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Updates on global movement in regulation of Advanced Therapeutics

13 January 2016

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Pharmaceuticals and Medical Devices Agency, Japan
Contents

• Introduction
• New regulatory Framework for Cell therapy
• Examples of Review
• Quality System Requirement
• Facilitate Development
Japan’s Performance on NDA Review

New active substance (NAS) median approval time for six regulatory authorities in 2004-2013

CIRS (Centre for Innovation in Regulatory Science) R&D 55 http://cirsci.org/node/73
NEW REGULATORY FRAMEWORK for Cell Therapy Products
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 Affaires Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)**

- **The Act on the Safety of Regenerative Medicine**

These two acts were 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)
Background for New Legislations (came into effect on 25 November 2014)

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 was needed to enhance safety of regenerative medicine.
→ The 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 medical products and establishment of new framework were needed.
→ Revision of the Pharmaceutical Affairs Law (name changed to The Pharmaceuticals, Medical Devices Act (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

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

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain licence

So far 41 facilities have got licenses (30 November 2015)
**Rules for hospitals and clinics**

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

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

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

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

Production and marketing of regenerative and cellular therapeutic products by firms

Commercial IND and product approval system

* Two laws will be enacted in November 2014
Regenerative medicine & cell therapy in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Pharmaceuticals and Medical Devices Act. (PMD Act.)

**Academic Research Purpose**

Clinical Research using human stem cells

108 protocols approved
(as of November 2014 - before new legislation)

**Commercial Product Marketing Authorization Purpose**

Cellular/Tissue based Products

4 approved marketed products

22 clinical trials initiated (including 8 gene therapy products)
(〜October 2015)

Under the new legislation, as of 30 November 2015:
70 new clinical research plans,
1820 medical care plans have been notified to MHLW

Covered by MHLW

Covered by MHLW and PMDA

Medical care

Covered by MHLW
Regenerative Medical Products in the PMD Act

Former Pharmaceutical Affairs Law (PAL)

PMD Act (Revised PAL)

◆ 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 live human/animal 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 ("Processed cells") 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.
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 clinical benefit
- Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug guidelines too much?
PMDA’s Philosophy (September 2008)

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions. We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.
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
# Early Access schemes of ICH 3 parties

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

Various agencies have various approaches to accommodate patient access.
US Accelerated approvals and development in Japan (drugs for life-threatening disease and unmet medical needs)

- Superior clinical benefit at Phase II study
- Orphan designation applicable

Accelerated approval

Confirmed Effectiveness

Withdrawal

Phase I

Phase II

Phase III

Foreign Phase I

Foreign Phase II

Local Phase I

Local Phase II

Review
US Break through therapy designation and Japanese drug development (Nobel MOA, higher efficacy)

Development lag has been expanded by the regulatory system difference
Conditional Marketing Authorisation of EU

1. Scope: medicinal products for
   • Seriously debilitating or life-threatening diseases
   • Emergency threats (WHO, EU Commission)
   • Orphan medicinal products

2. A Conditional MA may be granted when, although comprehensive clinical data have not been provided, all of the following requirements are met:
   a) Benefit/Risk balance is positive
   b) It is likely that comprehensive clinical data will be provided
   c) Unmet medical needs will be fulfilled
   d) Benefit to public health of immediate availability outweighs risks that additional data are still required

3. Conditional MA will be subject to specific obligations to complete ongoing studies, or to conduct new studies with a view to confirming the positive Benefit/Risk balance.

4. Such authorisation shall be valid for one year, on a renewable basis.

5. Financial penalties in case of infringement of the specific obligations
Concept of Adaptive Pathways

• Expand access of the new drug to the patient population in a staged approach

The goal of this concept is to expedite access
Pharmaceuticals and Medical Devices Agency

Pre-clinical Data

Clinical Data
(No. of Patients)

CT NDA

Marketing authorization

Unknown Adverse Event

Drugs for chronic disease

Adaptive licensing model

e.g. VIOXX

Unknown Adverse Event

Unknown Adverse Event

Unknown Adverse Event

Pharmaceuticals and Medical Devices Agency
Pharmaceuticals and Medical Devices Agency

**Expedited approval system under PMD Act**

**[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 continues
- Re-application within a period (max. 7 years)
- Marketing authorization or Revocation
- Marketing continues

*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.

Post-marketing safety measures must be taken, including prior informed consent of risk to patients.

