Japan's Regenerative Medicine Environment
- A Guide to Understand the Pathways to Get Approval in Japan
Dedicated to Human Health through the Popularization of Regenerative Medicine

For the industrialization of “Regenerative Medicine,” we collaborate to solve issues, and strive to improve people’s quality of life.

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Disclaimer: The opinions contained within this booklet are the opinions and interpretations of CJ PARTNERS and/or FIRM, and do not necessarily indicate endorsement or affirmation of the PMDA, the MHLW or other Japanese governmental agencies.

Reference: ASRM, PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act

*1: The “promulgation” of the Act was on Nov. 27, 2013.
Japan Has Two Epoch-Making Acts Regulating Its Regenerative Medicine Market:

1. The Act on the Safety of Regenerative Medicine (ASRM)
2. The Pharmaceuticals and Medical Devices Act (PMD Act)

The establishment of a broad-reaching conditional/term-limited approval system under the PMD Act for regenerative medical products puts Japan far ahead of their international competition.

High-Level Introduction to Japan’s Regulatory Environment

Japan has two laws regulating its regenerative medicine market: the Act on the Safety of Regenerative Medicine (ASRM) and the revised Pharmaceutical Affairs Act (PMD Act). The establishment of a broad-reaching conditional approval system under the PMD Act for regenerative medical products puts Japan far ahead of their international competition.

### ASRM

<table>
<thead>
<tr>
<th>Category</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Official Name</td>
<td>Act on the Safety of Regenerative Medicine (ASRM)</td>
</tr>
</tbody>
</table>
| Effective Date | November 25, 2014 *

#### Purpose

- Establish steps for the practice of regenerative medicine in order to ensure the safe and ethical administration of regenerative medicine technologies
- Ensure the safe yet accelerated adoption of specific processed cellular products by establishing a manufacturing permit system

#### Key Definitions

- Regenerative Medicine: Medical care that involves the use of regenerative medicine technologies.
- Regenerative Medicine Technologies: Medical care that involves the use of processed cellular products to reconstruct/restore/repair the human body (or its functions) or to cure/prevent a disease. Depending on their risk-level, these technologies are sub-divided into three classes.
- Specific Processed Cellular Products: Processed cellular products produced under the guidance of a medical institution, for the purposes of “clinical research” or “medical treatment at one’s own expense,” and meant for the treatment of a specific patient.

#### ASRM

Reference: ASRM, PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act

* The “promulgation” of the Act was on Nov. 27, 2013.

### PMD Act

<table>
<thead>
<tr>
<th>Category</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Official Name</td>
<td>Pharmaceuticals and Medical Devices Act (PMD Act)</td>
</tr>
<tr>
<td>Effective Date</td>
<td>August 10, 1960 (Amended as of November 25, 2014)</td>
</tr>
</tbody>
</table>

#### Purpose

- Revise the previous Act to provide a route to market for regenerative medicine that is more in sync with the current industry/patient needs
- Establish regulations for regenerative medicine that are independent of regular ethical drugs, medical devices, and non-medical/cosmetic products
- Conditional Approval: A system of approval put in place for those regenerative medical products that have all of the following conditions, and allow for the sale of said products for up to 7 years:
  - Do not have any major safety concerns
  - Have “probable” efficacy
  - Are not uniform in nature

#### Key Definitions

- Regenerative Medical Products: 1) Processed live human/animal cells that are intended to be used in order to:
  - Reconstruct/restore/repair the human/animal body
  - Cure/prevent a human/animal disease; or
  2) Gene therapy products for in vivo gene therapy (including oncolytic virus) or ex vivo gene therapy

Reference: Pharmaceuticals and Medical Devices Agency (PMDA)
The Pharmaceuticals and Medical Devices Act (PMD Act) — Revised “Pharmaceutical Affairs Act (PAA)” —

Background of the amendment of the “Pharmaceutical Affairs Act”

- The existing framework in Pharmaceutical Affairs Act does not fit with the characteristics of regenerative medical products
- It is difficult to gather and evaluate the data for efficacy of regenerative medical products in the short term.

To secure a prompt and safe provision of regenerative medical products, a new framework is needed

The expedited approval system for regenerative medical products

After the safety is confirmed and its efficacy is assumed, products will be approved with conditions and a limited term in order to enable prompt delivery of the products to patients.

After its safety is confirmed and its efficacy is assumed, the products can be approved under specific conditions and within a specified limited term for the sake of prompt delivery of its benefits to patients.

Expedited approval system under PMD Act

[Traditional approval process]
Clinical study Phased clinical trials (confirmation of efficacy and safety) Marketing authorisation Marketing

[New scheme for regenerative medical products]
Clinical study Conditional trial (likely to predict efficacy, confirming safety) Conditional trial (term-limited authorization) Marketing (Further confirmation of efficacy and safety) Marketing authorization or Revocation Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

Source: Pharmaceuticals and Medical Devices Agency (PMDA)
Japanese Unique Conditional/Term-Limited Approval System

Conditional Approval

Conditional approval is a system that provides companies with the opportunity to market their regenerative medical products after early stage clinical trials in the world’s second largest pharmaceutical market. Furthermore, as all conditionally approved products will be covered by Japanese NHI, their drug price will be 70% reimbursed by the government.

Regenerative Medical Product Conditional Approval

The PMD Act differs from the law that it revised (i.e., the PAA: Pharmaceutical Affairs Act) by the inclusion of Regenerative Medical Products as a stand-alone medical category with a novel “conditional approval” system. This system is summarized below:

1. If the Regenerative Medical Product, that a corporate entity is looking to obtain sales/manufacturing approval for, satisfies all of the following conditions:
   - It does not have any major safety concerns
   - It has “probable” efficacy
   - It is not uniform in nature
   Then said entity can obtain input from a sub-committee of the Pharmaceutical Affairs and Food Sanitation Council and receive conditional approval for said Regenerative Medical Product’s release.

2. Entities that receive conditional approval for a specific Regenerative Medical Product must re-apply for a full release within the timeframe provided to them under said approval (no longer than seven years)

Regenerative medical products are produced by processing cells in most cases. This “processing” can introduce certain risks including “the manifestation of additional properties that differ from the cells that were originally processed” and “an inconsistency of quality.” To help adequately deal with these inherent risks, regenerative medical products that are provided with conditional approval must stay within the following boundaries:

- They must not be carcinogenic
- Conditional approval must not be longer than seven years, and during this period measures must be taken to ascertain the proper use of the regenerative medical products
- Upon re-application they must demonstrate adequate efficacy & safety

Route to Market under the PMD Act

Conditional approval is not guaranteed for Regenerative Medical Products that meet the requirements delineated at the left. Rather, the PMDA reserves the right to decide on which Regenerative Medical Products will be allowed the shortened path to market.

Conditions Placed on Conditionally Approved Products

Japan’s NHI is only supposed to cover those items that have demonstrated clinical efficacy and allowing conditionally approved therapies to be covered by NHI was counterintuitive. However, by treating them in a similar manner to orphan drugs, the MHLW was able to extend insurance coverage to conditionally approved regenerative medical products.

Conditional Approval for Regenerative Medical Products vs. Regular Approval for Pharmaceuticals

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Clinical Trials</th>
<th>Efficacy Evidence</th>
<th>Post Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceuticals</td>
<td>Evaluation is conducted on suitably sized clinical trials which are determined based on disease characteristics</td>
<td>Controlled clinical trial that exhibits a statistically significant difference</td>
<td>Conduct post-marketing observation studies (PMOS) as necessary</td>
</tr>
<tr>
<td>Orphan Drugs</td>
<td>Evaluation frequently needs to be done based on a small number of study participants due to patient scarcity</td>
<td>There are cases when it is difficult to conduct rigorous statistical analysis</td>
<td>Follow-up investigations conducted on all patients (and/or follow-on clinical trials) to accumulate adequate data - stipulated condition of approval</td>
</tr>
<tr>
<td>Regenerative Medical Products (Conditional Approval)</td>
<td>Evaluation frequently needs to be done based on a small number of study participants due to patient scarcity</td>
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</table>

Reference: Presentation by the MHLW’s Medical Device and Regenerative Medical Product Evaluation Division
Japanese Expedited Authorization Scheme (Sakigake Designation)

The Ministry of Health, Labour and Welfare (MHLW) has established the “Strategy of SAKIGAKE” to go a step ahead of the world in the practice of commercializing innovative medical products. A project for the deployment of this strategy as a package covering from basic research to the clinical application has been launched rallying interdivisional efforts within the MHLW.

The Strategy of SAKIGAKE covers various aspects in the entire process of launching innovative medical products, i.e., translation of basic research to clinical application, clinical research/trials, approval reviews, safety, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion. It consists of two measures as follows;

SAKIGAKE Designation System: promoting R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medical products.

Scheme for Rapid Authorization of Unapproved Drugs: accelerating the application process of unapproved/off-label use of drugs for serious and life-threatening diseases by enabling the Council on Unapproved Drugs/Off-label Use to consider the data from western countries as valid if they satisfy certain conditions with a presumption of improvement of the environment for companies undertaking development of the product.

Source: Ministry of Health, Labour and Welfare (MHLW)
Website: http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html

Comprehensive Coverage of Conditional Approval

Biotechs that are developing regenerative medicine therapies have a plethora of programs from which to choose when considering the jurisdiction in which to develop their therapies. However, no program has as comprehensive coverage as Japan's Conditional/Term-Limited Approval.

Other
Life Threatening Serious Chronic
(Indication Type)
Other
Superior to
Existing Treatments
No Alternative

RMAT
(FDA)
Conditional/Term-Limited Approval
(PMDA)
Fast Track Designation
(FDA)
SAKIGAKE Designation
(PMDA)
CMA*1
EMA&

(Relationship to Existing Treatments)
Comparison of Various Programs Across the US, Europe, and Japan

Separate from those programs shown at left, each jurisdiction also has their own orphan drug programs:

• Orphan Drug Designation (FDA)
• Orphan Designation (EMA)
• Orphan Drug Designation (PMDA)

Additionally, the FDA has other Designations (Breakthrough, and Priority Review), while the EMA has Programs such as PRIME and Accelerated Assessment that are not represented in the image at left. However, no Designation/Program is as comprehensive in coverage as Japan's Conditional/Term-Limited Approval; making it an extremely favorable program for global regenerative medicine biotechs to take advantage of.

Reference: FDA, EMA, PMDA websites

*1: Can also be obtained if intended to be used in emergency situations or if designated as an orphan medicine

Japan's Global Position for Regenerative Medicine Biotechs

Market Size*1 Fundraising Legal Framework

While possessing a market size that is larger than any of Europe’s BIG 5, language barriers coupled with a traditionally difficult fundraising capacity meant that prior to Japan’s 2014 regenerative medicine related regulatory changes the country was seen as a lower priority by biotechs. However, these same regulatory changes have Japan in the limelight.

Reference: Outlook for Global Medicines through 2021(QuintilesIMS Institute)

*1: As of 2016 the US pharmaceutical market is roughly five times that of Japan
Comprehensive Coverage of Conditional Approval

Biotechs that are developing regenerative medicine therapies have a plethora of programs from which to choose when considering the jurisdiction in which to develop their therapies. However, no program has as comprehensive coverage as Japan’s Conditional/Term-Limited Approval.

Comparison of Various Programs Across the US, Europe, and Japan

(relationship to existing treatments)

<table>
<thead>
<tr>
<th>Condition Type</th>
<th>RMAT (FDA) &amp; EMA*1</th>
<th>CMA*1</th>
<th>EMA</th>
<th>PMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Threatening</td>
<td>Superior to existing treatments</td>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>Fast Track Designation (FDA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>SAKIGAKE Designation (PMDA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
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Reference: FDA, EMA, PMDA websites

*1: Can also be obtained if intended to be used in emergency situations or if designated as an orphan medicine

Japan’s Global Position for Regenerative Medicine Biotechs

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*1: As of 2016 the US pharmaceutical market is roughly five times that of Japan
Act on the Safety of Regenerative Medicine:

The wording of the ASRM necessitates that doctors be the gatekeepers of treatment. Pharmaceutical companies that would like to provide their drug/therapy to patients under this law would need to operate in non-traditional sectors of the market, such as operating as a Cell Processing Center (CPC), or receiving royalty payments.

3 Regenerative Medicine Technology Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Legal Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I Regenerative Medicine (High Risk)</td>
<td>The effects of the regenerative medicine technology on the patient’s well-being are either:  - not readily apparent; or  - potentially harmful</td>
<td>Regenerative medicine technologies that fall in this category are generally those that utilize IPS or ES cells</td>
</tr>
<tr>
<td>Class II Regenerative Medicine (Medium Risk)</td>
<td>The effects of the regenerative medicine technology on the patient’s well-being have the potential to have negative repercussions despite providing due care</td>
<td>Regenerative medicine technologies that fall in this category are generally those that utilize somatic (adult) stem cells</td>
</tr>
<tr>
<td>Class III Regenerative Medicine (Low Risk)</td>
<td>Regenerative medicine technology that does not fall under the other two risk categories</td>
<td>Regenerative medicine technologies that fall in this category are generally those that utilize processed somatic (adult) cells</td>
</tr>
</tbody>
</table>

Route to Market under the ASRM

1. Medical institution submits “Plan to Provide Regenerative Medicine” to appropriate Committee for Regenerative Medicine
2. Review by a Certified Special Committee for Regenerative Medicine (CRM)
3. MHLW receives medical institution’s notification
4. Health Science Council Review (90 days)
5. Medical institution commences provision of regenerative medicine based on their Plan

As treatments under the ASRM must be provided by a medical institution for the purposes of “medical research” or as a “medical treatment at one’s own expense,” therapies provided under this framework are not covered by Japan’s NHI.

The risk categorizations under the ASRM are determined as follows. Almost all pertinent uses will fall either under the Class I or Class II Regenerative Medicine categories.

Determining Risk Categorization of Regenerative Medicine Technologies

1. Is the technology excluded by Cabinet Order?*
   - NO
2. Do you use human ESCs, iPSCs (or cells similar to iPSCs) for the technology?
   - NO
3. Does the technology involve a transferred gene or protein?
   - NO
4. Do you use xenogeneic cells for the technology?
   - NO
5. Do you use any allogeic cells in the technology?
   - NO
6. Do you use stem cells?
   - NO
7. Do you intend to regenerate/fix/repair the human body or its functions?
   - NO
8. Homologous use?
   - NO

Technology is out of the scope of the ASRM

Class I Regenerative Medicine

Class II Regenerative Medicine

Class III Regenerative Medicine

Reference: ASRM, Guidebook to the Revised Pharmaceutical Affairs Act*.

*1: List of current CRMs under section 1-15-1
<https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/saisei_iryou/>
RMIT (Regenerative Medicine Industrialization Tactical Committee) of FIRM is Happy to Serve You

RMIT is an organization that was created within FIRM in 2015 for the purpose of accelerating industrialization for the regenerative medicine. It offers several types of assistance and partnering facilitations for the mutual benefit of clients and FIRM companies. Since there are diverse technological challenges to the business development in relation to regenerative medicine, it is difficult for a single company to carry out all the tasks required over the value chain, encompassing from R&D to marketing, by themselves alone. Thus, it is important to manage successful partnerships with a wide variety of relevant companies. People who are attempting to launch new businesses in the field of regenerative medicine in Japan may face tough challenges in finding appropriate partners, or in dealing with regulations. We intend to assist them in overcoming these challenges.

**Expanding Pipelines for Regenerative Medicine Industrialization**

Our Mission

1. Assist in business matching between players in industry
2. Facilitate the creation of start-up companies
3. Develop and promote hubs for Regenerative Medicine Industrialization

**Our services**

1. **Point-of-contact for partnering assistance**

The RMIT Committee assists in resolving various issues related to the industrialization of regenerative medicine and cell/gene therapy by responding to requests and inquiries from clients globally.

The operational headquarters are located at the Nihonbashi Life Science Building, Tokyo, Japan. It tries to facilitate partnering opportunities between clients, e.g., established corporations, SMEs, start-ups, or academia, world-wide, and FIRM member companies (more than 240 companies as of the end of May 2018).

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**RMIT Committee (Regenerative Medicine Industrialization Tactical Committee)**

- **Nihonbashi Office**
- **Entities Interested in Regenerative Medicine Industrialization (Domestic/Overseas)**
- **Regenerative Medicine Crossroad**
- **Requests Relating to Regenerative Medicine Industrialization**
- **Responses to Inquiries and/or Requests**
- **Discussion with Relevant Companies**
- **Matching with FIRM Member Companies**
- **FIRM Member Companies**
- **Non-FIRM Members**

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Forum for Innovative Regenerative Medicine | 09
2. Organizing Conferences; “Regenerative Medicine Crossroad® in Tokyo”

A crossroad is where people meet, where discussions start, and where friendships begin. We have organized this series of events to facilitate effective networking between those who seek partners or licensees in Japan in order to develop their products or to germinate their technology seeds.

**Fostering Regenerative Medicine Development in Japan**
Regenerative Medicine Industrialization Tactical Committee (RMIT)

**FIRM Calls for Speakers**
to its Business Partnering Event;

**Regenerative Medicine Crossroad® in Tokyo**

**Crossroad**
A crossroad is where people meet, where discussions start, and where friendships begin. We have organized this event series to facilitate effective networking between those seeking partners or licensees in Japan in order to develop their products or to germinate their technology seeds.

**Target Organizations for Speakers**
Typically, targeted organizations are clinical development companies or technology seed holders who seek partners in order to bring their products to development or to find licensees in Japan.

**Event Structure**
This half-day session consists of concurrent oral presentations and multiple one-on-one partnership meetings, followed by a networking mixer at the end of the day.

**Demographics**
We have successfully accommodated 35 speaker groups and over 700 individuals as attendees over the first seven Crossroad events. The demographics are shown below (the data from the seventh is being processed).
3. Preparing an Industrialization Demonstration Site

With the aim of the rapid pipeline commercialization of regenerative medical products either inside or outside of Japan, an optimum eco-system that supports vital research, coordinates diverse services, and responds to various inquiries and requests has been discussed and designed into a “one-stop solution provider” for the entire process from research and development to clinical trials at the location of Tonomachi, Kawasaki, which is a part of the International Strategic Zone of Kanagawa Prefecture.

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