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<th>Page #</th>
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<td>22</td>
</tr>
</tbody>
</table>
Japan’s Regenerative Medicine Regulatory Environment
The “Act on the Safety of Regenerative Medicine” and a revision to the “Pharmaceutical Affairs Act” were promulgated by the Japanese government on Nov. 27, 2013 with the aim of providing a route to market that was more in sync with current industry/patient needs. Both laws came into force the following year on Nov. 25, 2014.

### Japanese Regenerative Medicine Landscape Prior to Nov. 25, 2014

#### Main Governing Rules/Regulations
- Medical Care Act
- Medical Practitioners' Act

#### High-Level Background Information
- As treatment that falls under this category is not covered by the Japanese National Health Insurance (NHI), time to market is drastically reduced
- Treatment is provided by doctors at clinics and private practice in areas such as:
  - Cellular immunotherapy of cancers
  - Augmentation mammoplasty using adipose-derived Stem Cells

#### # of Studies that were in Progress
- N/A

---

### Prior Regenerative Medicine Regulatory Landscape

#### Main Governing Rules/Regulations
- Medical Care Act
- Medical Practitioners' Act
- Industry Guidelines

#### High-Level Background Information
- Large University Hospitals follow guidelines that are put in place by the Japanese Ministry of Health, Labour and Welfare (MHLW) in order to conduct clinical research on stem cell treatments for various diseases/ailments/conditions
- Expenses are covered by the hospitals that provide the therapy treatment

#### # of Studies that were in Progress
- 84

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### Clinical Trials + Marketed Drugs/Therapies

#### Main Governing Rules/Regulations
- Pharmaceuticals Affairs Act

#### High-Level Background Information
- The traditional route to market involving clinical trials
- 2 therapies had been approved:
  - Autologous Cultured Epidermus Japan Tissue Engineering Co., Ltd.
  - Autologous Cultured Cartilage Japan Tissue Engineering Co., Ltd.
- Further therapies were in the pipeline:
  - Allogeneic MSC GVHD Treatment JCR Pharmaceuticals Co., Ltd.
  - Autologous Skeletal Myoblast Sheet Terumo Corporation

#### # of Studies that were in Progress
- 6
# 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).

## 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>
<tr>
<td>Effective Date</td>
<td>November 25, 2014*1</td>
</tr>
</tbody>
</table>
| Purpose        | • Establish steps for the practice of regenerative medicine in order to ensure the safe and ethical administration of regenerative medical technologies  
                  • Ensure the safe yet accelerated adoption of specific processed cellular products by establishing a manufacturing permit system                  |

## 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</td>
</tr>
</tbody>
</table>
| Purpose        | • Revise the previous Act so as 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 from regular ethical drugs, medical devices, and non-medical/cosmetic products |

## Key Definitions

### ASRM

- **Regenerative Medicine**: Medical care that involves the use of regenerative medical technologies.
- **Regenerative Medical 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 3 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.

### PMD. Act

- **Regenerative Medical Products**: Medicinal products, produced by corporate entities for an unspecified large number of people, that involve human/animal cell culturing in order to:
  - Reconstruct/restore/repair the human/animal body
  - Cure/prevent a human/animal disease
  - Obtain a gene expression
- **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:
  - They do not have any major safety concerns
  - They have “probable” efficacy
  - They are not uniform in nature

---

Reference: ASRM, PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act  
*1: The “promulgation” of the Act was on Nov. 27, 2013.
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 Risk Categories of Regenerative Medical Technologies

<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 medical technology on the patient's well-being are either: • not readily apparent; or • the effects of the regenerative medical technology on a patient's wellbeing are potentially harmful</td>
<td>Regenerative medical technologies that fall under 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 medical technology on the patient's well-being have the potential to have negative repercussions despite providing due care</td>
<td>Regenerative medical technologies that fall under this category are generally those that utilize somatic (adult) stem cells</td>
</tr>
<tr>
<td>Class III Regenerative Medicine (Low Risk)</td>
<td>Regenerative medical technology that does not fall under the other 2 risk categories</td>
<td>Regenerative medical technologies that fall under this category are generally those that utilized 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)*1**
3. **Review by a Certified CRM*1**
4. **Medical institution notifies the MHLW of their “Plan to Provide Regenerative Medicine”**
5. **Health Science Council Review (90 days)**
6. **MHLW receives medical institution’s notification**
7. **Medical institution commences provision of regenerative medicine based on their Plan**

#### Class I Regenerative Medicine
- Class II Regenerative Medicine
- Class III Regenerative Medicine

### Act on the Safety of Regenerative Medicine (1/2)

- 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.

Reference: ASRM, Guidebook to the Revised Pharmaceutical Affairs Act

*1: List of current CRMs found under section 1-15-1 <http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/saisei_iryou/>
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 Medical Technologies

1. **Is the technology excluded by Cabinet Order**[^1]?  
   - **NO**  
   - **YES**  

2. **Do you use human ESCs, iPSCs (or cells similar to iPSCs) for the technology?**  
   - **NO**  
   - **YES**  

3. **Does the technology involve a transferred gene or protein?**  
   - **NO**  
   - **YES**  

4. **Do you use xenogeneic cells for the technology?**  
   - **NO**  
   - **YES**  

5. **Do you use any allogeneic cells in the technology?**  
   - **NO**  
   - **YES**  

6. **Do you use stem cells?**  
   - **NO**  
   - **YES**  

7. **Do you intend to regenerate/fix/repair the human body or its functions?**  
   - **NO**  
   - **YES**  

8. **Have you cultured the cells?**  
   - **NO**  
   - **YES**  

9. **Homologous use?**  
   - **NO**  
   - **YES**  

---

[^1]: Blood transfusions that use processed cells, hematopoietic stem cell transplantations, assisted reproductive technologies, etc.

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Reference: ASRM and related guidelines, Guidebook to the Revised Pharmaceutical Affairs Act, PMDA presentations
Pharmaceuticals and Medical Devices Act (1/4)

The Pharmaceuticals and Medical Devices Act (PMD. Act) instituted a conditional approval system for Regenerative Medical Products in Japan. The minute details of this new path are still being defined, but Terumo Corporation became the first company to receive conditional approval with its HeartSheet product on Sept. 18, 2015.

Conditional Approval for Regenerative Medical Products

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, 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:
   - It does not have any major safety concerns
   - It has “probable” efficacy
   - It is not uniform in nature

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 7 years)

Regenerative medical products are oftentimes produced by processing cells. 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 conditional approval must stay within the following boundaries:

- They must not be carcinogenic
- Conditional approval must not last longer than 7 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 and safety

Route to Market under the PMD. Act

• Conditional approval is not guaranteed for Regenerative Medical Products that meet the requirements delineated at left. Rather the PMDA reserves the right to decide on which Regenerative Medical Products will be allowed the shortened path to market.
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><strong>Pharmaceuticals</strong></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><strong>Orphan Drugs</strong></td>
<td>• Evaluation oftentimes 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) so as to accumulate adequate data <strong>-stipulated condition of approval-</strong></td>
</tr>
<tr>
<td></td>
<td>• Controlled clinical trials are oftentimes difficult to perform</td>
<td></td>
<td>• Limit the number of medical institutions that are allowed to administer the drug so as to ensure proper use <strong>-stipulated condition of approval-</strong></td>
</tr>
<tr>
<td><strong>Regenerative Medical Products (Conditional Approval)</strong></td>
<td>• Evaluation oftentimes needs to be done based on a small number of study participants due to patient scarcity</td>
<td>• There are oftentimes cases when it is difficult to conducts rigorous statistical analysis</td>
<td>• Follow-up investigations conducted on all patients (and/or follow-on clinical trials) so as to accumulate adequate data <strong>-stipulated condition of approval-</strong></td>
</tr>
<tr>
<td></td>
<td>• Controlled clinical trials are oftentimes difficult to perform</td>
<td></td>
<td>• Limit the number of medical institutions that are allowed to administer the drug so as to ensure proper use <strong>-stipulated condition of approval-</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Cellular heterogeneity make it difficult to evaluate</strong> based on a fixed/limited number study participants</td>
<td></td>
<td>• Limit the number of years of approval to a term of no more than 7 years <strong>-stipulated condition of approval-</strong></td>
</tr>
</tbody>
</table>

Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division
Pharmaceuticals and Medical Devices Act (3/4)

Treating conditionally approved regenerative medical products along the same lines as orphan drugs extends beyond allowing them to be covered by Japan’s NHI. The level of efficacy that one needs to obtain for conditional approval is also analogous.

Conditionally Approved Regenerative Medical Products ≈ Orphan Drugs

Reference: Presentation by the Japanese Society for Regenerative Medicine and Presentation by the PMDA
Whether one is able to obtain conditional approval is at the discretion of the regulatory authorities and guidelines are not yet available. However, the recent approvals of TEMCELL® HS Inj. and HeartSheet provide indications of what the regulators look for when they provide conditional approval (i.e. instances where statistical comparison is difficult).

**TEMCELL® HS Inj.**

Japan-based clinical trial consisted of a single-cohort of 25 patients

US-based clinical trial contained 51 placebo patients

Determined to have adequate efficacy for approval

**HeartSheet**

Japan-based clinical trial consisted of only 7 patients

Difficult to evaluate due to cellular heterogeneity

Difficult to evaluate due to patient scarcity

19 patients received treatment though clinical research and this data combined with the trial data was enough to provide “adequate safety” & “probably efficacy” data

Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division
Japan’s NHI Pricing
NHI Pricing Methods

Depending on its categorization, a regenerative medical product’s NHI reimbursement price will be determined by different calculation methods. For those categorized as pharmaceuticals, the “Cost Calculation Method” will most likely be the go-to choice for the foreseeable future.

### Different Methods for Calculation of NHI Reimbursement Price

**Similar Efficacy Comparison Method (I) / (II)**
- This pricing method is used when a comparator drug is available for comparison
  - (I): New drug is eligible for premiums
  - (II): New drug is not novel enough to be eligible for premiums

There are various premiums that can be ascribed to a drug (multiple possible):
- **Innovativeness**: 70% ~ 120%
- **Usefulness (I)**: 35% ~ 60%
- **Usefulness (II)**: 5 ~ 30%
- **Marketability (I)**: 10% ~ 20%
- **Marketability (II)**: 5%
- **Paediatric Use**: 5% ~ 20%
- **Kit**: 5%
- **First in Class Drug**: 10%

**Cost Calculation Method**
- This pricing method is used when no comparator drug is available for comparison

The price of pharmaceuticals that fall under this category is determined by summing the following items:
- **Production Cost**: determined at cost
- **Operating Income**: determined using data from the *Handbook of Industrial Financial Data*
- **Distribution Cost**: determined using data from the *Survey of the Prescription Pharmaceutical Industry of Japan*
- **Consumption Tax**: currently 8%

**Medical Device (STM) Method**
- Technical fee (TF) and/or specialty treatment materials (STM) reimbursement are ascribed based on the medical devices classification (I ~ IV and determined at approval) and categorization:
  - A1: gauze, suture, etc.
  - A2: cardiogram equipment, etc.
  - B: me too products (catheters, etc.)
  - C1: technical fee already established but a new functional category needs to be established
  - C2: New technical fee and new functional category must be created

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Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division
### NHI Pricing Examples

JCR Pharmaceutical’s TEMCELL® HS Inj. was categorized as a pharmaceutical with its NHI reimbursement price calculated using the “Cost Calculation Method.” On the other hand, Terumo Corporation’s HeartSheet was categorized as a medical device.

#### TEMCELL® HS Inj. [JCR Pharmaceuticals]

<table>
<thead>
<tr>
<th><strong>Pricing Category</strong></th>
<th>Pharmaceutical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Human cell/tissue products (Somatic Stem Cells)</td>
</tr>
<tr>
<td><strong>Generic Name</strong></td>
<td>Allogeneic bone marrow-derived hMSC</td>
</tr>
<tr>
<td><strong>Therapeutic Category</strong></td>
<td>Treatment of acute GVHD after hematopoietic stem cell transplantation</td>
</tr>
</tbody>
</table>

**Dosing Regimen**

2m hMSCs per kilogram of the patient (with each bag being diluted in 18mL of saline solution) will be slowly (4mL/min) administered via IV drip.

Patients are to receive 2 doses per week (with dosing intervals of at least 3 days) for 4 weeks. If symptoms persist, patients may receive a further course of treatment whereby they receive 1 dose per week for 4 weeks.

#### HeartSheet [Terumo Corporation]

<table>
<thead>
<tr>
<th><strong>Pricing Category</strong></th>
<th>Medical Device (C2 - New Functionality, New Technology)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
<td>Autologous Skeletal Myoblast Sheets</td>
</tr>
</tbody>
</table>

#### HeartSheet A Kit

<table>
<thead>
<tr>
<th><strong>Method</strong></th>
<th><strong>Cost Calculation Method (JPY)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Production Cost</td>
<td>5,389,054</td>
</tr>
<tr>
<td>Operating Income</td>
<td>331,810</td>
</tr>
<tr>
<td>Distribution Cost</td>
<td>167,924</td>
</tr>
<tr>
<td>Consumption Tax</td>
<td>471,103</td>
</tr>
<tr>
<td>Overseas Adjustment</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total Price (rounded to the nearest ‘0,000 JPY)**

6,360,000

#### HeartSheet B Kit

<table>
<thead>
<tr>
<th><strong>Method</strong></th>
<th><strong>Cost Calculation Method (JPY)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Production Cost</td>
<td>1,386,638</td>
</tr>
<tr>
<td>Operating Income</td>
<td>85,377</td>
</tr>
<tr>
<td>Distribution Cost</td>
<td>83,504</td>
</tr>
<tr>
<td>Consumption Tax</td>
<td>124,442</td>
</tr>
<tr>
<td>Overseas Adjustment</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total Price (rounded to the nearest ‘0,000 JPY)**

1,680,000

Reference: Documentation from the results of the 313th Meeting of the MHLW’s Central Social Insurance Medical Council (with TEMCELL listed under 補-4-1 and HeartSheet listed under 補-4-2 at [http://www.mhlw.go.jp/stf/shingo2/200001041329.htm](http://www.mhlw.go.jp/stf/shingo2/200001041329.htm))
Japanese Regenerative Medicine Market
Japanese Regenerative Medicine Market

Japan’s innovative regenerative medicine market is highly regulated, and a small number of domestic manufacturers exert great influence. Success in this market requires a competitively priced and adequately differentiated product as well as a strong working relationship with the PMDA.

Key Factors for Market Success

- Adequately differentiate your products from those of your competitors
- Obtain competitive manufacturing support
- Regularly engage the PMDA in conversation to ensure your products are ascribed a reasonable price

Market Characteristics

5 Forces Analysis

Suppliers
- A comparative lack of domestic entities with manufacturing know-how leads to higher prices for those that do have such know-how/experience

New Entrants
- The recent regulatory changes have allowed for an expedited route to market for regenerative medicine and has many pharmaceutical companies considering entry

Competitors
- A number of high profile domestic autologous (and increasingly allogeneic) products are already garnering much of the spotlight in Japan

Substitutes
- Depending on the indication, cheaper, more well-known and less invasive alternatives exist within a doctor’s current arsenal of treatments

Buyers
- If product is covered by the national health insurance scheme, the price will be determined every two years by regulators

The Japanese regenerative medicine market is highly innovative compared to other products regulated under the PMD. Act though it has a slightly less rigorous regulatory environment than traditional pharmaceuticals.
Japanese Industry is getting behind the government’s push to forward regenerative medicine and cellular therapies in Japan. Pharmaceutical companies in particular are increasingly expressing interest in the field. For non-Japanese firms looking for a way into the market, such firms are convenient spring boards with their regulatory knowhow and experience.

**Market Participants**

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMO/CPC</td>
<td>FSTECH, MEDI-SET, ROHTO, PharmaBio, MEDI-SET, TAKARA, IBC, ASAHI GLASS</td>
</tr>
<tr>
<td>CRO</td>
<td>CMIC, I’CROS, EPS GROUP, POC, Clinical Research, Inc.</td>
</tr>
<tr>
<td>SMO</td>
<td>I’rom, EP-Mint Co., Ltd., Site Support Institute Co., Ltd.</td>
</tr>
<tr>
<td>Pharmaceutical Company</td>
<td>Takeda, astellas, FUJIFILM, TERUMO, Sumitomo Dainippon Pharma, Healios,</td>
</tr>
<tr>
<td></td>
<td>EISAI, OLYMPUS, SUZUKEN</td>
</tr>
<tr>
<td>Distribution Company</td>
<td>MEDIPAL HOLDINGS, alfresa, TOHO</td>
</tr>
<tr>
<td>Other</td>
<td>Kawasaki, Irvine Scientific, TAISEI, TAKENAKA, OLYMPUS, HITACHI</td>
</tr>
</tbody>
</table>
Only 4 “Regenerative Medicine Consultations” have taken place in the 10 months since the PMD. Act came into force on Nov. 25, 2014. Most of the consultations for regenerative medical products can therefore be assumed to have been either “Pre-Consultations” or “Manufacturing Quality/Safety Consultations.”

<table>
<thead>
<tr>
<th>PMDA Consultations</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015 (~Sept.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Consultation (I)</td>
<td>118</td>
<td>302</td>
<td>237</td>
<td>271</td>
<td>80</td>
</tr>
<tr>
<td>Pre-Consultation (II)</td>
<td>153</td>
<td>254</td>
<td>346</td>
<td>325</td>
<td>171</td>
</tr>
<tr>
<td>Face-to-Face Consultation</td>
<td>31</td>
<td>40</td>
<td>123</td>
<td>85</td>
<td>34</td>
</tr>
<tr>
<td>Pharmaceutical Consultation</td>
<td>20</td>
<td>28</td>
<td>66</td>
<td>48</td>
<td>19</td>
</tr>
<tr>
<td>Medical Device Consultation</td>
<td>6</td>
<td>5</td>
<td>38</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Regenerative Medicine Consultation*1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Regenerative Medicine Manufacturing Quality/Safety Consultation</td>
<td>5</td>
<td>7</td>
<td>19</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Release Roadmap Consultation*1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division

*1: Commenced on November 25, 2014
In a testament to Japan’s seeming greater focus on cellular-based technologies, there are many more early stage R&D products for “Cell Therapies” than there are “Gene Therapies” in Japan. However, both types of therapies are considered to be regenerative medical products within the PMD Act.

### R&D Status of Regenerative Medicine aimed for Japan

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cell Therapies</th>
<th>Gene Therapies</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Project*¹</td>
<td>6</td>
<td>1</td>
<td>[Sumitomo Dainippon/Healios/SighRegen (1)], [Cardio (1)], [SBI Biotech (1)], [Regience/Osaka University (1)], etc.</td>
</tr>
<tr>
<td>Pre-Clinical</td>
<td>13</td>
<td>1</td>
<td>[CellSeed (2)], [J-TEC (1)], [Caladrius Biosciences (1)], [Pluristem (1)], [Nagoya University (7)], etc.</td>
</tr>
<tr>
<td>Phase I</td>
<td>10</td>
<td>3</td>
<td>[Regeneus (1)], [MEDINET (1)], [Athersys (1)], [RepliCel (2)], [MolMed (1)], [ID Pharma (1)], etc.</td>
</tr>
<tr>
<td>Phase II</td>
<td>4</td>
<td>5</td>
<td>[MEDINET (1)], [Caladrius Biosciences (1)], [National Cerebral and Cardio Center (1)], [Shiseido/RepliCel (1)], [AnGes MG (1)], etc.</td>
</tr>
<tr>
<td>Phase III</td>
<td>2</td>
<td>1</td>
<td>[Rohto/Nuo (1)], [Cytori (1)], [AnGes MG/Sosei/Mitsubishi Tanabe/Osaka University (1)]</td>
</tr>
<tr>
<td>Approved/Marketed</td>
<td>4</td>
<td>0</td>
<td>[JCR Pharma/Mesoblast (1)], [Terumo (1)], [J-TEC (2)]</td>
</tr>
</tbody>
</table>

red font = cell therapies  
orange font = gene therapies  

### Therapeutic Categories

- **Oncology & Immunomodulators**  
- **Cardiovascular**  
- **Dermatology**  
- **Musculoskeletal**  
- **Genito-Urinary**  
- **Sensory Organ**  
- **CNS**  

The “Oncology & Immunomodulators” and “Cardiovascular” categories combine to account for 64% of the regenerative medical products currently being developed in Japan.

The “Musculoskeletal” category occupies a lower position than has been predicted for the industry.

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Reference: EvaluatePharma®

*¹: There are many other research projects that are in place within university settings
**Corporate Developments in JPN Regenerative Medicine**

As Japan looks to further its standing as a global leader in the field of regenerative medicine, both domestic and foreign companies are looking to take advantage of this truly unique turn of events.

### Foreign Companies Looking Towards Japan

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Japan Developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athersys (ATHX:NASDAQ)</td>
<td>Announced partnership and license agreement with Healios K.K. for novel cell therapy treatments including MultiStem on 08 JAN 2016</td>
</tr>
<tr>
<td>Avita Medical (AVH:ASX)</td>
<td>Announced signing of a distribution agreement with INDEE Medical for their ReCell® device on 14 JAN 2016</td>
</tr>
<tr>
<td>Cynata (CYP:ASX)</td>
<td>Japanese firm Regence K.K. announced that they had signed an LOI regarding a future strategic alliance with Cynata on 03 DEC 2015</td>
</tr>
<tr>
<td>Cytori (CYTX:NASDAQ)</td>
<td>Announced first patient enrollment/treatment in their Japanese physician-initiated ADRESU trial for Cell Therapy™ on 03 SEPT 2015</td>
</tr>
<tr>
<td>Mesoblast (MESO:NASDAQ)</td>
<td>TEMCELL® HS Inj. (Prochymal) approved in Japan on 18 SEPT 2015 and NHI price commencement date was on 26 NOV 2015</td>
</tr>
<tr>
<td>Pluristem (PSTI:NASDAQ)</td>
<td>Announced on 21 DEC 2015 that it had reached an agreement with the PMDA on the design for a 75-patient trial for PLX-PAD</td>
</tr>
<tr>
<td>RepliCel (RP:TSX.V)</td>
<td>Announced a Collaboration and Technology Transfer Framework Agreement with Shiseido for their RCH-01 therapy on 29 MAY 2013</td>
</tr>
<tr>
<td>Regeneus (RGS:ASX)</td>
<td>Announced that they were targeting Japan for their allogeneic off-the-shelf cell therapy for OA, Progenza, on 26 NOV 2014</td>
</tr>
</tbody>
</table>

### Japanese Pharma on the Move

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Regenerative Medicine Developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astellas (4503:TSE)</td>
<td>Announced the establishment of a Regenerative Medicine unit on 01 APR 2014, and to announce acquisition of Ocata Therapeutics on 10 NOV 2015</td>
</tr>
<tr>
<td>Fujifilm (4901:TSE)</td>
<td>In addition to the continued efforts of subsidiary J-TEC, Fujifilm also announced the acquisition of Cellular Dynamics International on 30 MAR 2015.</td>
</tr>
<tr>
<td>Kaneka (4118:TSE)</td>
<td>Announced the establishment of an R&amp;D facility in Kobe on 27 NOV 2015; they aim to develop amniotic stem cell therapies</td>
</tr>
<tr>
<td>Kyowa Kirin (4151:TSE)</td>
<td>On 03 DEC 2015, multiple news outlets reported that Kyowa Kirin was teaming up with CiRA to investigate cancer immunotherapies using iPSCs</td>
</tr>
<tr>
<td>ReproCELL (4978:TSE)</td>
<td>Announced the acquisition of Biopta on 24 NOV 2015</td>
</tr>
<tr>
<td>Rohto (4527:TSE)</td>
<td>On 08 JAN 2016, news sources reported that Nuo Therapeutics and Rohto had signed an exclusive licensing/Distribution Agmt for Aurix in Japan</td>
</tr>
<tr>
<td>Sumitomo Dainippon (4506:TSE)</td>
<td>Looking to invest 2.2b JPY (~19m USD) to create a facility dedicated to culturing iPSCs, to help develop Japan’s first iPSC drug</td>
</tr>
<tr>
<td>Takeda (4502:TSE)</td>
<td>Takeda announces its intent to fund collaborative research in iPSC applications to the tune of 20b JPY (~170m USD); with a new facility built DEC 2015</td>
</tr>
</tbody>
</table>

Reference: FACTIVA, company press releases, various news articles
Appendix
CJ PARTNERS Company Profile

CJ PARTNERS Inc. offers management consulting and M&A advisory services by “made in Japan” Americans. Our mission is to bring the assets of a unique bicultural experience to serve Japan’s economy and society.

**Company Profile**

<table>
<thead>
<tr>
<th>Name</th>
<th>CJ PARTNERS Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Founded</td>
<td>November 15, 2012</td>
</tr>
<tr>
<td>Address</td>
<td>Tech Hiroo Bldg. 9F</td>
</tr>
<tr>
<td>Contact</td>
<td>Tel: +81-(0)3-6277-0542</td>
</tr>
<tr>
<td>Services</td>
<td>Management Consulting, M&amp;A Advisory</td>
</tr>
<tr>
<td>Main Bank</td>
<td>Mizuho Bank, Ltd.</td>
</tr>
</tbody>
</table>

**Corporate Philosophy and Mission Statement**

Our Philosophy
- Support Japan Inc.’s global strategy as an International Advisor that speaks Japan’s linguistic, cultural and professional language.

Mission Statement
- Offer cutting edge service at affordable rates
- Act as the missing link between Japanese and non-Japanese businesses[*]
- Provide tailor-made global expansion strategies absent in Japan-local advisory firms
- Deliver results that serve Japan’s economy and society

**Managing Director Profile: Colin Lee Novick**

Deloitte Tohmatsu Consulting
- Management Consulting
  - April, 2007 → July, 2010

SMBC Nikko Securities
- M&A Strategy
  - August, 2010 → November, 2012

Project Examples:
- Japan market-entry for a non-Japanese regenerative medicine firm
- PMDA negotiation for a non-Japanese cellular therapy firm
- Clinical trial management for a Japanese pharma firm

**Managing Director Profile: Jason David Sieger**

Deloitte Tohmatsu Consulting
- Management Consulting
  - October, 2007 → September, 2011

SMBC Nikko Securities
- M&A Strategy
  - October, 2011 → November, 2012

Project Examples:
- JPN regulatory assistance for non-Japanese pharmaceutical firms
- Pre-M&A DD and financial advisory services re: a JPN gene therapy firm
- Out-license (to Japan) assistance for a non-Japanese pharma firm

[*]: “Non-Japanese businesses” refers to both large, multinational enterprises and smaller, more localized foreign enterprises.
ご清聴ありがとうございました

Thanks for Listening