Regulatory Update from MHLW/PMDA

Seiichi Inoue
Executive Director
Pharmaceuticals and Medical Devices Agency

5th Joint Conference of Taiwan and Japan on Medical Products Regulation
1 December, 2017
Today’s Agenda

1. Organizational Updates

2. Update of Recent Topics

3. Future Challenge

4. International Activities
   PMDA Asia Training Center
1. Organizational Updates
Regulatory Authorities in JAPAN

**MHLW**
- Final Authorization of applications
- Publishing Guidelines
- Advisory committee
- Supervising PMDA Activities

**PMDA**
- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials etc.
Major Services of PMDA

- Relief services for adverse drug reactions and for infections acquired through biological products
- Regulatory review of drugs, medical devices and regenerative medical products
- GLP/GCP/GPSP compliance assessments
- GMP/QMS/GCTP inspections

- Acceptance and web-based publication of submitted labeling information (package inserts)
- Collection and organization of safety information from authorization holders or medical institutions
2. Update of Recent Topics

Accelerated review systems
## Summary of the Accelerated review system

<table>
<thead>
<tr>
<th>Type</th>
<th>Area</th>
<th>Designation requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expedited review</td>
<td></td>
<td>Designation is not needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needed to expedite the review</td>
</tr>
<tr>
<td>Priority review</td>
<td>Any product categories</td>
<td>Designation is needed</td>
</tr>
<tr>
<td>SAKIGAKE (Forerunner designation)</td>
<td></td>
<td>1. Orphan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Apparent improvement of medical care and for severe diseases</td>
</tr>
<tr>
<td>Conditional Early Approval</td>
<td>Drugs</td>
<td>Designation is not needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.</td>
</tr>
<tr>
<td>Conditional and Time-limited Authorization</td>
<td>Medical Devices</td>
<td>Designation is not needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MDs in high clinical needs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Balancing the pre- and post-market requirements</td>
</tr>
<tr>
<td></td>
<td>Regenerative Medical Products</td>
<td>Designation is not needed</td>
</tr>
</tbody>
</table>
SAKIGAKE - General Timeframe

Ordinary Review

- Non-clinical
- Phase I/II
- Phase III
- Review
- Consultation

SAKIGAKE

- Designation
- Prior Review
- Review

3rd round pilot: Oct. 5 ~ Nov. 22, 2017

Designated in 1st round pilot (2016)
- 6 Pharmaceuticals
- 2 Medical Devices
- 3 Regenerative Products

Designated in 2nd round pilot (2017)
- 5 Pharmaceuticals
- 3 Medical Devices
- 3 Regenerative Products
- 1 In vitro Diagnostics
Facilitate development of medical products by academia by developing more reliable ROADMAP.

Contribute to promotion of clinical trials led by academia.

* In collaboration with the Japan Agency for Medical Research and Development (AMED), PMDA will proactively support establishment of an exit strategy via Pharmaceutical Affairs Consultation on R&D Strategy.
SAKIGAKE and Pharmaceutical Affairs Consultation on R&D Strategy (Concept)

Pharmaceutical Affairs Consultation on R&D Strategy

Preliminary Review & Evaluation
1. Innovative medical products
2. For serious diseases
3. Development & NDA in Japan being world’s first or simultaneous with other countries
4. Prominent effectiveness expected on non-clinical and early phase clinical studies

SAKIGAKE process with priorities

SAKIGAKE Designated Products

Products with Ordinary Review

Seeds
# SAKIGAKE vs Breakthrough therapy (US) vs PRIority MEdicines (EU)

<table>
<thead>
<tr>
<th>Establishment</th>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>April 2015 (trial)</td>
<td>July 2012</td>
<td>March 2016</td>
</tr>
</tbody>
</table>

## Designation Criteria

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
</table>
| • New mode of action  
• Life threatening or no radical treatment  
• Prominent efficacy  
• First NDA in the world | • Serious condition  
• Substantial improvement on clinically significant endpoint(s) | • Unmet medical need  
• Potential to address to unmet medical need |

## Project Manager

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
</table>
| • Review partner (Concierge) | • Senior manager  
• Cross-disciplinary project lead | • Dedicated contact point  
• Appointment of rapporteur |

