ACTO Satellite symposium
Japanese regulation of regenerative medicine

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Japan

The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA
Introduction of PMDA

Pharmaceuticals and Medical Devices Agency (PMDA)

- an Incorporated Administrative Agency (IAA)

PMDA’s Safety Triangle

- **Review**
  - Reduction in risk
- **Securing Safety and Efficacy**
- **Three-pillar System Unique to Japan**
- **Safety**
  - Continuous risk mitigation efforts
- **Japanese citizens**
- **Relief**
  - Relief measures for health damage caused by risk factors
Two Japanese Regulatory Authorities

- **Ministry of Health, Labor and Welfare (MHLW)**
  Planning basic policy, enforcement of administrative measures based on the law
  - Marketing authorization of pharmaceuticals and medical devices
  - Issue emergency safety information and direct product withdrawal
  - Safety measures for emergent and significant cases

- **Pharmaceuticals and Medical Devices Agency (PMDA)**
  Review, examination and data analysis
  - Scientific review, GMP/GLP/GCP inspection and consultation on the development of pharmaceuticals and medical devices for marketing authorization
  - Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices
Organization of PMDA

Chief Executive

Executive Director

Director of Center for Product Evaluation

Deputy Center Director (for Cellular and Tissue-based Products)

Deputy Center Director (for Medical Devices)

Senior Executive Director

Deputy Executive Director

Chief Management Officer

Chief Actuary

Chief Relief Officer

Offices of General Affairs / Office of Financial Management / Office of Planning and Coordination

Senior Executive Director

Executive Director

Associate Center Director

Associate Executive Director

Associate Center Director

Associate Center Director

Associate Executive Director

Chief Safety Officer

Chief Management Officer

Chief Actuary

Chief Relief Officer

Offices of Review Administration

Office of Review Management

Office of International Programs / International Liaison Officers

Offices of New Drug I-V

Office of Cellular and Tissue-based Products

Office of Vaccines and Blood Products

Office of OTC/Generic Drugs

Offices of Medical Devices I-III

Office of Conformity Audit

Principal Senior Scientist / Senior Scientists

Chief Safety Officer

Chief Actuary

Chief Relief Officer

Chief Executive

Executive Director

Associate Center Director

Associate Executive Director

Associate Center Director

Associate Center Director

Associate Executive Director

Number of Executives & Regular Employees: 708

- Review: 460
- Safety & GMP/ QMS inspection: 140

(As of 2013)
Contents

• Overview of environment, current regulation, policy of regenerative medicine in Japan
• The Act on the Safety of Regenerative Medicine
• The Act on Pharmaceuticals and Medical Devices (PMD Act – revised PAL)*
• Quality Assurance
• Consultation Mechanism
• Guidance for CMC, pre-clinical and clinical development
Health research regulations in Japan

Academic Purpose (other than MA)
- Observational studies
- Interventional studies
- Human Genome Analysis

Product Marketing Authorization Purpose
Interventional studies intended for application for MA of drugs and medical devices under Pharmaceutical Affairs Law (PAL)

Covered by MHLW itself
Covered by PMDA
Process required before the initiation of Clinical Trial

Clinical Trials outside of PAL

- Epidemiological Research
- Genome/Genome Analysis
- Other Clinical Research
- Human Stem Cell Clinical Trials
- Gene Therapy Clinical Trials

Guidelines on Clinical Trials Using Human Stem Cells
Guidelines for Gene Therapy Clinical Trials

Clinical Trials under Pharmaceutical Affairs Law (PAL)

J-GCP based on ICH-GCP

Institutional Review Board/Ethics Review Committee

- Ethical Guidelines for Epidemiological Studies
- Ethical Guidelines for Human Genome/Gene Analysis
- Ethical Guidelines for Clinical Studies

review by MHLW
review by PMDA

start of study
### Regenerative medicine & cell therapy in Japan

#### Medical Care Act (MCA)
- **Academic Research Purpose**
  - Clinical Research using human stem cells (under the Guideline for Human Stem Cell Clinical Research - since 2006)
    - 93 protocols approved (as of May 2014)
- **Cancer immunotherapy**
  - Six types of therapy are currently provided in approved university hospitals as “advanced care”
    * Partially covered by national health insurance

