Regulatory Trends
Regenerative Medicine in Japan

Ken Sakushima, MD, MPH, PhD.
Medical Reviewer,
Advanced Review with Electronic Data Promotion Group, PMDA, Japan

DISCLAIMER:
The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA.
1. New Regulatory Framework for Regenerative Medicine

- The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)
- The Act on the Safety of Regenerative Medicine

2. Examples of Product Review under the new regulation (PMD Act.)

3. SAKIGAKE Designation System
Outline

1. New Regulatory Framework for Regenerative Medicine
   - The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)
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3. SAKIGAKE Designation System
New Legislative Framework

Revision of the Pharmaceutical Affaires Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)

The Act on the Safety of Regenerative Medicine

Promulgated in Nov. 2013 by the Japanese Diet (Parliament) in line with the Regenerative Medicine Promotion Law.

Enacted on 25 Nov. 2014

Other related governmental policy:
- Healthcare and Medical Strategy Promotion Act (2014.5)
- Japan Medical Research Development Institution Act (2014.5)
Two Acts Regulating Regenerative Medical Technology & Product

All medical technologies using processed cells which safety and efficacy have not yet been established

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on the Safety of Regenerative Medicine

Medical Care or Academic Research Purpose

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

Commercial Product Marketing Authorization Purpose
Regenerative Medicine in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Under the new legislation, as of 31 January 2017:
109 new clinical research plans
3,434 medical care plans
have been notified to MHLW

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Regenerative Medical Products

4 products approved

54 clinical trial plans
(including 13 gene therapy products)
(~ Feb 2017)

Covered by MHLW

Covered by MHLW/PMDA
Overview of the Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit plans

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain license

Notification (Hospitals / Clinics) or Application for a license (Firms)

Cell Processors

Certified committee for regenerative medicine
Expedited Approval System under PMD Act

[Traditional approval process]

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

< 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

[New scheme] (for regenerative medical products)

Clinical study → Clinical trials (likely to predict efficacy, confirming safety) → Conditional/time-limited authorization → Marketing (Further confirmation of efficacy and safety) → Marketing or Revocation → Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
Evolving Early Access Schemes of ICH Regions

Each agency has similar approaches to accommodate patient access demand.

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Evidence Level of Efficacy: Drug (normal) vs. HCT/P

If there is no effective treatment available for the target population of the disease.
Review Pathway of Regenerative Medical Products

Application and review flow of regenerative medical product under the PMD Act

1. Sponsor
   - Marketing authorization application

2. PMDA
   - Review
     - Conditional/time-limited authorization path
     - Normal authorization path

3. MHLW
   - Advisory Committee (Pharmaceutical & Food Sanitation Council)
     - Marketing authorization (conditional time-limited)
     - Marketing authorization (normal)

4. PMDA and Prefecture
   - Business licenses applications (if use new facilities)

If the application meets the criteria (biological heterogeneity, etc.)
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Examples of Product Review under the new regulation (PMD Act.)

• 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. TEMCELL
   Allogeneic bone marrow mesenchymal stem cells (MSCs) for graft versus host disease (GVHD)

2. HeartSheet
   Autologous skeletal myoblast-derived cell sheet for serious heart failure due to ischemic heart disease

Review time less than 12 months
TEMCELL Clinical Studies

- **Japan**
  - JR-031-201/202 study (Phase I/II)
    Single arm clinical trial, 14 subjects. *Grade II-IV.*
  - JR-031-301 study (Phase II/III)
    Single arm clinical trial, 25 subjects. *Grade III-IV.*

- **Foreign (Prochymal®)**
  - 280 study
    Placebo-controlled RCT, 216 adults and 28 pediatric subjects. *Grade B-D.*
  - 275 study
    Single arm clinical trial, 75 pediatric subjects.
Evidence Level of Efficacy: TEMCELL

Drug (normal)

PMD Act.
(Regenerative medical products)

JRX-031-301
Conformatory study

JRX-031-201/202
Exploratory study

Foreign studies

Normal approval
HeartSheet

Process to Sheet Transplantation

Kit A
- Container for tissues harvested
- Kits for Serum separation

At Manufacturer
- Cell culture

Kit B
- Product Main Component
- Frozen myoblast cells
- Product Subcomponent
- Kits for sheet preparation And Media

In the CPF at Hospitals
- Produce cell sheets

Sheet transplantation

Myoblast Sheet

Image of a heart after sheet transplantation

Harvest muscle tissues

Biopsy from Quadriceps

Cell culture at Terumo’s facility

Modified from
file:///C:/Users/Nori/Documents/ATMP%20Cluster/20160421/Terumo%2020141031.pdf
http://www.terumo.com/about/pressrelease/2015/20150902.html
HeartSheet; Clinical Study

- Japan;
  - M-51073-21 study
    Single arm clinical trial, 7 subjects.

- Foreign; None

- Endpoint
  - Pre-specified
    LVEF (RI, CT, Echo)
  - Post-hoc
    Comprehensive clinical evaluation
    Survival (External control comparison)
Evidence Level of Efficacy: HeartSheet

Drug (normal) approval

PMD Act.
(Regenerative medical products)

Post-marketing

Confirmatory study

Exploratory study

M-51073-21

IND level

Marketing authorization

Probability of efficacy (evidence level)

Orphan level
HeartSheet; Post-marketing evaluation

- Concurrent external control comparison
  - Endpoint: Survival
  - Skeletal Myoblast Sheet: 60 subjects
  - Control: 120 subjects

Conditional and time-limited authorization

Time limit; 5 years
Challenges; Conditional/Time-Limited Authorization

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 )

CMC and quality assurance

✓ Limited qualification in early stage and quality control under GCTP) (validation, scalability, comparability)
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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**

1. Prioritized Consultation
   [Waiting time: 2 months → **1 month**]

2. Substantialized Pre-application Consultation
   [de facto review before application]

3. Prioritized Review
   [12 months → **6 months***]
   (* for new drug, new medical device)

4. Review Partner
   [PMDA manager as a concierge]

5. Substantial Post-Marketing Safety Measures
   [Extension of re-examination period]
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
Review
Reimbursement
Post Marketing

① Priority Consultations
② Prior-review
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

【Forerunner】
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

Prior review (rolling submission)
※ In some cases, may accept phase III data during review

Practical application of Innovative medical products
## Assignment of Sakigake for RM products

(As of Feb. 28, 2017)

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<th>Name of medical products</th>
<th>Target condition/disease</th>
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<td>STR01</td>
<td>Autologous bone marrow-derived mesenchymal stem cell</td>
<td>Neurological symptoms and disabilities caused by spinal cord injury</td>
</tr>
<tr>
<td>G47Δ</td>
<td>Growth-controlled oncolytic herpes simplex virus type 1</td>
<td>Malignant glioma</td>
</tr>
<tr>
<td>JRM-001</td>
<td>autologous cardiac progenitor/stem cells</td>
<td>Pediatric congenital heart disease (single ventricle physiology)</td>
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<table>
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<th>Second Round</th>
<th>Name of medical products</th>
<th>Target condition/disease</th>
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<td>CLS2702C/D</td>
<td>Epithelial cell sheet prepared by culturing autologous oral mucosal epithelial cell</td>
<td>Prevention of the formation of the esophageal stenosis after ESD</td>
</tr>
<tr>
<td>Allogeneic iPS cell-derived dopaminergic neural progenitor cells</td>
<td>Amelioration of neurological symptoms of Parkinson’s disease</td>
<td></td>
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<tr>
<td>Somatic stem cell</td>
<td>Manufactured from human stem cells obtained from adult bone marrow</td>
<td>Ischemic stroke (treatment window period of 18-36 hrs after the onset)</td>
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ESD: Endoscopic Submucosal Dissection
Thank you

Please visit the PMDA website
http://www.pmda.go.jp

Review Reports in English
http://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html