Pharmaceuticals and Medical Devices Agency
Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act.

**Very Japan specific regulation!!**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Biological device</th>
<th>Regenerative medical products</th>
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</thead>
<tbody>
<tr>
<td>Conditional and time limited approval</td>
<td>NA</td>
<td>✓</td>
</tr>
<tr>
<td>Adverse Drug Reaction Relief Fund</td>
<td>NA</td>
<td>✓</td>
</tr>
<tr>
<td>Infection Relief Fund</td>
<td>✓</td>
<td>✓</td>
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</table>

Private Insurance products will be available for clinical studies under the Act on the Safety of Regenerative Medicine.
Further acceleration......
SAKIGAKE Designation System

– To put innovative products into practice in Japan first in the world –

Designation Criteria
- Medical products for diseases in dire need of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

Designation Advantage
1. Prioritized Consultation [Waiting time: 2 months → 1 month]
2. Substantialized Pre-application Consultation [de facto review before application]
3. Prioritized Review [12 months → 6 months]
4. Review Partner [PMDA manager as a concierge]
5. Substantial Post-Marketing Safety Measures [Extension of re-examination period]

Designation Procedure
1. Initiation by applicant
2. Initiation by the MHLW
General Timeframe of Forerunner Review Assignment

【Standard】
- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies
  - Clinical trials I/II
  - Consultation on Clinical trials
  - phase III study
  - Review
  - Reimbursement
  - Post Marketing

① Priority Consultations
② Prior-review
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

【Forerunner】
- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies
  - Clinical trials I/II
  - Consultation on Clinical trials
  - phase III study
  - Prior review (rolling submission)
  - Review

※ In some cases, may accept phase III data during review

Practical application of Innovative medical products

Pharmaceuticals and Medical Devices Agency
Pilot scheme for FY2015 review under SAKIGAKE designation system (Timeline)

• The pilot project started in May 2015 for pharmaceuticals.
• Finally, 6 products were assigned for “Sakigake” on 27 October 2015.
• The schemes for medical devices and regenerative products follow in January 2016.
• Based on this pilot, we will consider expansion of full “Sakigake” in the future.
Examples of Product review
(specific points to consider for cellular therapy products)
Two authorized products under PAL
Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

**Autologous Culture Epidermis JACE**

- Transplantation of autologous cultured epidermis
- Skin biopsy
- Skin specimen
- Isolation of keratinocytes
- Sheet formation
- Cell seeding/ inoculation
- 3T3-J2 feeder cells

**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**

- Transplantation of autologous cultured cartilage (knee-joint)
- Area of detectible cartilage
- Collection of cartilage
- Cartilage specimen
- Cultured cartilage embedded in alarcollagen gel (about four weeks)
- Collection of periosteaum
- Cultured cartilage transplanted and covered with periosteaum

**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)
Two of the new product approvals under the new regulation (Update)

- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD (**normal approval**)
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease (**conditional and time-limited authorization** – 5 years, conducting post-marketing efficacy studies)

Note: Figures quoted from the company press release docs
Quality concept of hCTPs

Bio-pharmaceuticals

hCTPs

- Source materials, process variability
- In-process control
- Characterization
- Specification

- Difficult to cover every aspect of quality by specification
- Limited information can be obtained from characterization and specification
- Much more rely on in-process control to control quality
Safety assessments for cellular/tissue-based products

1. Inadvertent transformation
2. Effect by active-substances produced from-cells or tissues
3. Effect on normal cells or tissue
4. Inadvertent formation of ectopic tissue
5. Undesirable immunological reactions by products
6. Tumorigenicity or Carcinogenicity
7. Safety evaluation based on guidance for products for gene therapy, when the products have transgenes.
8. General toxicity
9. Effects on vital organs
10. Safety evaluation on impurities from manufacturing processes
### General considerations for general toxicity study

- **Cellular/Tissue based product**
  - Species differences in biological reaction
  - Heterogenous immune responses
  - Inappropriateness of conventional TK/ADME study

- **Products for gene therapy**
  - Species differences in infectivity or transduction efficiency
  - The determination of NOAEL
  - Dose-limiting toxicity
  - Worst-case scenario

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**Hazard Identification**

**Risk assessment**
Testing for tumorigenicity

*in vitro* Testing
- Karyotype → Genetic stability
- Soft agar colony formation assay → Proliferation independent on adhesion

