

Japanese Regulations for Quality and Safety of Regenerative Medicine and Cell Therapy

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& Gene Therapy Products

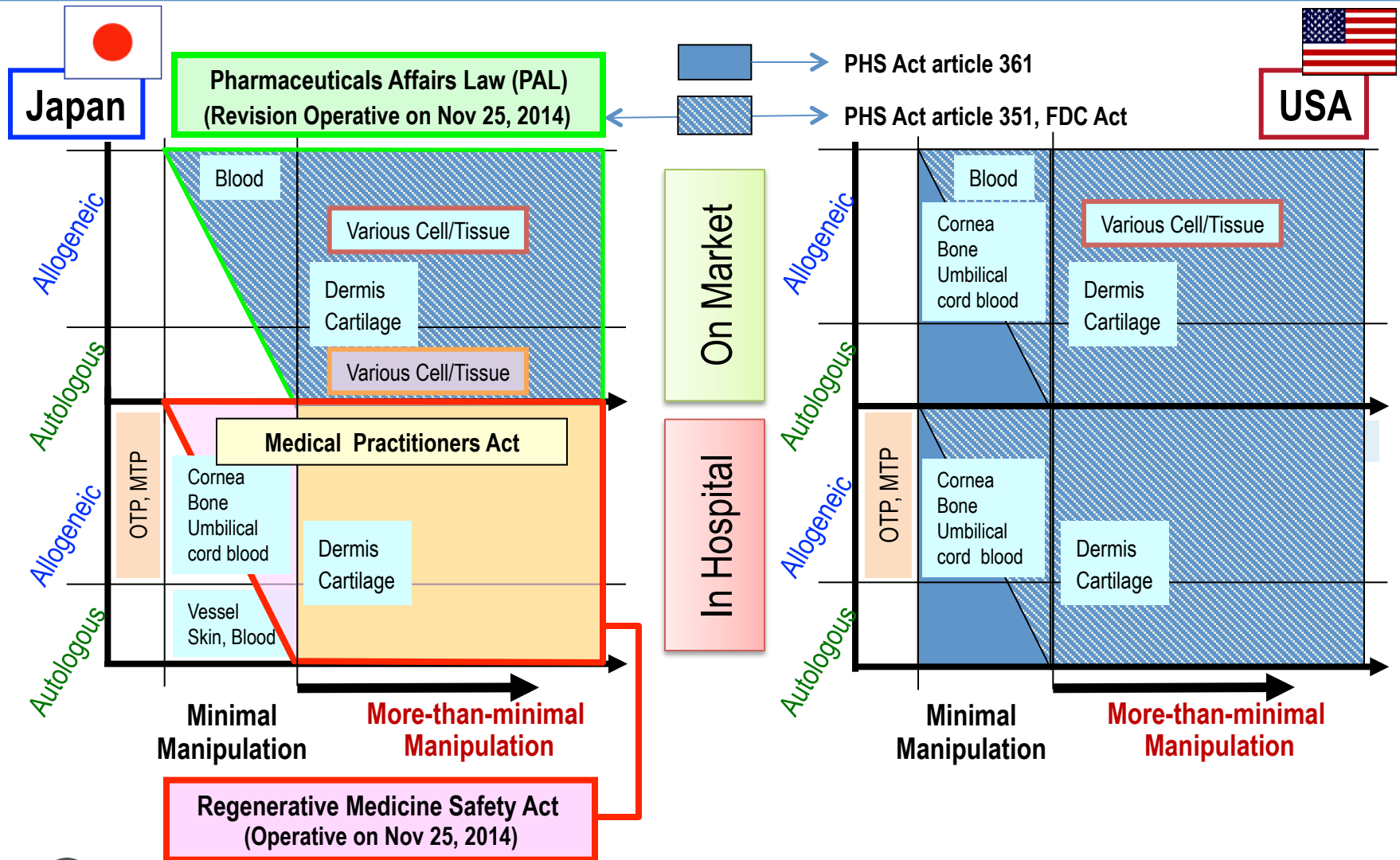
National Institute of
Health Sciences



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Regulation for Regenerative Medicine & Cell Therapy





“RM Product” vs. “Provision of RM/CT”