## Consultation

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
</table>
| • Priority consultation | • Intensive guidance on an efficient drug development program | • kick-off meeting about the overall development plan and regulatory strategy  
• Scientific advice at key development milestones |

## Rolling review

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Eligible (SAKIGAKE comprehensive assessment Consultation)</td>
<td>• Eligible</td>
<td>—</td>
</tr>
</tbody>
</table>

## Priority review

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Review within 6 months (shorter than 9 months in ordinal priority review)</td>
<td>• Not automatically designated</td>
<td>• Eligible (Accelerated assessment)</td>
</tr>
</tbody>
</table>

## Other

<table>
<thead>
<tr>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relation with drug pricing</td>
<td></td>
<td></td>
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</tbody>
</table>
“Conditional Early Approval System” is a system to put highly useful and effective drugs for treating serious diseases into practical use as early as possible.

[Candidate product] - Drugs that treat serious diseases for which there are limited treatment options and,
- Drugs that it is difficult to conduct clinical trials or it takes long period because the number of patients is small

[Requirement] MHLW/PMDA needs to
- Confirm a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials at the time of submission
- Clarify management of conditions for approval such as imposing to conduct research which is necessary for reconfirmation of post-marketing efficacy and safety

Standard regulatory review process

Conditional Early Approval System

- Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.
- Shorten overall review times for priority review products

Setting conditions for approval (e.g.)
- Reconfirmation of post-marketing efficacy and safety (including using real-world data)
- Setting requirements such as facility requirements if needed for proper use

ADR reports Post-marketing surveillance
Conditional Early Approval System for Drugs

Drugs eligible for the system should meet the all requirements from 1 to 4 listed below

1. Seriousness of indications
   - Diseases which have significant impact on lives (life-threatening diseases) or
   - Progress of disease is irreversible and the disease has a significant impact on daily lives
   - Others

2. Medical usefulness
   - No existing remedies, preventive therapies or diagnostics or,
   - Medical usefulness is better than that of existing remedies, preventive therapies or diagnostics in terms of efficacy, safety, and patient’s physical and mental burden

3. Being difficult to conduct confirmatory clinical trials or considered to take considerable time to complete trials because of a limited number of patients

4. Considered to have of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials

* “Handling of priority review and others” (Notification 0122 No.12 issued by the Director of Pharmaceutical Safety and Environmental Health Bureau, Notification 0122 No.2 issued by the Director of Medical Device Evaluation Division, January 22, 2016)
Accelerate approval of MDs in high clinical needs by balancing the pre- and post-market requirements, based on the lifecycle management of the MDs.

- Implementation of **Post-market Risk Management Measures**
- Data collection to confirm use results, long-term performance

**Conditional Early Approval for Innovative MDs**

- **Planning Post-market Risk Management Plan (draft)**

**Present**

- Long period

**Collection of clinical data**

**Review**

**Approval**

**Market - Use**

**Cooperation with academia**

**Partial change application (e.g. expanded indication, etc.)**
Conditional and Time-limited Authorization of Regenerative Medical Products

Conventional Regulatory Approval Process

Clinical research → Clinical trial (Confirmation of efficacy and safety) → Approval → Marketing

Regulatory System that Facilitate Early Patient Access

Clinical research → Clinical trial (likely to predict efficacy, confirmation of safety) → Conditional and time-limited authorization → Marketing further confirmation of efficacy and safety → Marketing Authorization or Revocation of the conditional approval → Continued marketing

Re-Application (or Expiration) within max. 7yrs
Pharmaceutical Affairs Consultation on R&D Strategy on Regenerative Medical Products

Breakdown of Consultations on Regenerative Medical Medical Products

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs</th>
<th>Regenerative Medicine</th>
<th>Medical Device</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2011</td>
<td>6</td>
<td>20</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>2012</td>
<td>5</td>
<td>28</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>2013</td>
<td>13</td>
<td>32</td>
<td>48</td>
<td>93</td>
</tr>
<tr>
<td>2014</td>
<td>46</td>
<td>66</td>
<td>58</td>
<td>170</td>
</tr>
<tr>
<td>2015</td>
<td>66</td>
<td>66</td>
<td>16</td>
<td>148</td>
</tr>
</tbody>
</table>

FY2012 Breakdown:
- Cell Therapy (Auto): 36%
- Cell Therapy (Allo): 55%
- Gene Therapy: 9%
- Raw Materials: 0%

FY2016 Breakdown:
- Cell Therapy (Auto): 35%
- Cell Therapy (Allo): 48%
- Gene Therapy: 13%
- Raw Materials: 4%
-IND Submission of Regenerative Medical Products-
(Clinical Trial Notification)

• Timing

The first notifications; **31 days before** (others; **2 weeks before**)

### IND Submissions by study type

<table>
<thead>
<tr>
<th>Study type</th>
<th>Cell therapy</th>
<th>Gene therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>Investigator</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Total IND</td>
<td>46</td>
<td>15</td>
</tr>
</tbody>
</table>

### IND Submissions by product type

<table>
<thead>
<tr>
<th>Product Type</th>
<th>FY2011</th>
<th>FY2012</th>
<th>FY2013</th>
<th>FY2014</th>
<th>FY2015</th>
<th>FY2016</th>
<th>PMD Act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Therapy</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Gene Therapy</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

(As of April 2017)
Points to Considers for the Evaluation of Regenerative Medical Products

- Cultured human autologous epidermal cell sheet for epidermolysis bullosa (draft)
- Cultured cartilage and products derived from somatic stem cells for articular cartilage repair (2016)
- Products derived from allogeneic iPS cells for articular cartilage repair (2016)
- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic iPS cells-derived retinal pigment epithelial cells (2014)
- Autologous iPS cells-derived retinal pigment epithelial cells (2013)
- Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010)
- Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)
2. Update of Recent Topics

Update on Medical Device
Single-use Medical Device (SUD) Reprocessing

- Japan has introduced SUD Reprocessing from July 2017

- Reprocessors need MAH
- Reprocessed SUD needs Approval as R-SUD
- Reprocessors take responsibility for R-SUD’s safety issue

Diagram:
- Scheme for SUD reprocessing
- Standard for Manufacturing and Quality control
- Regular inspection by PMDA (once a year)
- Manufacturer
- Manage
- disassembled
- Cleaning
- Reassemble, repair
- Disinfection
- CHECK
- Secure Traceability

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Facilitate Development of International Standard for Evaluation method for Innovative MDs

To Enable early introduction of innovative MDs all over the world
I. Facilitate development of evaluation method (Practical, non-clinical, properly predict effectiveness and safety)
II. Facilitate development of such evaluation method into International Standard

Research
- Support research (Grant)
- Research Evaluation methods
- Propose Standard

Establish Evaluation methods
- MHLW
- Committee
  - Regulatory, Academia, Industry
    - Select project
    - Evaluate project
    - Support proposal of Standard

Develop Standard
- International Conference
- ISO, IEC, etc.
- Support to selection of projects
- Support Proposal of Standard

MHLW
PMDA
3. Future Challenge
Towards “Regulatory Science Center”
Review/Consultation/Safety for the Next-Level Science

BIG DATA

NDA Data
(indiv. clin. data, etc.)

Medical Records
(MID-NET, etc.)

- Sophisticated NDA review and Consultation
- Cross-Products Analysis
- Risk Evaluation with Pharmaco-epidemiological data
- Utilization of Real World Data to pre/post market evaluation

Expected establishment:
From April, 2018
MID-NET® Project

The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients).

An integrated real-time EMRs database with high quality
Clinical Innovation Network (CIN)
Promotion of Regulatory Science

Science Board

Collaboration with academia

Universities
Research Institutes
Medical institutions

Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies.
Outcome of the Science Board

1st term (FY2012 - 2013)

- Summary of discussion on the assessment of the current status of personalized medicine related to development and regulatory review (2014)
- Summary of discussion on non-clinical pharmacological studies on anticancer drugs (2013)
- Current perspective on evaluation of tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells (iPSCs) and iPSCs as their starting materials (2013)

2nd term (FY2014 - 2015)

- Discussion on Evaluation of Medical Devices in Pediatric Use (2015)
- Report on the use of non-clinical studies in the regulatory evaluation of oncology drugs (2016)
- Current Status and Perspectives of Placebo-Controlled Studies (2016)
1. Clinical evaluation of rare cancer
   - Discuss current situation of clinical evaluation and possible evaluation methods of
disease areas in which efficacy of drug by comparative studies is difficult, such as in
rare cancers, due to the number of patients is specifically limited among rare diseases
(no more than 50,000 patients).

