

Regulatory Perspectives of Japan

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1. Government's Policy

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

Ministry of Education,
Culture, Sports, Science and
Technology

Basic research

Cabinet Office establishes basic strategy, and each ministry collaborates to promote regenerative medicines

Ministry of Health,
Labour and Welfare
(MHLW)

Clinical trials

Ministry of Economy,
Trade and Industry

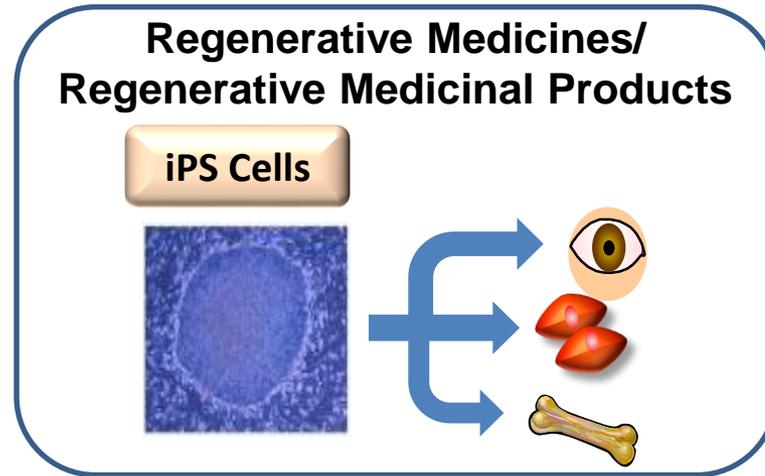
Establish
industrial
base

**Regenerative Medicine Promotion Law
(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

2. Two Acts Regulating Regenerative Medicines

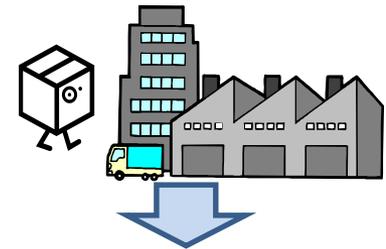


Providing regenerative medicines within hospitals and clinics



The Act on the Safety of Regenerative Medicines

Producing regenerative and cellular therapeutic products in firms

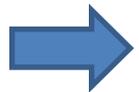


Amendment of Pharmaceuticals Affairs Act (PAA)

* The Amended Pharmaceutical Affairs Act and the Act on the Safety of Regenerative Medicine were enacted in November 2013, and will be enforced within 1 year

3. Background of New Legislations

1. Current guideline is not based on the law
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

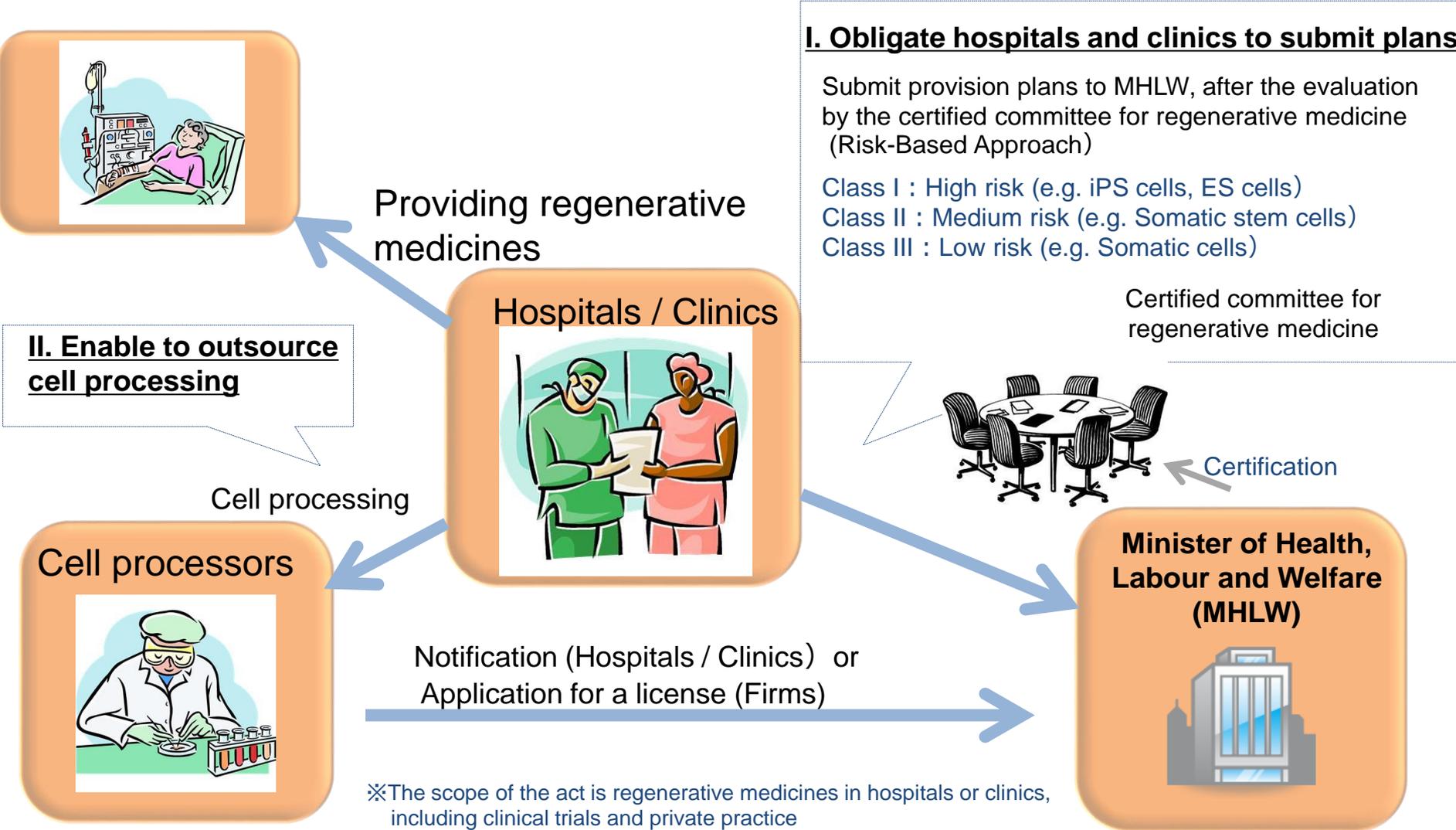
3. The existing framework in Pharmaceutical Affairs Act does not fit for the characteristics of regenerative and cellular therapeutic products



Definition of regenerative and cellular therapeutic products and establishment of new framework are needed

→ Amend Pharmaceutical Affairs Act (name change to PMD Act)

4. Overview of the Act on the Safety of Regenerative Medicine



5-1. Amendment of Pharmaceutical Affairs Act

◆ **Strengthen Safety Measures regarding Drugs, Medical Devices**

- Specify relevant party's obligation to ensure quality, safety, and efficacy of drugs and medical devices.
- MAH's obligation to notify revised Package insert reflecting the latest findings

◆ **Regulation suited specifically for Medical Devices**

- Independent Chapter for "Medical Devices"
- Third party certification system
- Quality Management System (QMS)
- Other revisions related to medical devices

◆ **Regulation suited specifically for Regenerative Medicinal Products**

- Creation of the regulations for Regenerative Medicinal Products
- Introduction of approval system with condition/period

5-2. The Act on Pharmaceuticals and Medical Devices (PMD Act)

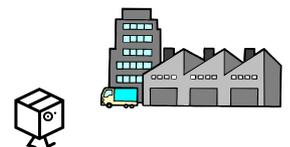
Background of the amendment of Pharmaceutical Affairs Act

Difficult to gather and evaluate the data for efficacy of regenerative and cellular therapeutic products in a short time

➔ To secure prompt and safe provision of regenerative medicine, new framework is needed

Expedited approval system for regenerative medicinal products

After the safety is confirmed and efficacy is assumed, products will be approved with conditions and a limited term in order to enable prompt provision of the products to patients.



5-3. Regulatory Framework

Marketing authorization of the products derived from processed human cells/tissues are regulated by the PMD Act and related regulatory documents.

1. Pharmaceuticals & Medical Devices Act

2. MHLW Ministerial Notification

3. MHLW Ministerial Ordinance

4. MHLW Administrative Letters

- Japanese Pharmacopoeia (JP), PAA 41
- Standards for Biological Ingredients, PAA 42
- Minimum Requirements for Vaccines, Antitoxins and Blood Products, PAA 42
- Good Clinical Ordinance (GCP)
- Good Post-Marketing Surveillance Practices (GPMSP)
- Notifications

5-4. Guidelines

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 Cells

- 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)

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)

5-5. Definition of “Regenerative Medicinal Products” in PMD Act

<Chapter 1 Article 9>

Provisional Translation

The term “Regenerative Medicinal Products” (as “SAISEI-IRYOU-TOU-SEIHIN” 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 or functions** of human or animal body.  Regenerative Medicinal Products

B To **treat or prevent disease** in humans or animals.

 Cell Therapy Products

(2) The articles which are **intended to use in the treatment of disease** in humans or animals, and are **transgened to express in human or animal cells**.  Gene Therapy Products

5-6. Definition of Cell/Tissue Processing

Provisional Translation

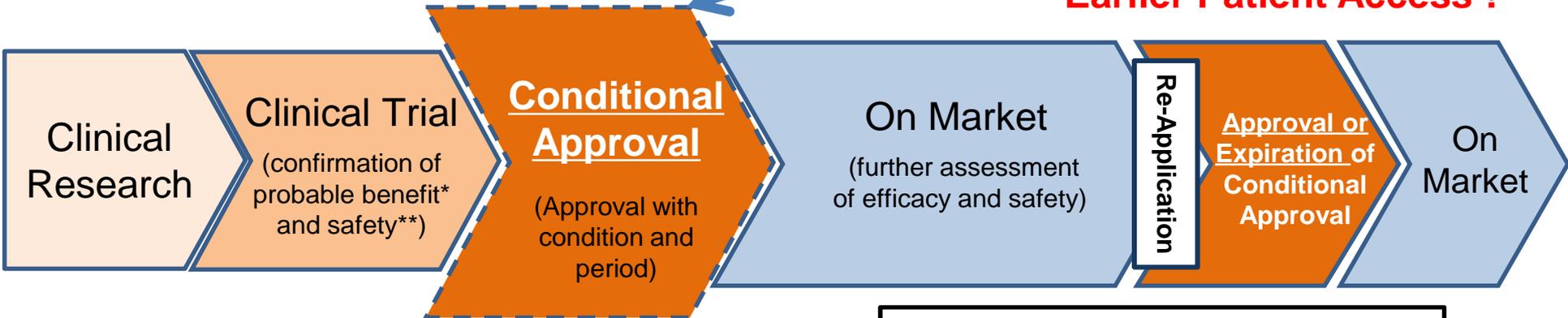
- Any processing of a cell or tissue with the aim of treating a patient, repairing or regenerating tissue, which includes
 - propagation and/or differentiation of a cell or tissue,
 - production of a cell line,
 - pharmaceutical or chemical treatment to activate cell,
 - altering a biological characteristic,
 - 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 γ -irradiation, freezing, thawing, and such similar procedures regarded as minimal manipulations are **NOT** considered to be processing.

5-7. New Approval System in PMD Act

【Previous Pathway of Approval System】



【New Pathway of Approval System】



※ Leading to Earlier Patient Access !

Informed Consent through the explanation of possible risk with taking post-market safety measures

* Probable benefit: Assumption of efficacy with small patient population.
 ** Safety: Earlier detection and evaluation of adverse events.

For more information,
Please visit the PMDA website
<http://www.pmda.go.jp>



A screenshot of the PMDA website homepage. The header includes the PMDA logo, the text '独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency', and a language selector set to 'English'. The main content area features a navigation menu on the left, a central banner with 'PMDAの理念' (PMDA's Vision), and several informational boxes. One box highlights '医薬品・医療機器の説明書(添付文書) 審査報告書などの情報については、こちらをご覧ください。' (Information on drug/medical device instructions, etc., is available here). Another box lists '警告情報' (Warning Information), '副作用情報' (Adverse Reaction Information), and '禁忌情報' (Contraindication Information). A red banner at the bottom provides information about compensation for C型肝炎 infection victims. The right sidebar contains '採用情報' (Recruitment Information) and '医療機関の皆様' (Dear Healthcare Providers).

*Thank you for
your attention!*