*in vivo* Testing
- Testing using immuno-deficient animals → Tumorigenicity in vivo

The necessity should be considered on a case-by-case basis depending on the product characteristics.
Evidence Level of Efficacy: Drug (normal) vs. HCT/P

If there is no effective treatment available for the target population of the disease.
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)
Safety and Efficacy evaluation of limited number of subjects in the trial for conditional approval

- Challenge on new designs and statistical methodologies for small population
- How to secure evidence level
  - Design: controlled? / blinded? possibility?
  - Clinical endpoint (efficacy): clinical significance, objectiveness, surrogacy, etc.
- At least, Maximize the information from a single subject in terms of safety and efficacy.
- Post-marketing study, further confirmatory study?
Challenges of Conditional and Time-limited Authorization

• **Clinical study in post-marketing**: RCT may be difficult for confirmation in some cases (single arm study with pre-agreed threshold or observational case / control study) in the postmarketing settings
  - monitoring, collection and use of real-world data, post-authorisation, as a complement to RCT data (like Adaptive pathway of EU)

• **Reimbursement**: Question on consistency with regulatory approval and on acceptance of clinical data for HTA payers (Pricing for the two products were set by Central Health Insurance Council on 18 November 2015)

• **CMC and quality assurance**: limited qualification in early stage and quality control under GMP/GCTP (validation, scalability, comparability)
Quality System Requirements

GMP type regulation
Consistent parts of the two Acts

GCTP = Good gene, Cell, Tissue based Product Manufacturing Practice

The Act on the Safety of Regenerative Medicine
Medical technologies using processed cells (except clinical trials under PMD Act.)

PMD Act. (revised PAL)
Regenerative Medical Products

Manufacturer (Licensed)
Outside hospital
Cell processing
Commission
Hospital
Cell collection
Cell processing
Transplant
GCTP
Manufacturer (Licensed)
Obtaining Cell
Cell Processing
Delivery of cell product
再生医療法
薬機法
Overall picture of CMC development

【Typical Development】

Non-Clinical Study

Phase 1

Clinical Study

Phase 2

Early access review timeline

Approval

Post-Approval

Target product Profile

Establishment of Design Quality and Product Quality by CMC study

Process Validation

Control Strategy

Control strategy

Control strategy

Control strategy

Quality Attributes

CQA

Process Parameters

CPP

Consistency

Equivalency

Knowledge Control/Quality Risk Management

Investigational Product GMP

GMP
Key Consideration of GCTP

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.
Facilitate Development
Scientific Advice Scheme
Pharmaceutical Affairs Consultation on R&D Strategy for scientific advice

- Basic Research: Pharmaceuticals and Medical Devices candidates
- Strategic Consultation:
  - Quality Study
  - Non-Clinical Study
  - Clinical Trial (Up to POC studies)

Consultation on:
- Quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety
- Endpoints or sample size of early clinical trial

Further studies are handled by the Regular Consultation

Flow of Strategy Consultation:
- Introductory Consultation (744)
- Pre-Consultation (900)
- Face-to-Face Consultation (258)
  (7/1/2011 – 9/30/2014)
Pharmaceutical Affairs Consultation on R&D Strategy (category)

N of consultation

- **Regenerative medicine**
- **Medical Devices**
- **Drugs**

<table>
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<tr>
<th>Year</th>
<th>Consultations</th>
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<td>FY2012</td>
<td>20</td>
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<tr>
<td>FY2013</td>
<td>120</td>
</tr>
<tr>
<td>FY2014</td>
<td>80</td>
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66 consultations come under regenerative category in FY2015
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 Considers 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)
Outcome of the Science Board of PMDA

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:

- 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 (21 August 2013)
  - Manufacturing and quality of cellular products during the early development in cell processing facilities (14 August 2015)
PMDA for the world

-To create society to receive the essential forefront medicines-

Swift approvals of innovative products

Full measures by use and application of medical information

Japanese citizens

Relief

Convey Japanese technology to the world

Cooperate with all agencies in the world

Swift relief for occurred health damage

Contribute to the world’s medicine

Regulatory Science

Review
Thank You for your attention!

Daisaku Sato, Ph.D.
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Thanks to my colleagues of Office of Cellular and Tissue-based Products

Literature available in English:


*Pharmaceuticals and Medical Devices Agency*