: ~ Nov. 24, 2014

* : Nov. 25, 2014 ~

	RM Product	Provision of RM/CT
Purpose	Manufacturing & Marketing of the Product	Development & Provision of the Medical Treatment
Regulatory Framework	<p>Pharmaceuticals Affairs Law (PAL)[#]</p> <p>Pharmaceuticals and Medical Devices Act* (PMD Act, Revised PAL)</p> <p>GLs and Standards for Assuring the Q/S of Cell-Based Therapeutic Products and Gene Therapy Products</p>	<p>Medical Practitioners Act</p> <p>GLs on Clinical Research using Human Stem Cells[#] (MHLW Notification No.380 (2010))</p> <p>Regenerative Medicine Safety Act*</p> <p>Ethical GLs for Clinical Studies (MHLW Notification No. 415 (2008))</p> <p>GLs for Gene Therapy Clinical Research (MHLW & MEXT Notification No.2 (2004)) [in vivo gene therapy]</p>
GCP Compliance	Mandatory	Not Mandatory
Review	<p>Pharmaceuticals & Medical Devices Agency (PMDA)</p> <p>Ministry of Health Labour & Welfare (MHLW)</p>	<p>Certified Committee for RM* [for Class 3 RM/CT]</p> <p>Certified Special Committee for RM* [for Class 1 & 2 RM/CT]</p> <p>MHLW [for Class 1 RM/CT and in vivo gene therapy]*</p>

Regenerative Medicine & Cell Therapy in Japan

Clinical researches using human stem cells (**RM/CT Provision**) (under the Guideline for Human Stem Cell Clinical Trials)

90 clinical trials have been approved as of February 2014

Cancer immunotherapy (**RM/CT Provision**)

Six types of therapy are currently provided in approved university hospitals as “advanced care”

* Partially covered by national health insurance

No statistics available for those provided outside of national health insurance scheme

Regenerative medical products (**under Pharmaceutical Affairs Law**)

Number of marketed products : 2

(JACE (autologous cultured epidermis), JACC (autologous cultured cartilage))

Number of MAA submitted: 2

(allogeneic mesenchymal stem cells for GVHD, autologous myoblast sheet for heart failure)

As of Oct 2014

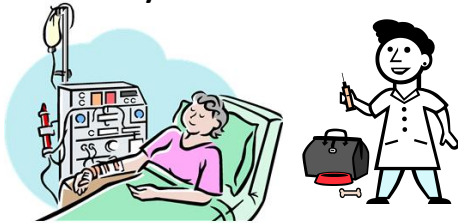
Number of clinical trials on going : 9 (including 2 gene therapy products)



Two Acts regulating RM/CT

Regenerative Medicine
Cell Therapy

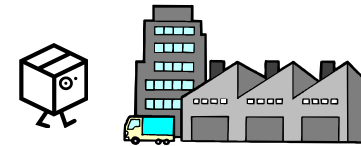
All medical **technologies** using processed cells which safety and efficacy have not yet been established



The Act on the Safety of RM
(RM Safety Act)*

It may be similar to researcher-initiated
(non-commercial) IND application system

