Exposition of New Regulation in the Revision of Pharmaceutical Affairs Law - For Correct Understanding of “Conditional & Time Limited Approval”

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Current Health research regulations in Japan

Health Research

Clinical Trials

Sponsor-Investigator Health Research

Clinical Trials under PAL

Sponsor-Investigator CTs

Company-sponsor CTs

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
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 & 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)

108 protocols approved (as of November 2014)

Cellular/Tissue based Products

2 marketed products
- JACE (autologous cultured epidermis)
- JACC (autologous cultured cartilage)

12 clinical trials initiated (including 3 gene therapy products) (~October 2014)

Medical care

Cancer immunotherapy

Six types of therapy are currently provided in approved university hospitals as “advanced care”
* Partially covered by national health insurance

Covered by MHLW

Covered by MHLW and PMDA

Pharmaceutical Affairs Law (PAL)
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)
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 human 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 (=Pharmaceutical 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

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

**Autologous Culture Epidermis JACE**

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

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

**Autologous Cultured Cartilage JACC**

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.)

Marketing authorization for medical device on 27 July 2012 (submission: 24 August 2009)
The Pharmaceuticals and Medical Devices Act (PMD Act)

- Separate category and definition of “regenerative medical products”

Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells.

To secure timely provision of safe regenerative medicines, a new regulatory framework is needed.

Expeditied approval system for regenerative medical products

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.
Expedited approval system under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, such as non-uniform quality reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]

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

[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)
- Marketing authorization or Revocation
- Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
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)
Evidence level of efficacy: Drug (normal) vs. HCT/P

If there is no effective treatment available for the target population of the disease:

- Drug (normal)
  - Marketing authorization
  - IND level
  - Some cases: statistical uncertainty
  - Orphan level
  - Confirmatory study
  - Exploratory study

- PMD Act. (Regenerative medical products)
  - Marketing authorization
  - IND level
  - Conditional and time-limited approval
  - Exploratory study
  - Confirmatory study
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
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

It may be similar to researcher initiated IND application system
Overview of the Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit plans to the Ministry

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain licence

Provision of regenerative medicine

Cell processing

Hospitals / Clinics

Cell processors

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.
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
- Cell processing
- Transplant

Regenerative Medical Products

PMD Act. (revised PAL)

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

- **Be independent:** depend neither on drug rules nor on device rules. **You have to decide for yourself!**
- **Mode of Action (MOA):** How to demonstrate pre-clinical MOA beyond the difference of spices?
- **Quality:** limited information on characterization of bio-products in early stage and quality control under GMP/GCTP (validation, scale) at approval time
- **Translational bridge (from hospital to manufacturers):** coordinate modality of the GCTPs of both Acts and share knowledge & experiences
- **Continuation of clinical study:** RCT may be difficult for confirmation (single arm study or observational case study with pre-agreed threshold)
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 Appendix 1 (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)

Guidelines on Ensuring Quality and Safety of Products Derived from Processing:
- Human (Autologous) Somatic Stem Cells
  PFSB/MHLW Notification No.0906-2 (2012)
- Human (Autologous) iPS-like Cells
  PFSB/MHLW Notification No.0906-4 (2012)

Guidelines on Ensuring Quality and Safety of Products Derived from Processing:
- Human (Allogenic) Somatic Stem Cells
  PFSB/MHLW Notification No.0906-3 (2012)
- Human (Allogenic) iPS-like Cells
  PFSB/MHLW Notification No.0906-5 (2012)
- Human Embryonic Stem Cells
  PFSB/MHLW Notification No.0906-6 (2012)

Good Tissue Practice
Basic Technical Requirements
### Related Guidelines for Products 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)
- 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)
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)
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
Schedule

• November 2013 Promulgation of two laws

• 6 August 2014 Release cabinet and ministerial ordinances

• 12 August 2014 onward Release guidance notifications: submission, GLP, GCP, GPSP, CT notification, CT AE reports, ADR/Defect reports, Labelling, periodic report, GCTP......

(So far 38 technical guidance have been notified, 10 more by the end of November)

• 25 November 2014 Enactment of two laws
Summery

• In line with the commitment of the administration, Japan is undergoing regulatory reform to support and accelerate R&D of regenerative medicine
• To expedite the access to new promising regenerative medicine in a safe and effective manor
• PMDA will also facilitate R&D by giving scientific/regulatory advice to the sponsors from early stage of development
Thank you for your attention

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Literature available in English: