietary Name and Drug Name of FOBs
  
  (PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013)

- Questions & Answers regarding Guideline
  

- New supplement (Q&A) published on 15 December 2015
Data requirement of biosimilars in Japan

New biologics Application

- CMC
- Characterization, CQA, functional analysis
- Pre-clinical study
- Clinical study

Biosimilar Application

- Original manufacturing
- Biosimilarity / Comparability
- + original testing
- + Published information

Pharmaceuticals and Medical Devices Agency
Consultation for Biosimilars

<table>
<thead>
<tr>
<th>Fiscal year (from April 1 to March 31)</th>
<th>No. of consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
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<tr>
<td>2008</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
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<tr>
<td>2010</td>
<td>5</td>
</tr>
<tr>
<td>2011</td>
<td>10</td>
</tr>
<tr>
<td>2012</td>
<td>15</td>
</tr>
<tr>
<td>2013</td>
<td>20</td>
</tr>
<tr>
<td>2014</td>
<td>25</td>
</tr>
<tr>
<td>2015</td>
<td>10</td>
</tr>
</tbody>
</table>

Based on date of application
As of October 26, 2015

<table>
<thead>
<tr>
<th>Product type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td>2</td>
</tr>
<tr>
<td>ESAs</td>
<td>6</td>
</tr>
<tr>
<td>Insulins (incl. analogues)</td>
<td>5</td>
</tr>
<tr>
<td>mAbs &amp; fusion proteins</td>
<td>35</td>
</tr>
<tr>
<td>G-CSFs</td>
<td>4</td>
</tr>
<tr>
<td>FSHs</td>
<td>2</td>
</tr>
<tr>
<td>Enzymes</td>
<td>1</td>
</tr>
</tbody>
</table>
Topics for Biosimilar Development

- Comparative assessment of quality attributes
  - Reference product
  - How similar is similar.
  - Statistical approach is mandatory?

- Design of comparative efficacy studies
  - Population
  - 95%CI vs. 90%CI
  - Risk ratio vs. Risk difference

- Etc.
Overview of Q&As (December 2015)

- 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
  - Report procedure
Can a sponsor use non-Japan sourced reference product in comparability exercise?

- If a sponsor needs to use non Japan-sourced RP in comparability exercise, it is required to explain that the non-Japan sourced RP is the representative of the Japan sourced RP by analytical assays and publicly available information.
Is toxicity study (repeat-dose toxicity study) required for biosimilar development?

• Basically, a sponsor 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.

• These approach should be on a case-by-case basis. PMDA recommends to use our consultations
### Examples of Clinical Data package

<table>
<thead>
<tr>
<th></th>
<th>Infliximab BS I.V. infusion 100mg [NK] / [CTH]</th>
<th>Insulin glargine BS Injection [Lilly] etc.</th>
</tr>
</thead>
</table>
| **PK equivalence** | Clinical Pharmacology Study (Japanese)  
  • RA patients (104) | Foreign Clinical Pharmacology Study  
  • Healthy volunteers (80)  
  • PD marker: glucose infusion rate |
| **PD equivalence** | Foreign Phase III Study  
  • RA patients (602)  
  • Endpoint: ACR20% improvement (30w.) | Multi-regional CT (incl. 100 Japanese)  
  (for reference)  
  • Type 1 DM patients (535)  
  • Endpoint: HbA1c |
**Biosimilar Naming Rule**

Japanese Accepted Name (JAN)

```plaintext
### (genetical recombination) [XXX Biosimilar 1 (2, 3, ⋯)]
```

- JAN given in accordance with *PFSB Notification No.0331001/March 31 2006*.
- Non-glycosylated protein can use the same JAN as the RP.