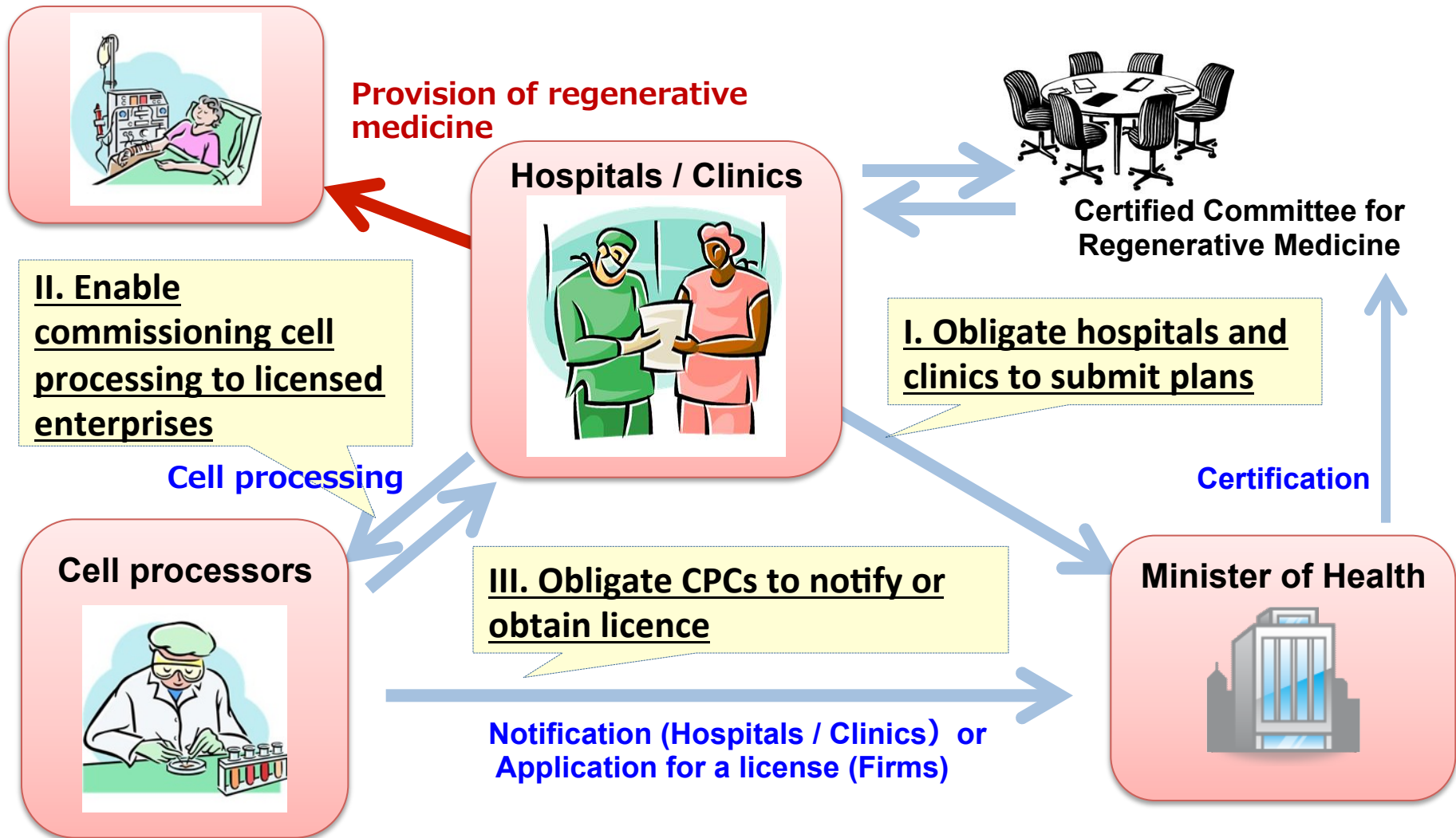
Production and marketing of regenerative and cellular therapeutic **products** by firms



