Update on Regulatory Landscape of Regenerative Medicine in Japan

5 February 2020
Yoshiaki Maruyama, Ph.D.
Review Director,
Office of Cellular and Tissue-based Products
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
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

Enacted on 25 November 2014

The Act on Pharmaceuticals and Medical Devices (PMD Act)

Commercial Product Marketing Authorization Purpose
Risk Classification Regenerative Medical Technology

Note:
In vivo gene therapy is currently out of scope
Rules for Hospitals and Clinics

Safety Act

High Risk (class I)
- Hospitals / Clinics
- Plan
- Submission
- Certified special committee for regenerative medicine
- Evaluation
- MHLW
- Health Science Council
- Provision (Within 90 days)
- Change order (Within 90 days)

Middle Risk (class II)
- Hospitals / Clinics
- Plan
- Submission
- Certified special committee for regenerative medicine
- Evaluation
- MHLW
- Provision

Low Risk (class III)
- Hospitals / Clinics
- Plan
- Submission
- Certified committee for regenerative medicine
- Evaluation
- MHLW
- Provision

Special committee = 57

Committee = 96

Plans (3,785)
Medical care 0
Clinical research 19

(As of 30 November 2019)

Rules for Hospitals and Clinics

Pharmaceuticals and Medical Devices Agency

4th India - Japan Medical Products Regulation Symposium 2019
Cell Processing Facility

Safety Act

Outside hospital
- Corporate factory, etc
- Processing, storage

Within hospital
- Medical institution
- Collection
- Processing, storage
- Transplant

Licensed (Local) = 66 sites
Accreditation (Overseas)
- 6 sites (Korea)
- 1 site (China)
- 2 sites (Taiwan)

Notified = 2,711 sites

(As of 30 November 2019)
Organizations and Authorities in Japan

MHLW

- Health Policy Bureau
- Pharmaceutical Safety and Environmental Health Bureau

PMDA

- Office of Cellular and Tissue based Products
- Office of Manufacturing Quality and Compliance
- Office of Safety II

R&D Division

- Medical Device Evaluation Division

Certified committees

Safety Act

MAHs

Manufacturing Sites

CPFs

Hospitals

Approval Decision, License Execution

Product Review

Site Inspections

PMD Act

4th India - Japan Medical Products Regulation Symposium 2019
Approved Plans (iPS) 2019-
Under The Act on the Safety of Regenerative Medicine
Japan approves world-first trial using iPS cells to treat spinal cord injuries

The health ministry on Monday approved the world’s first clinical test in which artificially derived stem cells will be used to treat patients with spinal cord injuries.
Clinical study OK’d for cornea transplant using iPS cells

The Asahi Shimbun
March 6, 2019 at 16:25 JST

A health ministry panel on March 5 approved a clinical study on what will be the world’s first transplant of cornea cells created from human iPS cells on a patient.

A team led by Kohji Nishida, professor of ophthalmology at Osaka University, expects to conduct its first transplant as early as June.
Kyoto University seeks approval to use iPS cells in treatment for damaged knees

KYOTO - Kyoto University said Wednesday it has asked for government approval to conduct a clinical trial that involves transplanting cartilage made from induced pluripotent stem (iPS) cells to treat damaged knee joints.

Under the plan, a team led by Noriyuki Tsumaki, a professor at the university who specializes in cell induction and regulation, will culture iPS cells to create cartilage tissue and transplant it into knees. The university said it submitted the plan to the health ministry on Nov. 7 for a review by its special panel.

The team has already tested the treatment on a rat and found it to be effective. It has also confirmed that the treatment carries low risk of rejection, fibrosis reaction or causing cancer, it said.

A board set up at the university approved the plan in October.

It is hoped that the new treatment will help treat patients who have damaged or degenerated cartilage due to injuries or illnesses.

Cartilage tissue covers joint bones and absorbs shock. A joint cannot move smoothly if part of the cartilage tissue is damaged due to injury or if it turns fibrous due to aging.

While there is a treatment in which normal cartilage tissue is transplanted, it is
Two Acts Regulating Regenerative Medical Technology & Product

Regenerative Medicine

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
  - Enacted on 25 November 2014

- The Act on Pharmaceuticals and Medical Devices (PMD Act)
  - Commercial Product
  - Marketing Authorization Purpose
Consultation and Review Pathway

Consultations
- After completion of exploratory study meeting
- Consultations on quality assurance
- Etc.

Application for Marketing Authorization

Review of Clinical Trial Protocol
(30 days-IND review)
* To prevent the occurrence or spread of hazard to the public.

Non-clinical

Clinical trial

Quality

Development

Consultation

Regulatory Science Strategy

After completion of exploratory study meeting
Consultations on quality assurance
Etc.
# Number of Consultations and INDs

## Face-to-face consultations on R&D strategy

<table>
<thead>
<tr>
<th>PMD Act</th>
<th>FY2014</th>
<th>FY2015</th>
<th>FY2016</th>
<th>FY2017</th>
<th>FY2018</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regenerative medical products#1</td>
<td>2</td>
<td>11</td>
<td>14</td>
<td>13</td>
<td>5</td>
<td>45</td>
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<td>Total</td>
<td>46</td>
<td>66</td>
<td>78</td>
<td>84</td>
<td>59</td>
<td>385</td>
</tr>
<tr>
<td>Face-to-face consultations for INDs#3</td>
<td>6</td>
<td>18</td>
<td>28</td>
<td>38</td>
<td>47</td>
<td>137</td>
</tr>
</tbody>
</table>

## Number of INDs#4

<table>
<thead>
<tr>
<th>PMD Act</th>
<th>FY2014</th>
<th>FY2015</th>
<th>FY2016</th>
<th>FY2017</th>
<th>FY2018</th>
<th>Total</th>
</tr>
</thead>
</table>

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#1: This consultation category was introduced on November 25, 2014.

#2: Some consultations were divided into multiple sessions over several days, to confirm the quality and safety of regenerative medical products before the submission of clinical trial notifications. The figures in brackets indicate the total number of sessions.

#3: For prior assessment consultations for regenerative medical products, the number of consultation categories was summed. (Set categories: quality/safety/efficacy, exploratory trial, confirmatory trial)

#4: Timing: The first notifications; 31 days before, Others; 2 weeks before. The figures in brackets indicate the Investigator-initiated Clinical Trials.
<table>
<thead>
<tr>
<th>#</th>
<th>Brand name</th>
<th>Non-proprietary name/</th>
<th>Indication or performance</th>
<th>Sponsor and website</th>
<th>Approval date</th>
<th>Conditional &amp; time-limited approval</th>
</tr>
</thead>
</table>
| 1  | JACE       | Human (autologous) epidermal cell sheet | 1. Serious and extensive burns  
JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Denis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately. | Japan Tissue Engineering Co., Ltd. http://www.jtec.co.jp/english/   | 29/10/2007   | No                                |
| 2  | JACC       | Human (autologous) Cultured Cartilage | 1. Giant congenital melanocytic nevi  
The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.  
| 4  | HeartSheet | Human (autologous) skeletal myoblast-derived cell sheet | Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all of the following criteria.  
Eligibility criteria:  
NYHA class III or IV heart failure; and  
Resting left ventricular ejection fraction ≤ 35% | Terumo Corporation http://www.terumo.com/                       | 27/07/2012   | No                                |
| 5  | Stemirac Inj. | Human (autologous) bone marrow-derived mesenchymal stem cells | Improvement of neurological symptoms and functional disorders associated with spinal cord injury only in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C.  
*Note: Bone marrow is collected within 31 days after injured and the product is administered as soon as it is manufactured.  
In clinical trial, IND was administered 40 ± 14 days after injured. | Nipro Corporation https://www.nipro.co.jp/en/                     | 28/12/2018   | Yes                               |
| 6  | Kymriah    | Tisagenlecleucel (CD19-directed genetically modified human (autologous) T cell) | Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse  
Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma | NOVARTIS https://www.novartis.com/                               | 26/03/2019   | No                                |
| 7  | Collatagene Intramuscular Injection 4 mg | Beperminogene plasmid (Hepatocyte growth factor (HGF) plasmid vector) | The treatment of ulcers in patients with chronic arterial occlusion (atherosclerosis obliterans and Bürger’s disease) who have not responded sufficiently to the standard drug therapy and are unable to undergo revascularization | AnGes, Inc. https://www.anges.co.jp/en/                           | 26/03/2019   | Yes                               |
Indication:
ALL
DLBCL

NOW APPROVED. The first and only CAR-T cell therapy* approved in two indications for B-cell malignancies.