#### Pharmaceutical Affairs Law (PAL)
- **Product Marketing Authorization Purpose**
  - 2 marketed products
    - JACE (autologous cultured epidermis)
    - JACC (autologous cultured cartilage)
  - 12 clinical trials initiated (including 3 gene therapy products) (~October 2014)

#### Covered by MHLW

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical care</td>
<td>JACE (autologous cultured epidermis), JACC (autologous cultured cartilage)</td>
</tr>
<tr>
<td>Cancer immunotherapy</td>
<td>12 clinical trials initiated (including 3 gene therapy products)</td>
</tr>
</tbody>
</table>

*Partially covered by national health insurance*
## Stem Cell Clinical Trials Approved in Japan (non-PAL)

<table>
<thead>
<tr>
<th>Source</th>
<th>Origin</th>
<th>No. of Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose Tissue</td>
<td>autologous</td>
<td>10</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>autologous</td>
<td>27</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>allogeneic</td>
<td>2</td>
</tr>
<tr>
<td>Cord Blood</td>
<td>autologous</td>
<td>1</td>
</tr>
<tr>
<td>Corneal Epithelium</td>
<td>autologous</td>
<td>1</td>
</tr>
<tr>
<td>Corneal Endothelium</td>
<td>allogeneic</td>
<td>1</td>
</tr>
<tr>
<td>Corneal Tissue</td>
<td>allogeneic</td>
<td>2</td>
</tr>
<tr>
<td>Dental Tissue</td>
<td>autologous</td>
<td>3</td>
</tr>
<tr>
<td>Myocardium</td>
<td>autologous</td>
<td>3</td>
</tr>
<tr>
<td>Nasal Epithelium</td>
<td>autologous</td>
<td>1</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>autologous</td>
<td>9</td>
</tr>
<tr>
<td>Periosteum or Chondrocyte</td>
<td>autologous</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>autologous</td>
<td>20</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>autologous</td>
<td>3</td>
</tr>
<tr>
<td>Synovial Tissue</td>
<td>autologous</td>
<td>4</td>
</tr>
<tr>
<td>IPS Cells</td>
<td>autologous</td>
<td>2</td>
</tr>
</tbody>
</table>

As of April 2014, MHLW
Government policy

- Integrated support from basic to clinical research
- Development of infrastructure to promote regenerative medicines
- Support utilizing iPS cells as a drug-discovery tool

Regenerative Medicine Promotion Act
(Enacted in May 2013)

Goals for the next 7 years
- Apply new drugs developed by iPS cells technology in clinical trials
- Increase the number of approved cellular therapeutic products
- Expand the target of illness in clinical trials
- Develop equipment or devices related to regenerative medicines
Background for new legislations

1. Needing legal basis for the guideline to secure safety of stem cell therapies
2. Growing need for collaboration between medical institutions and industry from the early stage of development

New legislation is needed for prompt and safe regenerative medicine.
→ Act on the Safety of Regenerative Medicine

3. The existing framework in Pharmaceutical Affairs Law does not fit for the characteristics of regenerative and cellular therapeutic products

Definition of regenerative and cellular therapeutic products and establishment of new framework are needed
→ Revised Pharmaceutical Affairs Law (name change to PMD. Act)
New legislative Framework

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the Regenerative Medicine Promotion Act, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

• Revision of the Pharmaceutical Affairs Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)

• The Act on the Safety of Regenerative Medicine

These two acts are scheduled to be enacted on 25 November 2014

Other related governmental policy:
• Healthcare and Medical Strategy Promotion Act (2014.5)
• Japan Medical Research Development Institution Act (2014.5)
# Regenerative Medicine regulation (comparison)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Japan</th>
<th>Corresponding regulation</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTN for <strong>technique</strong> (other than product IND) and medical practices</td>
<td><strong>Act on the Safety of Regenerative Medicine</strong></td>
<td></td>
<td>○ FDC Act. (IND/IDE)</td>
<td>○ ATMP regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ PHS Act. Section 361</td>
<td>○ IMP (EC Directive 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ Facility, cell collection, safety, manufacturing quality system (CFR 21 CFR1271)</td>
<td>□ Hospital Exemption ※</td>
</tr>
<tr>
<td>IND for <strong>product</strong> R&amp;D and <strong>NDA</strong> process</td>
<td><strong>Revised Pharmaceutical Affairs Law (PMD. Act)</strong></td>
<td></td>
<td>○ FDC Act. (IND/IDE)</td>
<td>○ ATMP regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ PHS Act. Section 351 (biologics review)</td>
<td>□ IMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ FDC Act (device review)</td>
<td>□ ATMP Regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ Facility, cell collection, safety, manufacturing quality system (CFR 21 CFR1271)</td>
<td>□ Product review</td>
</tr>
</tbody>
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Two Acts regulating regenerative medicine & cell therapy

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

The Act on the Safety of Regenerative Medicine

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

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted on 25 November 2014
Rules for hospitals and clinics

High Risk (class I)

- Hospitals / Clinics
- Plan
- Submission
- Certified special committee for regenerative medicine*
- 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*
- MHLW
- Provision

Low Risk (class III)

- Hospitals / Clinics
- Plan
- Submission
- Certified committee for regenerative medicine
- MHLW
- Provision

*Certified special committee for regenerative medicine is required to have highly specialized screening expertise and third-party characteristics (roughly 10 to 15 certified special committees for regenerative medicine across the country)
Overview of the Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit plans

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain licence

Certification

Minister of Health

Certified committee for regenerative medicine

Notification (Hospitals / Clinics) or Application for a license (Firms)
Manufacturing business License, allowing to contract cell processing to licensed enterprises

• CPC outside hospital
  If physician commission cell processing to a CPC outside hospital, license or accreditation by MHLW is required
  ✔ Manufacturing Business License for Local manufacturing site)
  ✔ Manufacturing Business Accreditation for Overseas manufacturing site

License/accreditation is subject to PMDA’s site inspection and compatible to business license/accreditation of PMD Act.
## Site regulation (Regenerative Medicine)

<table>
<thead>
<tr>
<th>Facility and equipment</th>
<th>The Act on the Safety of Regenerative Medicine</th>
<th>PMD Act.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>= Requirement of Business License /accreditation</strong></td>
<td><strong>Standard stipulated by Article 42</strong>&lt;br&gt;Local: License (PMDA inspection)&lt;br&gt;Overseas: Accreditation (PMDA inspection)</td>
<td><strong>Facility &amp; Equipment Regulation (Article 23-22)</strong>&lt;br&gt;Local: License (PMDA inspection)&lt;br&gt;Overseas: Accreditation (PMDA inspection)</td>
</tr>
<tr>
<td><strong>Manufacturing Control &amp; Quality Control</strong></td>
<td><strong>Standard stipulated by Article 44 (GCTP)</strong>&lt;br&gt;(PMDA/MHLW inspection)</td>
<td><strong>GCTP (Article 23-25. 6)</strong>&lt;br&gt;(PMDA inspection)&lt;br&gt;* when product approval and every 2 years interval after approval</td>
</tr>
</tbody>
</table>

GCTP (Good gene, Cell and Tissue Manufacturing Practice) (≈ Good Tissue Practice + GMP/QMS) and facility & equipment regulation will be applicable to both types of CPCs.
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Two acts regulating regenerative medicine & cell therapy

MHLW process

Regenerative Medicine

PMDA process

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

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted in November 2014

Company driven IND and product approval system
Revision of Pharmaceutical Affairs Law

◆ **Revisions of Drugs and Medical Devices Articles**
  - Relevant party’s obligations are specified to ensure quality, safety, and efficacy of drugs and medical devices.
  - MAH’s obligation to notify labeling and its revision, reflecting the latest findings

◆ **Revisions of Medical Devices Articles**
  - Independent Chapter for “Medical Devices”
  - Expansion of Third party certification system to higher risk devices
  - Quality Management System (QMS) adherent to ISO 13485
  - Other revisions related to medical devices

◆ **Additions for Regenerative Medical Products**
  - Definition and independent chapter for Regenerative Medical Products
  - Introduction of conditional/time limited approval system
Definition of “Regenerative Medical Products” in Japanese Legislation

- **Regenerative medical products** are defined as processed 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.