2. Facilitating R&D of Academia-originated Pharmaceuticals
   - Sort out problems of bottleneck of drug discovery in academia, and discuss their solutions

3. Artificial Intelligence and its application in medical field
   - Discuss “totally new elements of AI” by overviewing new technologies using AI and facilitate them into future medical device review and consultations.

Outcome documents will be published by March, 2018

PMDA Website (English)
http://www.pmda.go.jp/english/rs-sb-std/sb/outcome-docs/0001.html
4. International Activities
PMDA International Strategic Plan 2015

The primary responsibility of the Ministry of Health, Labour and Welfare (MHLW) is to promote a positive regulatory environment that supports access to safe, effective and innovative medical products, including pharmaceuticals, medical devices, and related health technologies, in Japan and abroad. To achieve this goal, the Ministry has established the Strategic Plan to Support the Innovation Policies of MHLW and MOHM, which is based on the Integrated Strategic Plan 2011-2015 (JSPP) of the National Institute of Health and Nutrition (NIH). The Strategic Plan aims to achieve the following objectives:

1. To enhance the regulatory system and promote the innovation of medical products.
2. To improve the quality of life for patients by improving the effectiveness and efficiency of the regulatory system.
3. To strengthen the international cooperation in the field of medical products.

The Strategic Plan includes the following key areas:

- Strengthening the regulatory system
- Improving the quality of life for patients
- Enhancing international cooperation

The Strategic Plan will be reviewed and updated regularly to ensure its effectiveness and relevance.
Bilateral collaboration

Confidentiality Arrangement signed
Joint symposium held
Cooperative Arrangement signed
Cooperative Arrangement on cooperation of pharmacopoeia signed

1: Cooperative Arrangement has been signed between the Interchange Association of Japan and East Asia Relations of Taiwan

MRA: Japan-EC MRA (GLP, GMP)
Scope of GMP is under consideration to expansion.
Plan, design and coordinate training for Asian regulatory authority staff

- Provide **training opportunities** including **on-site training**

- Help raise the level of Regulations in Asia and the world.
- In FY2016, 161 regulators from 27 countries/regions participated.

**Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (Est. April 2016)**

Training seminar seminars to Regulatory Authority members by PMDA

- Lectures, case studies, and on-site training
- Establishing a centralized training center for multi-regional clinical trials

Outside Japan

PMDA Office

APEC regions
## PMDA - ATC Planned Trainings: FY2017

<table>
<thead>
<tr>
<th>No.</th>
<th>Contents</th>
<th>Date</th>
<th>Location</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Risk Management Plan (RMP)</td>
<td>May 18-19, 2017</td>
<td>Jakarta</td>
<td>30 participants from Indonesia</td>
</tr>
<tr>
<td>2</td>
<td>Pharmaceuticals Review</td>
<td>June 26-30, 2017</td>
<td>Tokyo (PMDA)</td>
<td>28 participants from 11 countries</td>
</tr>
<tr>
<td>3</td>
<td>Good Manufacturing Practice (GMP)</td>
<td>July 31- Aug. 4, 2017</td>
<td>Yamaguchi City</td>
<td>13 participants from 13 countries</td>
</tr>
<tr>
<td>4</td>
<td>Anti-infective Drugs</td>
<td>Oct. 3-4, 2017</td>
<td>Hanoi</td>
<td>30 participants from Vietnam</td>
</tr>
<tr>
<td>5</td>
<td>Medical Devices</td>
<td>Nov. 6 - 10, 2017</td>
<td>Tokyo (PMDA)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Good Registration Management (GRM)</td>
<td>Oct. 31- Nov. 2, 2017</td>
<td>Taipei</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pharmaceuticals Review</td>
<td>Dec. 12-15, 2017</td>
<td>Bangkok</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Multi-Regional Clinical Trial (MRCT)</td>
<td>Jan. 15-18, 2018</td>
<td>Tokyo (PMDA)</td>
<td></td>
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<tr>
<td>9</td>
<td>Pharmacovigilance</td>
<td>Feb. 5-8, 2018</td>
<td>Tokyo (PMDA)</td>
<td></td>
</tr>
</tbody>
</table>
Thank you!

多謝