Examples:
- Epoetin Kappa (genetical recombination) [Epoetin Alfa Biosimilar 1]
- Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]
- Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]
- Filgrastim (genetical recombination) [Filgrastim Biosimilar 3]
**Example of Indication extrapolation** *(Infliximab)*

- **Infliximab BS**

<table>
<thead>
<tr>
<th>Indications</th>
<th>R.P.</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis (incl. prevention of structural joint damage)</td>
<td>✓</td>
<td>Original ✓</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>✓</td>
<td>Original ✓</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>✓</td>
<td>Original ✓</td>
</tr>
<tr>
<td>Intractable uveoretinitis in Behcet's disease</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Psoriasis vulgaris, Arthropathic psoriasis, Pustular psoriasis, Psoriatic erythroderma</td>
<td>✓</td>
<td>Additional ✓</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

R.P.: Reference product

Comparative study
Overall picture of CMC activities through the product life cycle

- Product Quality Review
- Commercial Production
- Process Validation
- Knowledge Improvement
- Post-approval change
- Technical Transfer
- Development
- Process Research
- Report of Research and Development

Cycle that connects development and commercial production
## (Example) Post-Approval Change Reporting Categories

<table>
<thead>
<tr>
<th>Risk of Changes</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>Partial Change Application</td>
<td>Prior approval supplement (PAS)</td>
<td>Type II variation</td>
</tr>
<tr>
<td></td>
<td>(Approval needed before</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>implementing change)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Minor change Notification</td>
<td>Changes Being Effected (CBE), 30 days</td>
<td>Type IB variation</td>
</tr>
<tr>
<td></td>
<td>(within 30 days after</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>implementation/shipping)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td></td>
<td>Changes Being Effected (CBE)</td>
<td>Type IA\textsubscript{IN} variation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual Report</td>
<td>Type IA variation</td>
</tr>
</tbody>
</table>
Japan’s Science-based Effective/Efficient/Flexible Quality Regulation

Module 1(AF) - Legally binding
Approved matters or established conditions

Module 2 (QOS)

Module 3

Not-Changeable without regulatory procedures (PCA/MCN*)

Changeable without regulatory procedures (PCA/MCN*)

*; PCA: Partial Change Application (for major changes)
MCN: Minor Change Notification (for minor changes)
ICH Q12 has started its journey.

It may contain regulatory challenges (e.g. “Established Conditions”, PACMP).

However, by overcoming these challenges, ICH Q12 will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product.
Sharing of Information, Experience and Knowledge is Valuable!!
Proactively contribute to the international regulatory harmonization and cooperation by disseminating Japan’s knowledge on regulations (regulatory science) to the world.

⇒ Aim to resolve the global drug/device lag and contribute to global health
⇒ Revitalize the pharmaceutical and medical device industries

International Regulatory Harmonization Strategy setting out the mid–long term vision and priority of its measures
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
Work-sharing for efficiency (Strategy 2, 3)
MOU between the Chinese SFDA (present CFDA) and the Japanese MHLW, under which PMDA supports cooperative activities

** MOU concluded between Interchange Association and East Asia Relations Commission, but is being implemented through cooperation of related organizations.
Life Sciences Innovation Forum

Report to Committee on Trade and Investment
The APEC Regulatory Harmonization Steering Committee (RHSC) is established under the authority of the Life Science Innovation Forum (LSIF) to promote a strategic and coordinated approach to regulatory convergence and capacity building efforts within the APEC region.

RHSC Member Economy:
Canada, China, Chinese Taipei, Indonesia, Japan, Korea, Malaysia, Mexico, Peru, Philippines, Russia, Singapore, Thailand, U.S.
RHSC’s Goal

The goal of the RHSC is *to promote a more strategic, effective and sustainable approach to “regulatory convergence” within the APEC region.* The RHSC will facilitate the identification, design and implementation of projects that best meet the needs of Member Economies and the APEC region, and will work towards the adoption and implementation of harmonized international guidances and regulatory best practices for medical life sciences products. This will in turn support and promote greater regulatory cooperation in the region, including the exchange of information and the potential leveraging of resources.
APEC LSIF-RHSC

- Pharmaco-vigilance: Champion: Korea
- Combination Products: Champion: Taiwan
- Global Supply Chain Integrity: Champion: United States
- Biotherapeutics: Champion: Korea
- Cell and Tissue Based Therapeutic Products: Champion: Singapore
- Good Review Practice/Good Submission Practice: Champion: Taiwan and Japan
- Multi-Regional Clinical Trials/Good Clinical Practice Inspection: Champion: Japan and Thailand
Thank You for your attention!

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Thanks to my colleagues of Office of Cellular and Tissue-based Products