Under the Revised PAL (=Pharmaceuticals and Medical Devices Act. (PMD Act.)

Cellular and Tissue based Products and Gene therapy Products

Advanced-therapy medicinal products (ATMPs)

Regulation (EC) No 1394/2007
Scope of Manipulation to be regulated

(Definition)

1. **Manipulation to be regulated**
   - Artificial proliferation and differentiation of cells and tissues
   - cell lines
   - drug treatment for the purpose of activation
   - biological properties modification
   - combination with non-cellular components
   - genetic engineering modification
   - Isolation/separation of specific cell by biological and chemical treatment with agents
   - Cells for non-homologous use

   **Slightly wider scope than “more than minimal manipulation” of USFDA**

2. **Minimal manipulations** such as, treatment with antibiotics, washing, freezing, The gamma ray sterilization, simple isolation/separation without biological and chemical treatment are **not covered by the new regulation**

Blood transfusion (blood products), Hematopoietic stem cell transplantation, Assisted Reproductive Technology, except those derived from genetic engineering, iPS cells, are also excluded from the scope of the regenerative medicine regulation.
Two authorized products under PAL
Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

**Autologous Culture Epidermis JACE**

Marketing authorization for medical device on 29 October 2007 (submission: 6 October 2004)

**Indication:** serious burns treatment (limited to the burns of more than 30% of the body surface area)

**Autologous Cultured Cartilage JACC**

Marketing authorization for medical device on 27 July 2012 (submission: 24 August 2009)

**Indication:** Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints. (limited to a defect area of over 4cm² with no alternative therapy.)
Two of the new products application under the new regulation during grace period

• According to the news released by the sponsor companies, in September and in October 2014, two new product applications for marketing authorization were filed by PMDA

1. Bone marrow mesenchymal stem cells for GVHD
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease

Note: Figures quoted from the company press release docs
Benefit and Risk Balance Assessment

• Discussion of acceptable level of clinical effectiveness vs. patient access to the new therapy
• Weighing acceptable risk against expected benefit
• Based on regulatory sciences in terms of social responsibility for public health
The Basic Concept on Regulatory Science in PMDA

For further improvement of the quality of the three services such as Reviewing, Conducting Safety and Providing relief, PMDA needs to make exact prediction, assessment, and judgment based on convincing evidence adopting the latest scientific knowledge, and so, promotion of regulatory science research does become important.

(The Basic Concept on Regulatory Science in PMDA, Aug 10, 2011)
More comprehensive and stronger “Regulatory Science Bridge” will help us develop a drug in the future

# Early Access schemes of ICH 3 parties

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
<th>JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review</td>
<td></td>
<td>Priority review</td>
</tr>
<tr>
<td>Accelerated approval for serious or life-threatening illnesses</td>
<td>Conditional MA MA under exceptional circumstances</td>
<td>Conditional Approval for Oncology drug, Orphan drug Conditional &amp; Time-limited approval for regenerative medicine</td>
</tr>
<tr>
<td>Break through therapy &amp; Fast Track designation</td>
<td></td>
<td>Forerunner Review Assignment</td>
</tr>
</tbody>
</table>

Various agencies have various approaches to accommodate patient access though they have certain similarity.
How to expedite R&D and review for cellular and tissue based product

• Designed for unmet needs under the present treatment: limited number of patients available for CT
• Difficult to conduct controlled study to demonstrate “true end point” of clinical benefit
• Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug pathway too much?
To secure timely provision of safe regenerative medicines, a new regulatory framework is needed.

After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.
**Expediting approval system under PMD Act**

[Traditional approval process]

- Clinical study
- Phased clinical trials (confirmation of efficacy and safety)
- Marketing authorization

[New scheme for regenerative medical products]

- Clinical study
- Clinical trials (likely to predict efficacy, confirming safety)
- Conditional/term-limited authorization
- Marketing (Further confirmation of efficacy and safety)
- Re-application within a period (max. 7y)
- Marketing authorization or Revocation
- Marketing continues

*Post-marketing safety measures must be taken, including prior informed consent of risk to patients*
Review Pathway of regenerative medical products

Application and review flow of regenerative medical product under the PMD Act. (revised PAL)

Sponsor → Pharmaceuticals and Medical Devices Agency (PMDA)

If the application meets to the criteria (biological heterogeneity, etc.)

Conditional/time-limited authorization path → Review Report → Ministry of Heath, Labour & Welfare (MHLW)

Marketing authorization (conditional time-limited)

Normal authorization path → Advisory Committee (Pharmaceutical & Food Sanitation Council)

Marketing authorization (normal)

Likely to predict efficacy (clinical benefit)

- To approve products based on the limited data, such as surrogate endpoints in exploratory study.

- Similarity to accelerated approval of USFDA * The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (ref.)

- We have experiences in the orphan drug area.

Ref.) USFDA--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (57 FR 58958, Dec. 11, 1992)

- It applies to certain new drug products in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.
- Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- The drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.
- Approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit (such as OS).
- Postmarketing studies would usually be studies already underway.
- FDA may withdraw approval, if a postmarketing clinical study fails to verify clinical benefit; ............
Evidence level of efficacy: Drug (normal) vs. HCT/P

Drug (normal) vs. HCT/P

Mandatory:

- Drug (normal) approval
- Orphan level
- Marketing authorization

Optional:

- PMD Act. (Regenerative medical products)
- Approval
- Conditional and time-limited approval
- IND level

In the case where other effective therapy is not available for the target indication
Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act.

<table>
<thead>
<tr>
<th>Conditional and time limited approval</th>
<th>Biological device</th>
<th>Regenerative medical products</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>NA</td>
<td>√</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Drug Reaction Relief Fund</th>
<th>Biological device</th>
<th>Regenerative medical products</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>NA</td>
<td>√</td>
</tr>
</tbody>
</table>

| Infection Relief Fund             | √                 | √                           |

Private Insurance products will be available for clinical studies under the Act on the Safety of Regenerative Medicine
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Consistent parts of the two Acts

Medical technologies using processed cells (except clinical trials under PMD Act.)

The Act on the Safety of Regenerative Medicine

- Manufacturer (Licensed)
- Outside hospital
- Cell processing
- Commission
- Hospital
- Cell collection
- GCTP
- Cell Processing

Regenerative Medical Products

PMD Act. (revised PAL)

- Manufacturer (Licensed)
- Obtaining Cell
- Cell Processing
- Delivery of cell product
Structure of GCTP

Management & Supervision System
(shipment, deviation, change control, self-inspection, Training/education, complaint management, recall)

Product quality review

- Quality control system (labo. system)
- Supplier control system

Validation / Verification
- Manufacturing control system (operation performance of process, Sterility assurance, Product quality monitoring)
- Facility & equipment system (qualification, calibration, maintenance)

Document management system
(Product master file, specification, statement, SOPs, record)

Reflecting product marketing authorization documents

Quality Risk Management/ Knowledge management
GCTP (Good gene, Cell & Tissue Manufacturing Practice)

Quality System Requirement for regenerative medical technologies / products, considering the characters of these products; such as raw materials that cannot be sterilized

- Quality Risk Management
- Manufacturing Control (Sterility assurance, Prevention of Cross-contamination..)
- Quality control (Verification / validation, Quality review)
- Facility requirement

It is necessary to consider whether the risk is manageable,
- not only from the facility point of view,
- but from the effects of the manufacturing operation, such as the evaluation of performance.
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Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death
- Shortage of funds, Knowledge on Regulation and developmental strategy

Consultation on quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety

Consultation on endpoints or sample size of early clinical trial

Flow of Strategy Consultation
- Introductory Consultation (684)
- Pre-Consultation (813)
- Face-to-Face Consultation (209)
(7/1/2011 – 6/30/2014)
Basic Scientific Issues for Early Product Development, Evaluation and Control

