Regulatory Updates on Cellular Therapy Products in Japan

Daiju Okuda, Ph.D.
Principle Reviewer
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency (PMDA), Japan

September 10, 2013
ISCT North America Regional Meeting, Philadelphia, USA
1. Organizational Updates

2. Regulatory Framework for Cellular Therapy Products (CTPs)

3. Future Regulatory Aspects
MADE IN JAPAN

JAPANESE REGULATORY BODIES

Executive
The Cabinet

Legislative
The National Diet

Judiciary
The Supreme Court

Ministry of Health, Labour and Welfare (MHLW)

Ministry of ----
Ministry of ----
Ministry of ----
Ministry of ----
Ministry of ----

Planning basic policy, enforcement of administrative measures based on the law; such as approval and safety measures.

Pharmaceuticals and Medical Devices Agency (PMDA)

Review, examination and data analysis; such as scientific review, GMP/GLP/GCP inspection and consultation.
PMDA established the Science Board on May 14th 2012, as a high-level consultative body* to advance regulatory science and support PMDA to evaluate products with advanced science and technology.

* Members are external experts from medical, dental, pharmaceutical, engineering and other fields.

The Board will make recommendations on review policy for innovative products, development of guidelines, regulatory science research, improvements in the scientific aspects of review.

---

**The Science Board**

- Pharmaceuticals
- Medical Devices
- Bio-based products
- Cellular & Tissue-based products
PROMOTION OF PERSONNEL EXCHANGE
< Program for Cellular Therapy Products >

- Universities and research institutions
- Medical Institutions
- Osaka University, Center for iPS Cell Research and Application (CiRA)
- Kyoto University, Center for iPS Cell Research and Application (CiRA)
- RIKEN, Center for Developmental Biology
- Hokkaido University, Graduate School of medicine
- Chiba University, Graduate School of Medicine
- National Center for Child Health and Development
- Foundation for Biomedical Research and Innovation
- Quality Evaluation of Processed Cells
- Myoblast/Corneal Cell Sheets, Regeneration of Cartilage, etc.
- iPS Cells, Platelets, etc.

Develop Guidelines
Cultivate Human Resource

- Stroke
- Spinal Cord injury
- ES cells
Valley of Death
- Insufficient knowledge on regulation and development strategy

Consultation on quality or toxicity study of biologics, cellular therapy products

Consultation on endpoints or sample size of early clinical trial
1. Organizational Updates
2. Regulatory Framework for Cellular Therapy Products (CTPs)
3. Future Regulatory Aspects
DEFINITION OF CELL/TISSUE PROCESSING

● Any processing of a cell or tissue with the objective of propagation and/or differentiation of a cell or tissue, cell activation, and production of a cell line, which includes
  - pharmaceutical or chemical treatment,
  - altering a biological characteristic
  - combining with a noncellular component
  - manipulation by genetic engineering.

● The isolation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or $\gamma$-irradiation, freezing, thawing, and such similar procedures regarded as minimal manipulations are NOT considered to be processing.
Cellular therapy products will be regulated as **Drugs** or **Medical Devices** according to their characteristics.

- **Drugs**: Pharmacological action*
  
  * efficacy depends on biological active substances produced from cells

- **Medical Devices**: Physical or Structural action

**<EXAMPLE>**
- **✓** Allogeneic mesenchymal stem cells for GVHD
  
  → **Drugs**

- **✓** Autologous epidermis for burn
  
  → **Medical Devices**

- **✓** Autologous cartilage for traumatic cartilage defects
  
  → **Medical Devices**
Marketing authorization of Cellular Therapy Products derived from processed human cells/tissues are regulated by the PAL and related regulatory documents.

1. Pharmaceutical Affairs Law (PAL)
2. MHLW Ministerial Notification
3. MHLW Ministerial Ordinance
4. MHLW Administrative Letters

- Guidelines
- Japanese Pharmacopoeia (JP), PAL 41
- Standards for Biological Materials, PAL 42
- Minimum Requirements for Vaccines, Antitoxins and Blood Products, PAL 42
### Guidelines for CTPs

**Good Tissue Practice (GTP)**
- Standards for Biological Ingredients *(2003)*
- General Principles for the Handling and Use of Cellular/Tissue-based Products *(2000)*

**Product Evaluation**
- Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue
  - Autologous *(2008)*
  - Allogeneic *(2008)*
- Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem
  - Autologous Somatic Stem Cells *(2012)*
  - Autologous iPS-like Cells *(2012)*
  - Allogeneic Somatic Stem Cells *(2012)*
  - Allogeneic iPS-like Cells *(2012)*
  - Embryonic Stem Cells *(2012)*
- Points to Consider for the Evaluation of Specific Products
  - Cell sheet for heart failure *(2010)*
  - Corneal epithelial cell sheet *(2010)*
  - Corneal endothelial cell sheet *(2010)*
  - Articular cartilage repair *(2010)*
  - Cell sheet for periodontal tissue regeneration *(2011)*