The Act on Pharmaceuticals and
Medical Devices (PMD Act, Revised PAL)*

* These two acts come into force on
November 25, 2014

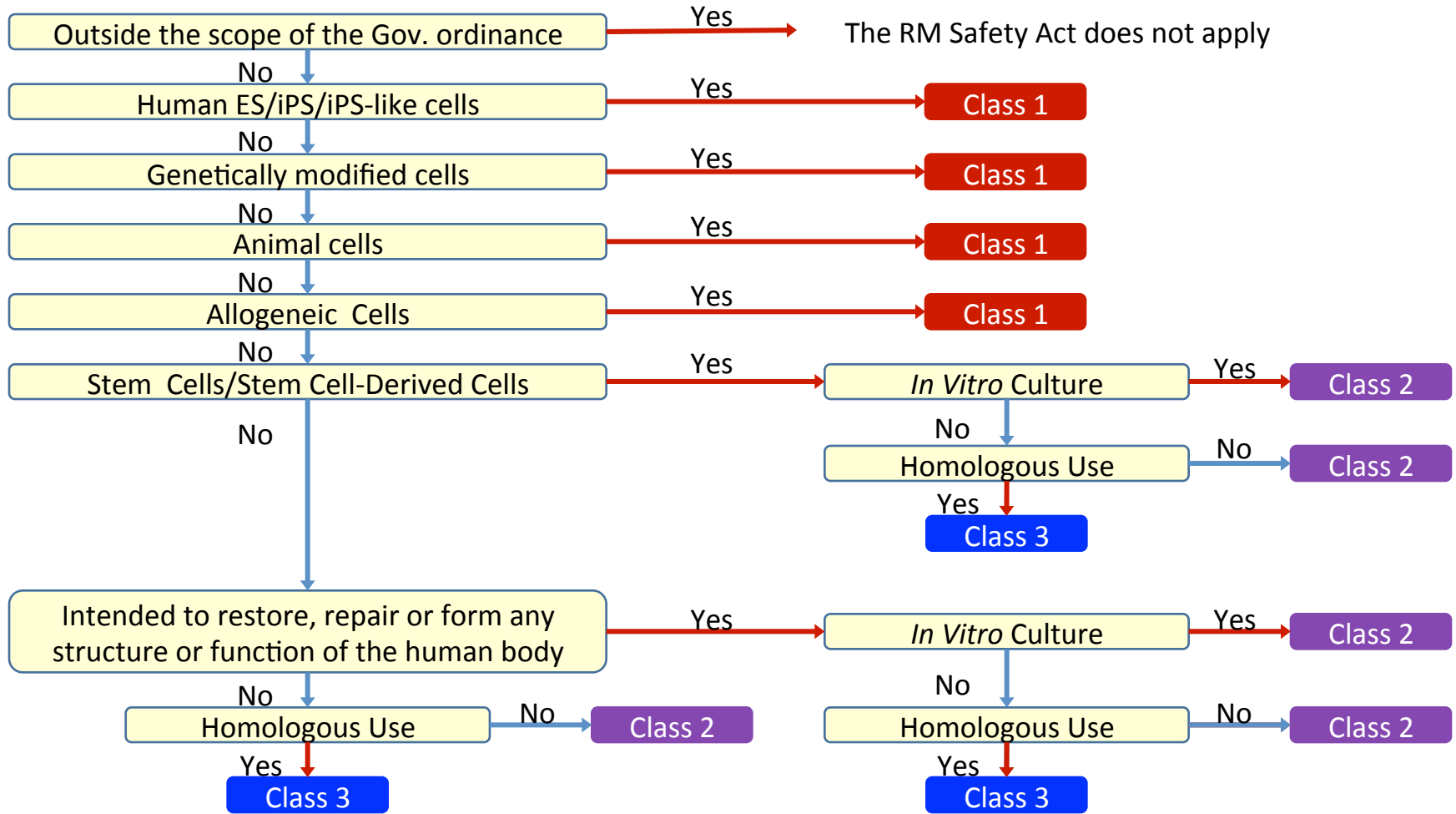
Overview of the RM Safety Act



Classification of RM/CT under the RM Safety Act

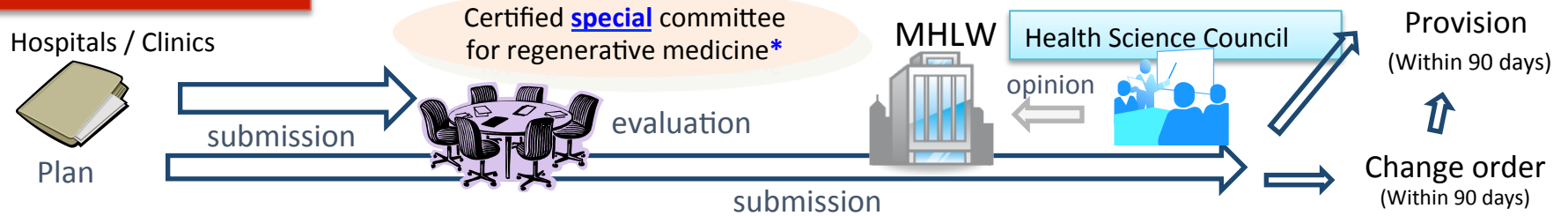
- **Class 1: High Risk**
(e.g. RM/CT using iPS/ES cells)
- **Class 2: Middle Risk**
(e.g. RM/CT using somatic stem cells)
- **Class 3: Low Risk**
(e.g. RM/CT using somatic cells)

Classification of RM/CT under the RM Safety Act

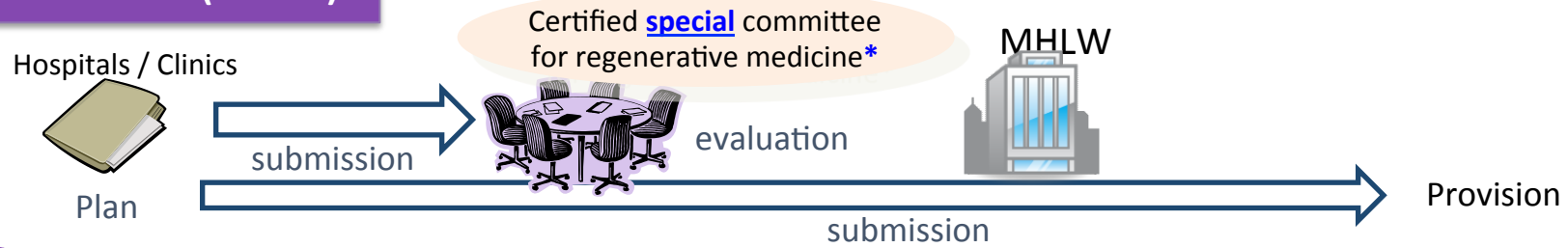


RM/CT at Hospitals and Clinics under the RM Safety Act

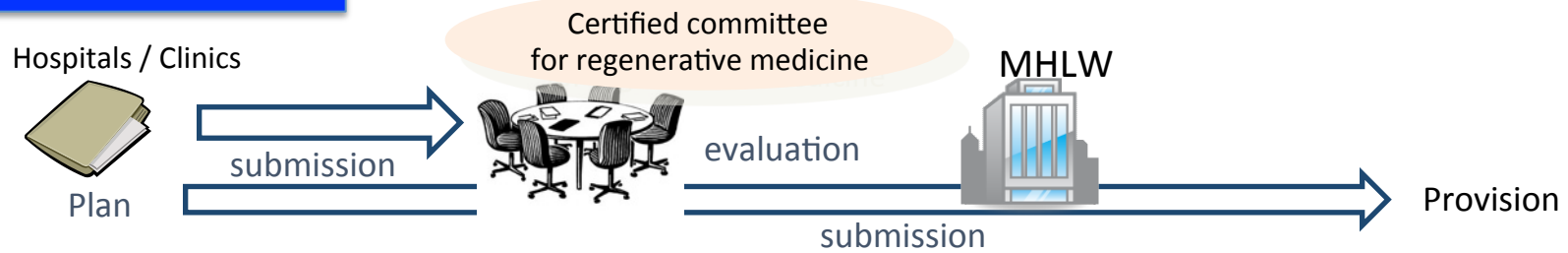
High Risk (Class 1)



Middle Risk (Class 2)



Low Risk (Class 3)

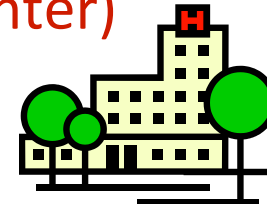


*Certified **special** committee for regenerative medicine is required to have highly specialized screening expertise and third-party characteristics (roughly 10 to 15 certified special committees for regenerative medicine across the country)

Manufacturing Business License or Notification

- Hospital in-house CPC (Cell Processing Center)

- ✓ Notification of facility and equipment



- 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 Foreign manufacturing site