- Justification of source and selection of human cells that serve as raw materials including autologous or allogeneic donor screening criteria and eligibility

- Justification of source and selection of animal materials that serve as culture medium, scaffold, etc. in terms of virus inactivation/removal and ruminant prion transmission

Required to conform to “Minimum requirement for biological source materials” (Minister Notification May 2003 – revised September 2014)
PMDA’s Experiences: Frequently asked Issues on Designing Clinical Studies during consultation

- Clinical Indications, positioning with respect to existing treatment line
- Identifying patient population (Inclusion and exclusion criteria)
- Suitability of efficacy endpoints
- Effect of co-administered drugs or surgery
- Difficulty in setting parallel control arms
- Difficulty in keeping blindness due to surgical operations
- How to set threshold: Availability of historical data on target diseases, Availability of clinical data of similar products
- Number of patients
  - Limited number due to severity of disease/therapeutic line
  - Limited manufacturing capacity and target diseases
  - Limited surgical proficiency for transplantation
- Feasibility of MRCT including Japanese
- Methods of post-marketing long term data collection to demonstrate effectiveness
## Case of Face to Face consultation

<table>
<thead>
<tr>
<th>Consulter</th>
<th>Product under development</th>
<th>Intended performance, Intended use, Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Neuroscience, NCNP Department of Molecular Therapy</td>
<td>Morpholino oligos (Antisense)</td>
<td>Remedy for Duchenne muscular dystrophy (DMD)</td>
</tr>
<tr>
<td>Shin’ich Takeda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Medicine and Therapy, Medicine (ART), Tohoku University School</td>
<td>PAI-1 Inhibitor (TM5509)</td>
<td>Hematogenic recovery of cord blood transplantation</td>
</tr>
<tr>
<td>of Medicine, Toshio Miyata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Center for iPS Cell Research and Application (CiRA), Kyoto University,</td>
<td>iPS Cell (Allo)</td>
<td>Starting Materials for cellular &amp; tissue based products derived from iPS Cells</td>
</tr>
<tr>
<td>Shinya Yamanaka</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sapporo Medical University, Osamu Honmou</td>
<td>Mesenchymal Stem Cell (Auto)</td>
<td>Improvement of neurological sign, activities of daily living disorders in daily activities, and dysfunction associated with Stroke</td>
</tr>
<tr>
<td>CYBERDYNE INC.</td>
<td>ROBOT SUIT HAL (Hybrid Assistive Limb®) and partial Equipment</td>
<td>Devices for assistive movement with in patients. Planed to introduce models which differ in intended use or indications.</td>
</tr>
<tr>
<td></td>
<td>for the subset of function of HAL used for movement training</td>
<td></td>
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We have been given scientific advices to the sponsors, based on the scientific discussions, related to the Science Board.
Contents

• Overview of environment, current regulation, policy of regenerative medicine in Japan
• The Act on the Safety of Regenerative Medicine
• The Act on Pharmaceuticals and Medical Devices (PMD Act – revised PAL)*
• Quality Assurance
• Consultation Mechanism
• Guidance for CMC, pre-clinical and clinical development
Preclinical review and requirement

• Consultation (Scientific advice)

• Clinical Trial Notification Review

• Review Process
Somatic Cells/Stromal Cells

Selection of Cells that are Suitable for Reprogramming etc.

Cell Line

Relevant Pluripotency to Differentiate into the Target Cells, Potency of Self-Renewal

Cell Bank

Potential of Differentiation to Next Target Cells, Potency of Self-Renewal, Stability

Intermediate(s)

Relevant Cells Can Be Processed (e.g. differentiate) to Desired Product

Final Products

Serving Innovative treatments for Sevier Diseases, Marked loss of QOL or Lack of Existing Relevant Therapies

Evaluation of Q/S/E

Inactivation and/or Elimination of Undifferentiated Cells

Characterization, Constant Supply, Stability & Renewal

Characterization, Stability

Source, Biological Features, Biological
System of general guidelines for quality and safety (pre-clinical) for Human Cell & Tissue-Based Products since 2000.