THE TRANSFORMATION OF CANCER TREATMENT IS HERE

Explore how KYMRIAH is transforming the treatment of cancer by selecting an indication below.

https://www.novartis.co.jp/news/media-releases/prkk20180423-1
Press release in Japanese)
Desirable development model of regenerative medical products for conditional and time-limited approval

Maruyama et al., Cell & Gene Therapy Insights 2019; 5(6), 561-568
AnGes Obtains Conditional Approval in Japan for HGF Gene Therapy to Treat Critical Limb Ischemia

AnGes, Inc., a biopharmaceutical company focused on developing innovative gene-based medicines for treating serious diseases, announced today that they have obtained conditional approval (“Approval with Conditions and Time Limit”) from the Japanese Ministry of Health, Labour and Welfare (MHLW) for HGF plasmid to treat patients with critical limb ischemia (CLI).

HGF plasmid is the first gene therapy product to be approved in Japan, for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerotic obliterans and Buerger’s disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. AnGes applied for marketing approval to the MHLW in January 2018 based on positive results from the randomized, placebo-controlled phase three trial and investigator-led clinical study conducted in Japan. HGF plasmid is one of the first gene therapy products to be approved for a non-genetic disease with chronic and progressive symptoms.

Indication:
Ulcer healing for CLI patient

https://www.anges.co.jp/en/project/proj_develop.html
Assigned SAKIGAKE Designation
4th round, announced by 8th April 2019
Lead the world in the practical application of innovative medical products

Accelerate R&D through supporting each stage

Strengthen the structure of PMDA (consultation, review, safety measures in terms of quality and quantity)

Promotion of Regulatory Science (Developing guidelines/assessment for the state-of-the-art technology)

The Strategy of SAKIGAKE covers from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion.
Outline

Telomelyn is a gene-modified oncolytic adenovirus in which selectively replicate in cancer cells by introducing human telomerase reverse transcriptase (hTERT) promoter. Oncolytic adenovirus has much potential for cancer immunotherapy because its viral replication is highly immunogenic, and oncolysis induced by such virus releases tumor antigen and provides costimulatory danger signals. From the result of phase 1 clinical study in the US, OBP-301 showed abscopal effect, which non-injected tumor as well as injected tumor was regressed in melanoma patients after single injection into one single tumor and found that not only increasing infiltration of CD8 and antigen presenting cells but diminishing Treg cells in injected tumor site.

Oncolyx has been conducting phase 1 clinical study of Telomelyn for hepatocellular carcinoma in Korea and Taiwan and phase 2 clinical study for melanoma in the US. We will also soon initiate phase 2 study for esophageal cancer in combination with radiation, and another study for esophageal cancer in combination with a check-point inhibitor in Japan.
SanBio announces SB623 regenerative cell therapy for traumatic brain injury has received Ministry of Health, Labour and Welfare (MHLW) Sakigake designation

Tokyo, Japan—Apr. 8, 2019—The SanBio Group (SanBio Co., Ltd. and SanBio, Inc.), a scientific leader in regenerative medicine for neurological disorders, announced today that SB623, a regenerative cell therapy that the Group is developing globally for the treatment of chronic motor deficit resulting from traumatic brain injury (TBI), has received the Sakigake Designation for innovative medical products from the Ministry of Health, Labour, and Welfare (MHLW) of Japan.

The Sakigake Designation System was unveiled in June 2014 as part of the “Strategy of SAKIGAKE” by an MHLW project team to lead the world in the practical application of innovative medical products. It is a scheme for rapid authorization of innovative pharmaceutical products initially developed in Japan for which exceptional effectiveness can be expected based on preclinical results and early-stage clinical trials. The Sakigake Designation System targets regenerative medicines that treat serious diseases which urgently require innovative therapies.

SanBio’s proprietary regenerative cell medicine SB623, which has been granted the Sakigake Designation, is made from modified and cultured adult bone marrow-derived mesenchymal stem cells that undergo temporary genetic modification. Implantation of SB623 cells into injured nerve tissue in the brain is expected to trigger the brain’s natural regenerative ability to recover lost motor functions.
Thank you for your attention!

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