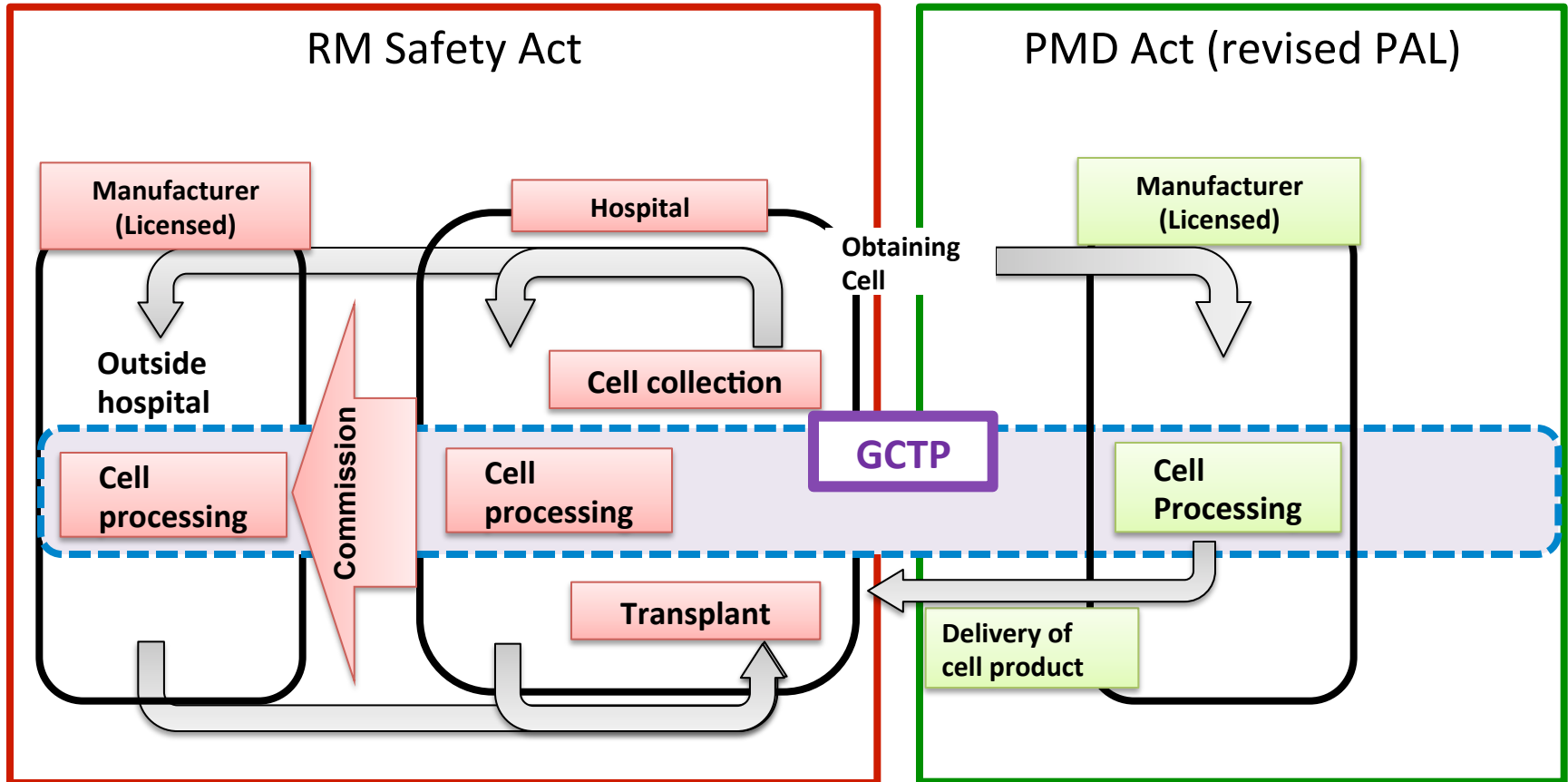
License/accreditation is subject to PMDA's site inspection and compatible to business license/accreditation of PMD Act.

Both types of CPCs need to be compliant with GCTP (Good gene, Cell & Tissue Practice (≈Good Tissue Practice + GMP/QMS))

Consistent parts of the two Acts

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

Regenerative Medical Products



GCTP (Good gene, Cell & Tissue Practice)

MHLW Guidance Notification No.93 (2014)

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

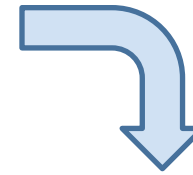
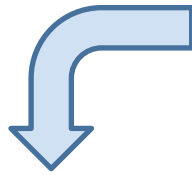
- Quality Risk Management
- Manufacturing Control (Sterility assurance, Prevention of Cross-contamination..)
- Quality control (Verification / validation, Quality review)
- Facility requirement

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.

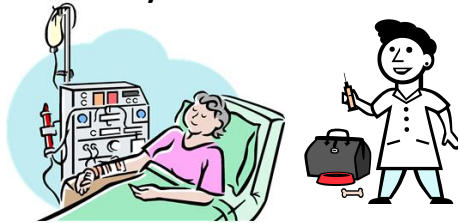


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* These two acts come into force on November 25, 2014



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

Session 6 (Dr. D. Sato, 11:00AM)



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Notifications & Guidelines for RM Products

- Promulgation of PMD Act and RM Safety Act (Nov 27, 2013)
- Cabinet and Ministerial Ordinances (Aug 6, 2014)
- Guidance notifications:
submission, GLP, GCP, GPSP, CT notification,
CT AE reports, ADR/Defect reports, Labelling,
periodic report, **GCTP** **Standards of Biological Ingredients**.....
(So far 32 technical guidance have been notified, 20 more by the end of November)
- Enactment of the two Acts (Nov 25, 2014)

Q/S Guidelines for Cell/Tissue-Processed Products

Good Tissue Practice (GTP) Guidelines

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

Standards for Biological Ingredients
MHLW Public Notice No.210 (2003)
Amendments (MHLW Public Notice No.375 (2014))

Good gene, Cell and Tissue Practice (GCTP) Guidelines

Good Practices for Manufacturing and Quality Management of Regenerative Medical Products
MHLW Guidance Notification No.93 (2014)

Basic Technical Requirements

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

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

Guidelines on Ensuring Quality and Safety of Products Derived from Processed :

- **Human (Autologous) Somatic Stem Cells**
- **Human (Autologous) iPS-like Cells**

PFSB/MHLW Notification No.0907-2 & 4 (2012)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed :

- **Human (Allogenic) Somatic Stem Cells**
- **Human (Allogenic) iPS-like Cells**
- **Human Embryonic Stem Cells**

PFSB/MHLW Notification No. 0907-3, 5 & 6 (2008)

Standards for Biological Ingredients (SBI)

MHLW Public Notice No.375 (2014)/No.210 (2003)

The purpose

... is to ensure the quality, efficacy and safety of pharmaceutical products, quasi-pharmaceutical products, cosmetics and medical devices (hereafter “pharmaceuticals, etc.”) by establishing standards related to the measures that are required in the event that materials and ingredients used in the manufacturing of these pharmaceuticals, etc. are derived from biological sources (excluding plants) other than the person using the product (including those used during the manufacturing process, such as additives and media components).

Amendments of the Standards for Biological Ingredients (SBI)

MHLW Public Notice No.375 (2014)

- ◆ RM products, a new product category in the PMD Act, were included in the scope of the Standards.
- ◆ For the safe and rapid translation of RM products, the Standards were revised, based on the latest scientific knowledge on viral safety, the international views on the risk of BSE, *etc.*
- ◆ The revision is **NOT relaxation** of the Standards, but rationalization from sound scientific viewpoints, taking into account of characteristics of RM products and their clinical applications.

Amendments of SBI (1)

MHLW Public Notice No.375 (2014)

1. A therapeutic product that is already authorized for marketing can be used as an SBI-compliant ingredient for another therapeutic product, as long as the usage of the former is appropriate.
2. Human blood products, which are used as supplements, culture media *etc.* during the manufacturing process of therapeutic products, are excluded from the group of blood products for transfusions and blood plasma fractionation products.
3. In accordance with the Ordinance for Enforcement of the RM Safety Act and relevant documents, provisions for the protection of donors' rights were re-organized.

Amendments of SBI (2)

MHLW Public Notice No.375 (2014)

4. Inactivation and removal of infectious agents from human-derived ingredients can be omitted, if the reason is justified and described in the certificate of approval for marketing. (e.g. patient's serum for culturing an autologous RM product)

The record of production process for human-derived ingredients and its storage are not required in the Standards any more. If necessary, it should be kept as part of GMP.

5. Countries that can be an origin of ruminant animal-derived ingredients are expanded to those whose BSE risk became negligible, according to the latest risk assessment by OIE. (e.g. Japan and the U.S.)

The record of low risk ingredients derived from ruminant animals and its storage are not required in the Standards any more.

Amendments of SBI (3)

MHLW Public Notice No.375 (2014)

6. For animal cell/tissue-based products that have been ingredients for therapeutic products, the confirmation of the donor animal eligibility and its record as well as the storage of the record are not required any more, as long as the therapeutic products have been used at clinical setting and the animal cell/tissue-based products are produced by culturing cells derived from a well-characterized cell bank.

7. For animal-derived ingredients, the information like countries of origin and parts used as a source materials is not necessary, as long as the ingredients are confirmed to be derived from healthy donor animals.

The record of production process for animal-derived ingredients and its storage are not required in the Standards any more. If necessary, the record should be kept as part of GMP.

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Guidelines on Ensuring Quality and Safety of Products Derived from Processed :

- **Human (Allogenic) Somatic Stem Cells**
- **Human (Allogenic) iPS-like Cells**
- **Human Embryonic Stem Cells**

PFSB/MHLW Notification No. 0907-3, 5 & 6 (2012)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Human Cells/Tissues or Stem Cells

- Describe the **basic technical elements** to ensure the quality and safety of pharmaceuticals and medical devices derived from processing of **autologous** and **allogeneic** human somatic cells, tissues or stem cells.
- Clarify differences with respect to data requirements and evaluation between **marketing authorization applications** and **clinical trial applications**. For the latter, it is necessary to ascertain if there is any quality and safety problem that might pose an obstacle to initiate a clinical trial.

The Q/S Guidelines emphasize that:

- When conducting or evaluating tests on individual product, it is necessary to take flexible approaches **on a case-by-case basis** in line with the concept of the guideline and on the basis of type, characteristics and intended clinical use of the product in question.
- Reflection of scientific progress and accumulation of experience in relevant field is always encouraged.
- In the use of such an advanced therapeutic product for treating patients (**First-in-Man**) with severe and life threatening diseases or injuries, the **risk/risk balance with/without the advanced treatment** should be also taken into account, rather than just discussing unknown potential risk of a product.

Autologous vs. Allogeneic

Autologous Human Cells/Tissues

- **Infectious status of donor**, including infections of HBV, HCV, HIV, and HTLV.
- **Risk of proliferation or re-activation of virus in manufacturing processes**
- **Robust process control to minimize unevenness of “Custom-Made” products**
- **Limited amount of samples for quality evaluation of products**

Allogenic Human Cells/Tissues

- **History, source, derivation**
- **Donor screening/testing and donor eligibility** (compatibility with donor qualification criteria, including ethical and medical aspects; freedom from the presence of HBV, HCV, HIV, HTLV and pulvovirus B19 by screening and testing; exclusion of potential infection of CMV, EBV and WNV by testing; clinical history; experience of blood transfusion or implanting;genetic etc.)
- **Records of donor**
- **Derivation of cell strain**
- **Cell banking**
- **Potential Viral Presence in Products (Viral assay at the final product level)**
- **Immunological problems** (eg., rejection, GVHD etc.)

iPS cells vs. “iPS-like cells”

Human iPS cells

- ...are cells that originate from human somatic cells
- ...have been **reprogrammed** by forced introduction of genes, proteins or chemicals
- ...have **pluripotency** to differentiate into **all cell types of endoderm, mesoderm and ectoderm**
- ...have an ability or potential of self-renewal

Human iPS-like cells

- ...are cells that originate from human somatic cells
- ...have been **dedifferentiated** by forced introduction of genes, proteins or chemicals
- ...have **ability** to differentiate into **some cell type(s) of endoderm, mesoderm or ectoderm**
- ... have an ability or potential of self-renewal

Specific Points to Consider on Human iPS/ES Cell-Derived Products

- hiPSCs or hESC with **pluripotency** *per se* **may NOT always be the most suitable starting material** to differentiate into a specific desired cell product.
- Significance of derivation of **hiPS-like Cells** as a starting materials in addition to hiPS Cells
- Significance of derivation of **hESC-derived differentiated Cells** as a starting material in addition to hES Cells
- Significance of establishment of **well characterized stable cell banks** and/or relevant intermediate cell products
- Elimination/inactivation of **residual undifferentiated cells** during production process be critical.

Points to Consider on Process & Quality of RM Products

- Characterization and understanding of specific profiles of cells at critical steps (starting, intermediate, final) and their eligibility (differences in autologous/allogeneic)
- Eligibility of other raw materials and manufacture-related substances and their quality control (especially, eligibility of biological materials, no adverse impact of non-cellular/tissue component on desired cells)
- Verification of manufacturing process and constancy of manufacture
- Product consistency in terms of quality attributes such as identity, purity, homogeneity and potency
- Stability (storage conditions/expiration date, freezing & thawing processes, and shipping vessel & procedure)
- Quality control of final product through relevant combination of critical quality elements from products & process aspects



Thank you for your attention

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