**GMP/QMS**
- Standards for Manufacturing Control and Quality Control for
  - Drugs and Quasi-drugs *(2004)*
  - Medical Devices and In-vitro Diagnostic Reagents *(2004)*
- Standards for Manufacturing Control and Quality Control of Investigational Products *(2008)*
- Points to Consider on Manufacturing and Quality Control of Autologous CTBPs *(2008)*
## Two Tracks for Clinical Study in Japan

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Clinical Trial</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application for Marketing Authorization</td>
<td>Not for Marketing Authorization (advancing medical science and technology)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory Framework</th>
<th>Clinical Trial</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Affairs Law (PAL)</td>
<td>• Medical Practitioners’ Act</td>
<td>• Ethical GLs for Clinical Research (Ministerial Notification of MHLW No.415, 2008)</td>
</tr>
<tr>
<td></td>
<td>• GLs for Clinical Research using Human Stem Cells (Ministerial Notification of MHLW No. 425, 2006; Rev., No.380, 2010)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GCP compliance</th>
<th>Clinical Trial</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory</td>
<td></td>
<td>Not Required</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IND-Review</th>
<th>Clinical Trial</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IRB</td>
<td></td>
<td>• IRB</td>
</tr>
<tr>
<td>• PMDA/MHLW</td>
<td></td>
<td>• MHLW (for researches of stem cell and gene therapy)</td>
</tr>
</tbody>
</table>
## CLINICAL TRIALS OF CTPs IN JAPAN

(1) 6 Products (As of July 2013)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Cell/Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe heart failure due to chronic ischemic heart disease</td>
<td>Skeletal myoblast</td>
</tr>
<tr>
<td>Focal articular cartilage lesion in the knee</td>
<td>Chondrocyte</td>
</tr>
<tr>
<td>Neurologic manifestation due to cerebral infarction</td>
<td>Mesenchymal Stem Cell</td>
</tr>
<tr>
<td>Giant congenital melanocytic nevus</td>
<td>Epidermal Cell</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>Epidermal Cell</td>
</tr>
<tr>
<td>Steroid-refractory acute GVHD</td>
<td>Mesenchymal Stem Cell</td>
</tr>
</tbody>
</table>

Auto; Autologous, Allo; Allogenic
(2) 84 Registered* (As of July 2013)

*According to “Guideline for Clinical Research using Human Stem Cells” (No. 425, 2006; Rev., No.380, 2010)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Vessel</td>
<td>22</td>
</tr>
<tr>
<td>Retina/Cornea</td>
<td>13</td>
</tr>
<tr>
<td>Cartilage/Intervertebral Disk</td>
<td>11</td>
</tr>
<tr>
<td>Bone</td>
<td>8</td>
</tr>
<tr>
<td>Heart</td>
<td>8</td>
</tr>
<tr>
<td>Periodontium/Dental Pulp</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal (GI) Tract</td>
<td>3</td>
</tr>
<tr>
<td>Cerebrovascular Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Mamma</td>
<td>2</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>1</td>
</tr>
<tr>
<td>Urinary System</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
</tr>
<tr>
<td>Tympanic Cavity</td>
<td>1</td>
</tr>
</tbody>
</table>
REVIEW OF CLINICAL TRIALS FOR CTPs

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

Application for Marketing Authorization

Consultation on Strategy
* To ensure safety and quality.

Consultation on Conducting Clinical Trials

Quality
Non-clinical
Clinical trial
Development
## 1. Autologous cultured epidermis

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Oct. 29, 2007 (submitted on Oct. 6, 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target organ</td>
<td>Skin</td>
</tr>
<tr>
<td>Brand Name (Company)</td>
<td>JACE (Japan Tissue Engineering Co.,Ltd.)</td>
</tr>
</tbody>
</table>

**Notes**

Autologous cultured keratinocytes using Green’s technique in which keratinocytes derived from the patient's own skin tissue are co-cultured with irradiated 3T3-J2 cells derived from mouse fetuses as a feeder to form a sheet in approximately three to seven layers thick. This is indicated for the treatment of serious large burns that cannot be provided with a sufficient area of donor skin for autologous skin grafting, and of burns in which the total area of deep second-degree (deep dermal) and third-degree (full-thickness) burn is 30% or more of the total body surface area.
### 2. Autologous cultured cartilage

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Jul. 27, 2012 (submitted on Aug. 24, 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target organ</td>
<td>Bone /Cartilage</td>
</tr>
<tr>
<td>Brand Name (Company)</td>
<td>JACC (Japan Tissue Engineering Co.,Ltd.)</td>
</tr>
<tr>
<td>Notes</td>
<td>An autologous cultured cartilage to alleviate clinical symptoms by implanting it in the affected site of traumatic cartilage efficiency and osteochondritis dissecans (excluding knee osteoarthritis) in knee joints with a cartilage defective area of 4 cm² or more for which there are no other treatment options. Chondrocytes isolated from the non-load-bearing site of a knee joint of patients by taking a small amount of cartilage tissue are three-dimensionally cultured in atelocollagen gel to obtain this product. Clinical studies were conducted to evaluate the efficacy and safety of this product for patients with traumatic cartilage deficiency, osteochondritis dissecans, and knee osteoarthritis.</td>
</tr>
</tbody>
</table>
1. Organizational Updates
2. Regulatory Framework for Cellular Therapy Products (CTPs)
3. Future Regulatory Aspects
DEFINITION OF “REGENERATIVE MEDICINAL PRODUCTS” IN NEW PAL

- Chapter 1 Article 9
- The term “SAISEI-IRYOU-TOU-SEIHIN” (as Regenerative Medicinal Products in Japanese) used in this law refers to the articles (excluding quasi-drugs and cosmetics) specified in the following items which are specified by the government ordinance.

  (1) These articles specified in the following items which are intended to use in the treatment of disease in humans or animals, and are cultured and/or processed human or animal cells.

  A, To reconstruct, restore or reproduce the structure and functions of human or animal body.
  B, To treat or prevent disease in humans or animals

  (2) The articles specified in the following items which are intended to use in the treatment of diseases in humans or animals, and are transgene, to express in human or animal cells.

“Regenerative Medicinal Products” in new PAL include the “gene therapy” in addition to common CTPs. This concept is similar to “Advanced Therapy Medicinal Products (ATMPs)” in EU.
NEW APPROVAL SYSTEM FOR COMMERCIALIZATION OF REGENERATIVE MEDICINAL PRODUCTS

【Current System】

Clinical Research → Clinical Trial (confirmation of efficacy and safety) → Approval → Market-ing

【Proposed System】

Clinical Research → Clinical Trial (confirmation of probable benefit* and safety**) → Provisional Approval with condition → Marketing (further confirmation of efficacy and safety) → Approval or Expiration of provisional approval → Marketing

※Earlier Patient Access !

Informed Consent and Post Market Safety Measures

* Probable benefit: Confirmation of efficacy with small patient population.
** Safety: Earlier detection and evaluation of adverse events.
Clinical Research/Medical Practice

New Regenerative Medicine Law
To ensure safety of regenerative medicine by stipulating standards for medical facilities and processing/manipulation plants

Company Plants (with permission)
Processing
Outsourcing
Medical institutions (with notification)
Collection
Transplant

Marketing Authorization

Pharmaceutical Affairs Law
To ensure efficacy and safety of marketing products by stipulating manufacturing standards

Company Plants (with permission)
Processing
Outsourcing
New Law
PAL

OUTSOURCING OF PROCESSING OF CELL/TISSUE
PMDA Science Board, Cellular and Tissue-based Products Subcommittee suggested “the Report of Discussion on Tumorigenicity of Cellular and Tissue-based Products (CTBPs) Manufactured based on iPS Cells.” (2013/08/20)

In order to ensure the safety of cellular and tissue-based products, the subcommittee reported relevant issues focusing on “tumorigenicity”.

It is reported the scientific test methods available at present, and capabilities and limits of each test method, and presented the potential countermeasures.

Therefore, the report presents a summary on the development of cellular and tissue-based products from a scientific point of view and not requirements for regulatory approval of cellular and tissue-based products.
CONTENTS OF THE REPORT

- Tumorigenicity of Cellular and Tissue-based Products.
- Assessment on the Undifferentiated Cells/Tumorigenic Cell Contaminants and Tumorigenicity in Cellular and Tissue-based Products Derived from iPS cells.
- Assessment and Management of Tumorigenicity of Human (Allogeneic) iPS Cells Used for Manufacturing iPS Cell-derived Products.

Please access for more details

http://www.pmda.go.jp/english/scienceboard/scienceboard/20130820.html#list

* English ver. is in the make and will be up when ready. (as of September 9, 2013)
Thank you for your attention!

If you wish to contact us. Please access to our website
http://www.pmda.go.jp/english/contact/index.html

PMDA strongly supports the development of innovative products