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Update on Japan's Regulation of Cell-Based Therapeutic Products

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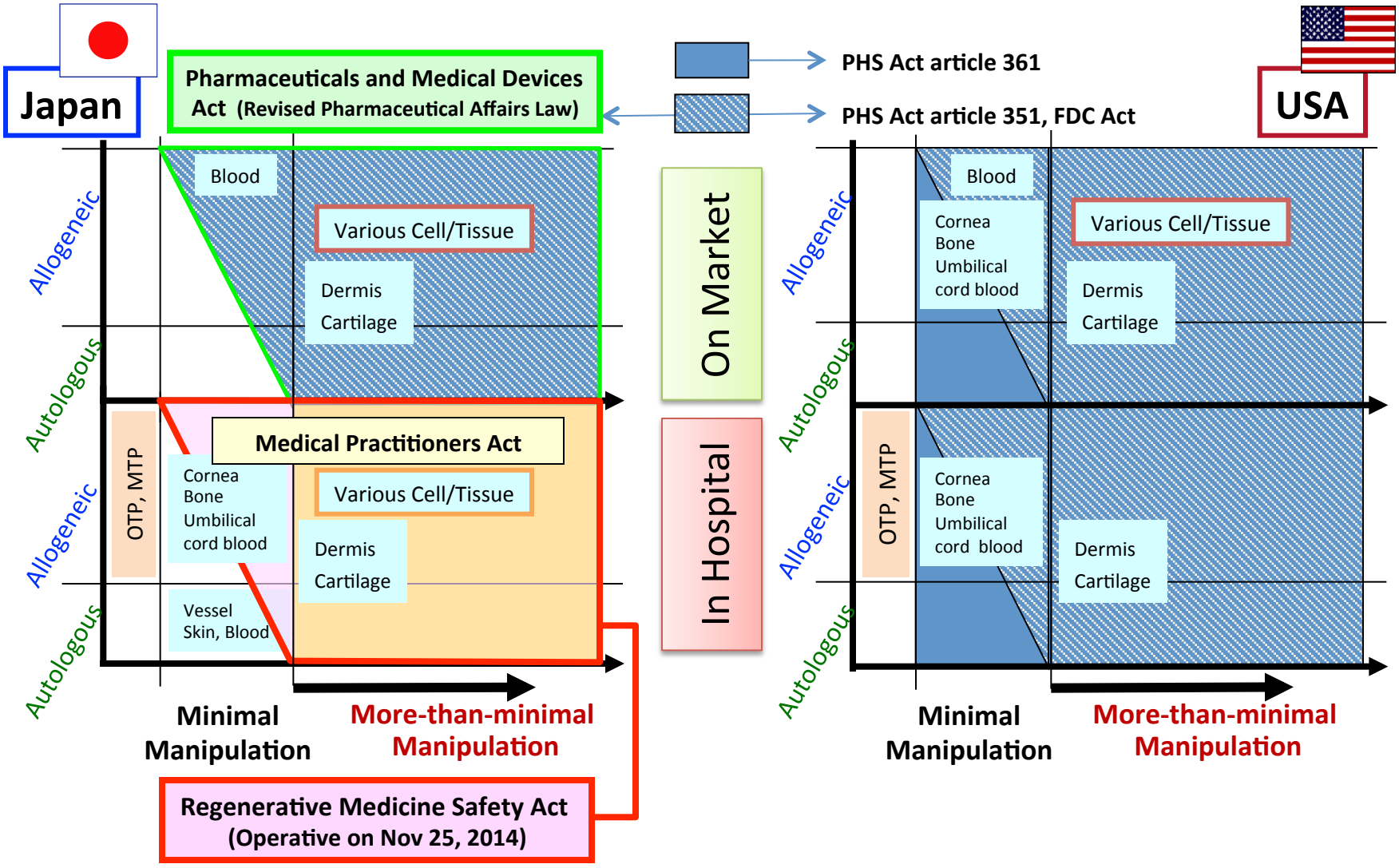
Regulation for regenerative medicine (RM)/cell therapy (CT)



Regenerative Medicine & Cell Therapy (RM/CT) in Japan

RM SafetyAct

Provision of RT/CT

Medical Care

3,172 registered protocols (as of July 31, 2016)