- **Standard for Biological Ingredients**

- **General Principles for the Handling and Use of Cells/Tissue-Based Products**
  - PFSB/MHLW Notification No.1314 Appendix1 (2000)

- **Guideline on Ensuring Quality and Safety of Products Derived from Engineered Human Cells/Tissue**
  - PFSB/MHLW Notification No.1314 Appendix 2 (2000)

- **Guideline on Ensuring Quality and Safety of Products Derived from Processing Human (Autologous) Cells/Tissue**
  - PFSB/MHLW Notification No.0208003 (2008)

- **Guideline on Ensuring Quality and Safety of Products Derived from Processing Human (Allogenic) Cells/Tissue**
  - PFSB/MHLW Notification No.0912006 (2008)

- **Guideline on Ensuring Quality and Safety of Products Derived from Processing: Human (Allogenic) Somatic Stem Cells**
  - PFSB/MHLW Notification No.0906-3 (2012)

- **Guideline on Ensuring Quality and Safety of Products Derived from Processing: Human (Allogenic) iPS-like Cells**
  - PFSB/MHLW Notification No.0906-5 (2012)

- **Guideline on Ensuring Quality and Safety of Products Derived from Processing: Human Embryonic Stem Cells**
  - PFSB/MHLW Notification No.0906-6 (2012)
Structure of the Q/S GLs

Chapter 1 General Rules

Chapter 2 Method of Manufacture

1. Raw Materials and Manufacture-Related Substances
   1. Starting cells/tissue for desired cells
   2. Raw materials and manufacture-related substances other than starting cells/tissue of desired cells

2. Manufacturing Process

3. Quality Control of Final Products

Chapter 3 Stability of Products

Chapter 4 Non-Clinical Safety Study of Products

Chapter 5 Studies to Support the Effect/Performance of Products

Chapter 6 Biodistribution/Localization in the Body

Chapter 7 Clinical Study
# Related Specific Guidelines for Products Evaluation

**Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue**

|-------------------|------------------|

**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)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)

**The Science Board Report. PMDA.**

- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials (2013)
Establishment of Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.
Outcome of the Science Board

Cellular & Tissue-based Products
- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials (Aug. 21, 2013)

Pharmaceuticals, Biologics
- Summary of Discussion on Non-clinical Pharmacology Studies of Anticancer Drugs (Dec. 10, 2013)
- Summary of the discussion on assessment of the current status of personalized medicine relating to drug development and review (Mar. 11, 2014)

The Science board outcome is to be contributed to resolve questions expected in the scientific consultation during development.
The Science board discussion, further

• Further to the discussion in the last term, in the present term following immediate discussion is on-going to support scientific consultations and reviews of PMDA:

1. Drugs
   - Necessity and condition of placebo-controlled trials for diseases under unmet medical needs
   - Effective utilization animal models for non-clinical testing to demonstrate POCs

2. Medical Devices
   - Application of numerical analysis for non-clinical testing
   - Evaluation of medical devices for pediatric use (including application of non-clinical testing)

3. Cellular & tissue-based products
   - Manufacturing and quality of cellular products during the early development in cell processing centers
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>November 2013</td>
<td>Promulgation of two laws</td>
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<tr>
<td>6 August 2014</td>
<td>Release cabinet and ministerial ordinances</td>
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<tr>
<td>12 August 2014 onward</td>
<td>Release guidance notifications: submission, GLP, GCP, GPSP, CT notification, CT AE reports, ADR/Defect reports, Labelling, periodic report, GCTP......</td>
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<tr>
<td>25 November 2014</td>
<td>Enactment of two laws</td>
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(So far 32 technical guidance have been notified, 20 more by the end of November)
Summery

• In line with the commitment of the administration, Japan is undergoing regulatory reform to support and accelerate R&D of regenerative medicine

• Expedite the access to new promising regenerative medicine in a safe and effective manner

• PMDA will also facilitate R&D by giving scientific/regulatory advice to the sponsors from early stage of development
Where to find information?

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Literature available in English: