Regulation of Regenerative Medicine in Japan

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Review Director,
Office of Cellular and Tissue-based Products
PMDA, Japan
Outline

• The Act on the Safety of Regenerative Medicine (Safety Act)

• The Act on Pharmaceuticals and Medical Devices (PMD Act)
  ✓ Evolving Early Access Schemes
  ✓ Develop Guidelines
Regulatory Framework for Regenerative Medicine in Japan

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 (Safety Act)

Medical Care or Clinical Research

The Act on Pharmaceuticals and Medical Devices (PMD Act)

Commercial Product Marketing Authorization Purpose
The Act on the Safety of Regenerative Medicine (Safety Act)

The Act on Pharmaceuticals and Medical Devices (PMD Act)

- Evolving Early Access Schemes
- Develop Guidelines
Regulatory Framework for Regenerative Medicine in Japan

Regenerative Medicine

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

The Act on the Safety of Regenerative Medicine (Safety Act)

Medical Care or Clinical Research

Production and marketing of regenerative and cellular therapeutic *products* by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)

Commercial Product
Marketing Authorization Purpose
These measures may help limit the unregulated marketing of unproven stem cell-based interventions as medical practice, which the JSRM previously worried would make Japan a “therapeutic haven” for predatory foreign firms.
Rules for Hospitals and Clinics

High Risk (class I)

Hospitals / Clinics

Plan submission

Certified special committee for regenerative medicine

Evaluation

MHLW Health Science Council

Opinion

Provision (Within 90 days)

Change order (Within 90 days)

Special committee = 48

Middle Risk (class II)

Hospitals / Clinics

Plan submission

Certified special committee for regenerative medicine

Evaluation

Provision

Committee = 102

Low Risk (class III)

Hospitals / Clinics

Plan submission

Certified committee for regenerative medicine

Evaluation

Provision

Plans (3,593)

Medical care

Clinical research

0

17

88

45

3,389

54

(As of 31 March 2017)
Risk Classification
Regenerative Medical Technology

Technology excluded by Cabinet Order
No → Out of the scope of application of the Act
Yes

Human embryotic stem cells, iPS cells, cells similar to iPS cells
No

Cells to which gene was introduced
No

Xenogeneic cells
No → Class I

Allogeneic cells
No → Class I

Stem cells are used
No

Purpose is reconstruction, repair or formation of human body structure of function
No

Homologous use
Yes → Class III
No → Class II

Cell culture
No

Homologous use
Yes → Class III
No → Class II

Class II

Class II

Class II

Class II
### Example of Risk Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong> (High risk)</td>
<td>Transplantation of retinal pigment epithelium sheets derived from autologous iPS cells in patients with age-related macular degeneration</td>
</tr>
<tr>
<td><strong>Class II</strong> (Meddle risk)</td>
<td>Autologous bone marrow cell infusion therapy for liver cirrhosis</td>
</tr>
<tr>
<td><strong>Class III</strong> (Low risk)</td>
<td>Activated lymphocyte therapy for malignancies</td>
</tr>
</tbody>
</table>
Cell Processing Facility

Outside hospital

Corporate factory. etc

Processing, storage

Licensed (Local)
= 52 sites

Within hospital

Medical institution

Collection

Processing, storage

Transplant

Notified
= 2,427 sites

Accreditation (Overseas)
= 4 sites (Taiwan)
= 1 site (Korea)

(As of 31 March 2017)
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The Act on the Safety of Regenerative Medicine (Safety Act)
Medical Care or Clinical Research

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)
Commercial Product Marketing Authorization Purpose
Regenerative medical products are defined as processed (more than minimal manipulation) live human/animal cells that are intended to be used 1) for either (1) the reconstruction, repair, or formation of structures or functions of the human body or (2) the treatment or prevention of human diseases, or 2) for gene therapy.
Before IND: Pharmaceutical Affairs Consultation on R&D Strategy

**FY2012**

- **Medical Device**: 16
- **Drug**: 58
- **Regenerative Medicine**: 13

**FY2016**

- **Medical Device**: 66
- **Drug**: 66
- **Regenerative Medicine**: 28

PMD Act
IND: Submission of the Clinical Trial Notification

• Attached documents
  ✓ Statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified.
  ✓ A protocol of the proposed clinical trial
  ✓ An explanation document used for informed consent
  ✓ Sample of “Case Report Form”
  ✓ Current investigator's brochure

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

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

(As of April 2017)
Marketing Authorization

**Autologous Culture Epidermis JACE**
- Indication:
  - Serious burns treatment
  - Wound after removal of giant congenital melanocytic nevus

**Autologous Cultured Cartilage JACC**
- Indication:
  - Traumatic cartilage defects and osteochondritis dissecans

**Autologous skeletal myoblast HeartSheet**
- Indication:
  - Serious heart failure due to IHD

**Allogeneic MSC TEMCELL HS Inj.**
- Indication:
  - Steroid refractory acute GVHD

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP
<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMCELL HS Inj.</td>
<td>868,680 JPN</td>
<td>10.8mL / bag</td>
</tr>
<tr>
<td></td>
<td>13,898,880 JPN</td>
<td>1 treatment course</td>
</tr>
<tr>
<td>HeartSheet</td>
<td>6,360,000 JPN</td>
<td>Kit A (Pre tissue collection)</td>
</tr>
<tr>
<td></td>
<td>1,680,000 JPN</td>
<td>Kit B (Sheet culture)</td>
</tr>
<tr>
<td></td>
<td>14,760,000 JPN</td>
<td>≈120,000USD</td>
</tr>
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<td>≈120,000USD</td>
<td>1 treatment course</td>
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Outline

• The Act on the Safety of Regenerative Medicine (Safety Act)

• The Act on Pharmaceuticals and Medical Devices (PMD Act)
  ✓ Evolving Early Access Schemes
  ✓ Develop Guidelines
## Evolving Early Access Schemes

<table>
<thead>
<tr>
<th>Type</th>
<th>US</th>
<th>EU</th>
<th>JP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan</td>
<td>Priority review Orphan designation</td>
<td>Accelerated review Orphan designation</td>
<td>Priority review Orphan designation</td>
</tr>
<tr>
<td></td>
<td>Accelerated review Orphan designation</td>
<td>Accelerated review Orphan designation</td>
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</tr>
<tr>
<td></td>
<td>Conditional MA MA under exceptional circumstances</td>
<td>Conditional MA MA under exceptional circumstances</td>
<td>Conditional &amp; Time-limited approval Approval for oncology drug, Orphan drug</td>
</tr>
<tr>
<td></td>
<td>Break through therapy &amp; Fast track designation (Rolling submission)</td>
<td>PRIME Pilot project on adaptive path (Rolling submission)</td>
<td>SAKIGAKE Forerunner review assignment (Rolling submission)</td>
</tr>
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</table>

**RMAT:** Regenerative Medicine Advanced Therapy Designation
Orphan Designation

(1) Number of patients
The number of patients who may use the drugs, medical device or regenerative medicine should be less than 50,000 in Japan (126.9 million people in 2016).

(2) Medical needs
- The drugs, medical devices or regenerative medicine should be indicated for the treatment of serious diseases, including difficult-to-treat diseases. In addition, they must be drugs, medical devices or regenerative medicine for which there are high medical needs satisfying one of the following criteria.
  - There is no appropriate alternative drug/medical device/regenerative medicine or treatment
  - High efficacy or safety is expected compared with existing products

(3) Possibility of development
- There should be a theoretical rationale for the use of the product for the target disease, and the development plan should be appropriate.

References: Criteria for Orphan Designation by the MHLW Minister (Pharmaceutical and Food Safety Bureau Notification No. 0401-11)
## Orphan Designation

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Anticipated intended use or indications on the designation</th>
<th>Name of applicant receiving designation</th>
<th>Date of designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPR-01</td>
<td>External fistulas due to Crohn's disease (including anal fistulas)</td>
<td>Nihon Pharmaceutical Co., Ltd.</td>
<td>12/12/2013</td>
</tr>
<tr>
<td>JR-031</td>
<td>Acute graft-versus-host disease</td>
<td>Japan Chemical Research Co., Ltd.</td>
<td>12/12/2013</td>
</tr>
<tr>
<td>Cultured human autologous epidermal cell sheet</td>
<td>Rapid epithelialization of lesions removed nevi in patients with giant congenital melanocytic nevi</td>
<td>Japan Tissue Engineering Co., Ltd.</td>
<td>11/25/2014</td>
</tr>
<tr>
<td>EYE-01M</td>
<td>Corneal epithelial stem cell deficiency</td>
<td>Japan Tissue Engineering Co., Ltd.</td>
<td>3/25/2015</td>
</tr>
</tbody>
</table>
| CTL019       | • CD19-positive B-cell acute lymphoblastic leukemia  
• CD19-positive diffuse large B-cell lymphoma  
• CD19-positive follicular lymphoma | Novartis Pharma K.K. | 5/25/2016 |

## Evolving Early Access Schemes

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<td>Conditional &amp; Time-limited approval</td>
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<td>serious or life-threatening illnesses</td>
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RMAT: Regenerative Medicine Advanced Therapy Designation
HeartSheet: First Conditional & Time-limited approval product

M-51073-21 study
- Single arm, 7 subjects.
- Endpoint
  LVEF (RI, CT, Echo)
  Comprehensive clinical evaluation
  Survival (External control comparison)

- Survival (Concurrent external control comparison)
- Skeletal Myoblast Sheet: 60 subjects
- Control: 120 subjects
- Time limit; 5 years

Autologous skeletal myoblast Indication: Serious heart failure due to IHD

Clinical study
- Conditional /Time-limited authorization
- Marketing
- Marketing authorization or Revocation
- Marketing continues

Clinical trials (likely to predict efficacy, confirming safety)

# Evolving Early Access Schemes

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RMAT: Regenerative Medicine Advanced Therapy Designation
SAKIGAKE Designation System

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]**

1. **Priority Consultations**
   - Non clinical studies, Clinical studies
   - Clinical trials I/II
   - Consultation on Clinical trials
   - Prior review on Clinical trials
   - Prior review on phase III study
   - Review
   - Reimbursement
   - Post Marketing

2. **Prior-review**
   - Non clinical studies, Clinical studies
   - Clinical trials I/II
   - Consultation on Clinical trials
   - Prior review (rolling submission)
   - Prior review on phase III study
   - Review
   - Reimbursement
   - Post Marketing

3. **Priority Review**
   - Non clinical studies, Clinical studies
   - Clinical trials I/II
   - Consultation on Clinical trials
   - Prior review on phase III study
   - Review
   - Reimbursement
   - Post Marketing

4. **Review Partner System**
   - Non clinical studies, Clinical studies
   - Clinical trials I/II
   - Consultation on Clinical trials
   - Prior review on phase III study
   - Review
   - Reimbursement
   - Post Marketing

**[Forerunner]**

1. **Priority Consultations**
   - Non clinical studies, Clinical studies
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   - Non clinical studies, Clinical studies
   - Clinical trials I/II
   - Consultation on Clinical trials
   - Prior review on phase III study
   - Review
   - Reimbursement
   - Post Marketing

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

**Practical application of Innovative medical products**
<table>
<thead>
<tr>
<th></th>
<th>Name of regenerative medical products</th>
<th>Target condition/disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Round</td>
<td>STR01 Autologous bone marrow-derived mesenchymal stem cell</td>
<td>Neurological symptoms and disabilities caused by spinal cord injury</td>
</tr>
<tr>
<td>(2016)</td>
<td>G47△ Growth-controlled oncolytic gene modified HSV-1</td>
<td>Malignant glioma</td>
</tr>
<tr>
<td>2nd Round</td>
<td>JRM-001 Autologous cardiac progenitor/stem cells</td>
<td>Pediatric congenital heart disease (single ventricle physiology)</td>
</tr>
<tr>
<td>(2017)</td>
<td>CLS2702C/D 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></td>
<td>Allogeneic iPS derived dopaminergic neuronal cells</td>
<td>Amelioration of neurological symptoms of Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>Somatic Stem Cell Adult bone marrow derived allogeneic stem cell</td>
<td>Ischemic stroke (treatment window period of 18-36 hrs after the onset)</td>
</tr>
</tbody>
</table>

(As of Feb. 28, 2017)
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  ✓ Evolving Early Access Schemes
  ✓ Develop Guidelines
Personnel Exchange Program

Universities and research institutions

Medical Institutions

Personnel Exchange

iPS Cells, Platelets, etc.

Kyoto University, Center for iPS Cell Research and Application (CiRA)

Osaka University, Graduate School of Medicine

Hokkaido University, Graduate School of Medicine

Chiba university, Graduate School of Medicine

National Center for Child Health and Development

RIKEN, Center for Developmental Biology

Foundation for Biomedical Research and Innovation

Quality Evaluation of Processed Cells

Myoblast/Corneal Cell Sheets, Regeneration of Cartilage, etc.

Stroke

Spinal Cord injury

ES cells

Develop Guidelines

Cultivate Human Resource
Points to Consider for the Evaluation of Specific 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)
Thank you for your attention!

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