Regulatory Updates
– Facilitating Early Patient Access –

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<th>Name of Commercial Interest</th>
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<tr>
<td>☐ Grants/Research Funding</td>
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<td>☐ Stock Shareholder</td>
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<td>☐ Consulting Fees</td>
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<td>☐ Employee</td>
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<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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Today’s topics

- Pharmaceutical Regulation in Japan
- Review of PMD Act
Today’s topics

▶ Pharmaceutical Regulation in Japan

▶ Review of PMD Act
Pharmaceutical Regulation in Japan

- **PAL**: Pharmaceutical Affairs Law
- **PMD Act**: Pharmaceutical and Medical Device Act

**2013**
- PMD Act

**2015**
- SAKIGAKE-designation system

**2017**
- Conditional Early Approval System

**2018~**
- Review of PMD Act

**2011**
- Regulatory Science Consultation
  (Former Pharmaceutical Affairs Consultation)

**2014**
- Conditional and Time-limited Authorization of Regenerative Medical Products

PAL: Pharmaceutical Affairs Law
PMD Act: Pharmaceutical and Medical Device Act
Regulatory Science Consultation on R&D Strategy

- 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 Regulatory Science Consultation on R&D Strategy.*
Conditional and Time-limited Authorization of Regenerative Medical Products

Conventional Regulatory Approval Process

Clinical research

Clinical trial
(Confirmation of efficacy and safety)

Approval

Marketing

Clinical research

Clinical trial
(likely to predict efficacy, confirmation of safety)

Conditional and time-limited authorization

Marketing

Authorization or Revocation of the conditional approval

Continued marketing

Re-Application (or Expiration) within max. 7yrs

Regulatory System that Facilitate Early Patient Access
Established the “SAKIGAKE-designation system” to apply innovative drugs/medical devices/regenerative medicines in practical use in Japan sooner than other countries, aiming at early practical application with various supports (granting approval in 6 months, i.e., half the usual time).

**Designating criteria**

1. Breakthrough treatment/diagnostic method: novel medical device in principle
2. Firstly developed and planed to submit application for approval in Japan (concurrent submission allowed)
3. Expected significant efficacy for a target disease, such as much improvement from existing treatment considering non-clinical data (mechanism of action, etc.) and early phase clinical data.

**Details of designation system**

1. Priority consultation
   - 2 months → 1 month
   - Communicating with consulters swiftly to shorten the time from submission to a clinical trial consultation

2. Enhanced pre-consultation
   - Substantive accelerated review
   - Enhanced pre-consultation meeting allowing English materials

3. Priority review
   - 12 months → 6 months
   - The goal of total review period is 6 months * Submission of the Phase 3 study results after the application may be permitted to shorten the time from development to granting approval

4. Review partner
   - PMDA concierge
   - Offering a concierge who supervises a necessary process including review, safety measure, quality management and quality assurance

5. Enhanced post-marketing safety measure
   - Prolongation of reexamination period
   - Improving post-marketing safety measure including expanding reexamination period, transmission of information overseas and collaboration with academic societies
## SAKIGAKE v.s. Breakthrough therapy (US) v.s. PRIority Medicines (EU)

<table>
<thead>
<tr>
<th></th>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
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</thead>
<tbody>
<tr>
<td>Establishment</td>
<td>April 2015</td>
<td>July 2012</td>
<td>March 2016</td>
</tr>
<tr>
<td>Designation Criteria</td>
<td>• New mode of action</td>
<td>• Serious condition</td>
<td>• Unmet medical need</td>
</tr>
<tr>
<td></td>
<td>• Life threatening or no radical treatment</td>
<td>• Substantial improvement on clinically significant endpoint(s)</td>
<td>• Potential to address to unmet medical need</td>
</tr>
<tr>
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<td>• Prominent efficacy</td>
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<tr>
<td></td>
<td>• First NDA in the world</td>
<td></td>
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<tr>
<td>Project Manager</td>
<td>• Review partner (Concierge)</td>
<td>• Senior manager</td>
<td>• Dedicated contact point</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cross-disciplinary project lead</td>
<td>• Appointment of rapporteur</td>
</tr>
<tr>
<td>Consultation</td>
<td>• Priority consultation</td>
<td>• Intensive guidance on an efficient drug development program</td>
<td>• kick-off meeting about the overall development plan and regulatory strategy</td>
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<tr>
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<td></td>
<td></td>
<td>• Scientific advice at key development milestones</td>
</tr>
<tr>
<td>Rolling review</td>
<td>• Eligible (SAKIGAKE comprehensive assessment Consultation)</td>
<td>• Eligible</td>
<td>—</td>
</tr>
<tr>
<td>Priority review</td>
<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>
<tr>
<td>Other</td>
<td>• Relation with drug pricing</td>
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The purpose of the Conditional Early Approval System for Pharmaceutical Products is to facilitate faster patient access to drugs offering high clinical utility with respect to severe diseases. Eligible drugs are those indicated for severe diseases with few effective treatments, for which confirmatory clinical trial execution is time-consuming or impracticable due reasons such as a small subject population. By requiring applicants to conduct post-marketing surveys as a condition for approval, this system enables swifter approvals of products demonstrating the necessary levels of efficacy and safety based on nonconfirmatory clinical study results. Conditionally approved product efficacy and safety will be re-examined through post-marketing vigilance activities.

Usual application review

Conditional early approval system

Examples of conditions for approval:
- Re-confirming product efficacy/safety during the post-marketing phase (Use of Real-World Data permitted)
- Establishing policies to ensure optimal product use by medical institutions, as necessary

Exploratory clinical studies*1, etc.

Confirmatory clinical studies*2

Application Submission and Review

Approval

Adverse drug reaction reporting
Post-marketing surveillance

ADR reports
Post-marketing surveillance

Usual face to face consultation

Eligibility for approval systems and consultation on data packages

Preparing a report on eligibility for Conditional Early Approval System (to promote designation process after application) Starting an evaluation for post-marketing investigations

*1 Small-scale, dose-finding clinical studies investigating drug efficacy and safety
*2 Large-scale clinical studies investigating the efficacy and safety of an established dosing regimen

Started in Nov. 1, 2017
Conditional Early Approval System for Medical Devices

Accelerate approval of MDs in high clinical needs by balancing the pre- and post-market requirements, based on the lifecycle management of the MDs.

- Present

Collection of clinical data → Review → Approval → Market - Use

Conditional Early Approval for Innovative MDs

Collection of clinical data

Cooperation with academia

Planning Post-market Risk Management

- Post-market Risk Management Plan (draft)

Implementation of Post-market Risk Management Measures

- Data collection to confirm use results, long-term performance

Partial change application (e.g., expanded indication, etc.)
STR01-The first *Sakigake*-designated Regenerative Medicine was approved in December 28, 2018

- STR01 (Autologous bone marrow-derived mesenchymal stem) is the first *Sakigake*-designated Regenerative Medicine which earned “Conditional and Time-limited Approval” on December 28, 2018. (Developed by NIPRO Medical Co., Ltd.)

- This is the *Regenerative Medicine for spinal cord injury* by intravenous infusion of autologous mesenchymal stem cells derived from patients’ bone marrow.
New active substance (NAS) median approval time for six regulatory authorities in 2008-2017 (Pharmaceuticals)

Centre for Innovation in Regulatory Science (CIRS), 2018, R&D Briefing 67
Today’s topics

- Pharmaceutical Regulation in Japan
- Review of PMD Act
Review of PMD Act

Background
Pharmaceuticals and Medical Devices Act (PMD Act)*: the regulation of medical products in Japan
- Mandatory review of the Act after the 5-years implementation (PMD Act was implemented in 2013)
- The review examines the results of the previous revision, trend of demography, innovation and future vision.
- Expert Committee in the Health Sciences Council started review discussion from April, 2018.
- The committee formulated the review report in December, 2018.

Main Theme
Three themes were discussed:
1. Ensuring early access to innovative pharmaceuticals & medical devices, and enhancing the safety measures
2. The role of community pharmacies and pharmacists, and the secure access to medicines
3. Enhancing the systems to ensure proper manufacturing, distribution and sales of pharmaceuticals & medical devices

* The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices
Theme 1: Ensuring early access to innovative pharmaceuticals & medical devices, and enhancing the safety measures

**Directions for Law Amendment**

The Committee concluded the following directions for law amendment:

1. **Streamline of Approval Process** for early patient access
2. Introduction of internationally harmonized **Quality Management System**
3. Strengthen **Safety Measures**
Review of PMD Act

(1) Streamline of Approval Process for early patient access
   ① “Conditional Early Approval System” and “SAKIGAKE Review Designation” should be legislated to clarify process and raise transparency.
   ② New Approval system for Medical Devices to reflect the characteristics of medical devices (considering innovative technologies; Big Data, AI etc.,)
   ③ Clarification of clinical trials process and ensuring safety of subjects

(2) Introduction of new Quality Management System
   ① Introduction of GMP and GCTP inspection per manufactory
   ② Revision of current QMS inspection
   ③ Introduction of Change Management Method for approved products concerning Quality using PACMP

(3) Strengthen Safety Measures
   ① Provide electronic information of Package Inserts
   ② Increase traceability of pharmaceuticals and medical devices
   ③ Utilize Patient Registry Data For safety measure