Class 1: 0
Class 2: 64
Class 3: 3,108

Clinical Research Using Cell-Processed Products

99 registered protocols
(as of July 31, 2016)

Class 1: 15
Class 2: 35
Class 3: 49

Covered by MHLW (Health Policy Bureau)

PMD Act

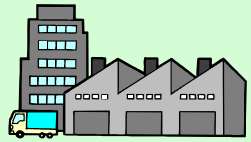
Product Marketing Authorization

Regenerative Medical Products

4 approved products

- autologous epidermis
- autologous cartilage
- allgeneic mesenchymal stem cells

- autologous cultured myoblast sheet (conditional/term-limited approval)



Covered by MHLW (Pharmaceuticals & Food Safety Bureau) and PMDA

“RM/CT as Medical Practice” vs. “Products for RM/CT”

	RM/CT as Medical Practice	Products for RM/CT
Purpose	Development & Provision of the Medical Treatment	Development, Manufacturing & Marketing of the Products
Regulatory Framework	**Regenerative Medicine Safety Act (RM Safety Act, enacted on Nov 25, 2014)** The Standards for the Provision of Regenerative Medicine (MHLW Ministerial Ordinance No.110 (2014)) Ethical GLs for Medical Researches on Human Subjects (MEXT/MHLW Notification No.3 (2014)) GLs for Gene Therapy Clinical Research (MHLW & MEXT Notification No.2 (2004)) [in vivo gene therapy]	**Pharmaceuticals and Medical Devices Act (PMD Act, Revised Pharmaceutical Affairs Law, enacted on Nov 25,2014)** GLs and Standards for Assuring the Quality/Safety of Cell-Based Therapeutic Products and Gene Therapy Products
GCP Compliance	**Not Mandatory**	**Mandatory**
GCTP Compliance	**Mandatory**	**Mandatory**
Review	Certified Committee for RM* [for Class 3 RM/CT] Certified Special Committee for RM* [for Class 1 & 2 RM/CT] Ministry of Health Labour & Welfare (MHLW) [for Class 1 RM/CT and *in vivo* gene therapy]*	Pharmaceuticals & Medical Devices Agency (PMDA) MHLW
Health Insurance	**Not or Partly Covered by the Public Insurance**	**Fully Covered by the Public Insurance**

Background for New Legislations

1. Needing some legal basis to ensure safety of cell therapies
2. Growing needs for collaboration between medical institutions and industry from the early stage of development

New legislation was needed for prompt and safe regenerative medicine.

→ **Regenerative Medicine Safety Act (RM Safety Act)**

3. The existing framework in Pharmaceutical Affairs Law (PAL) dose not fit for the characteristics of products for regenerative medicine and cell therapy.

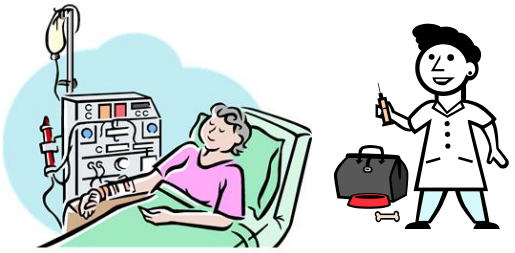
Definition of products for RM/CT and establishment of new framework are needed.

→ **Revised Pharmaceutical Affairs Law (Revised PAL, PMD Act)**

Two Acts Regulating RM/CT

Regenerative Medicine
Cell Therapy

Medical practices using processed cells, whose safety and efficacy have not yet been established



Production and marketing of **products for RM/CT** by firms

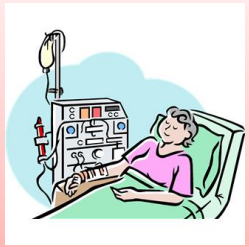
Regenerative Medicine Safety Act (RM Safety Act) *

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

* Two laws were enacted on 25 November 2014.

It may be similar to researcher initiated IND application system

Overview of the RM Safety Act



RM/CT as medical practices

Hospitals / Clinics

Certified Committee for Regenerative Medicine

II. Enable commissioning cell processing to licensed enterprises

I. Obligate hospitals and clinics to submit plans

Cell processing

Certification

Cell processors

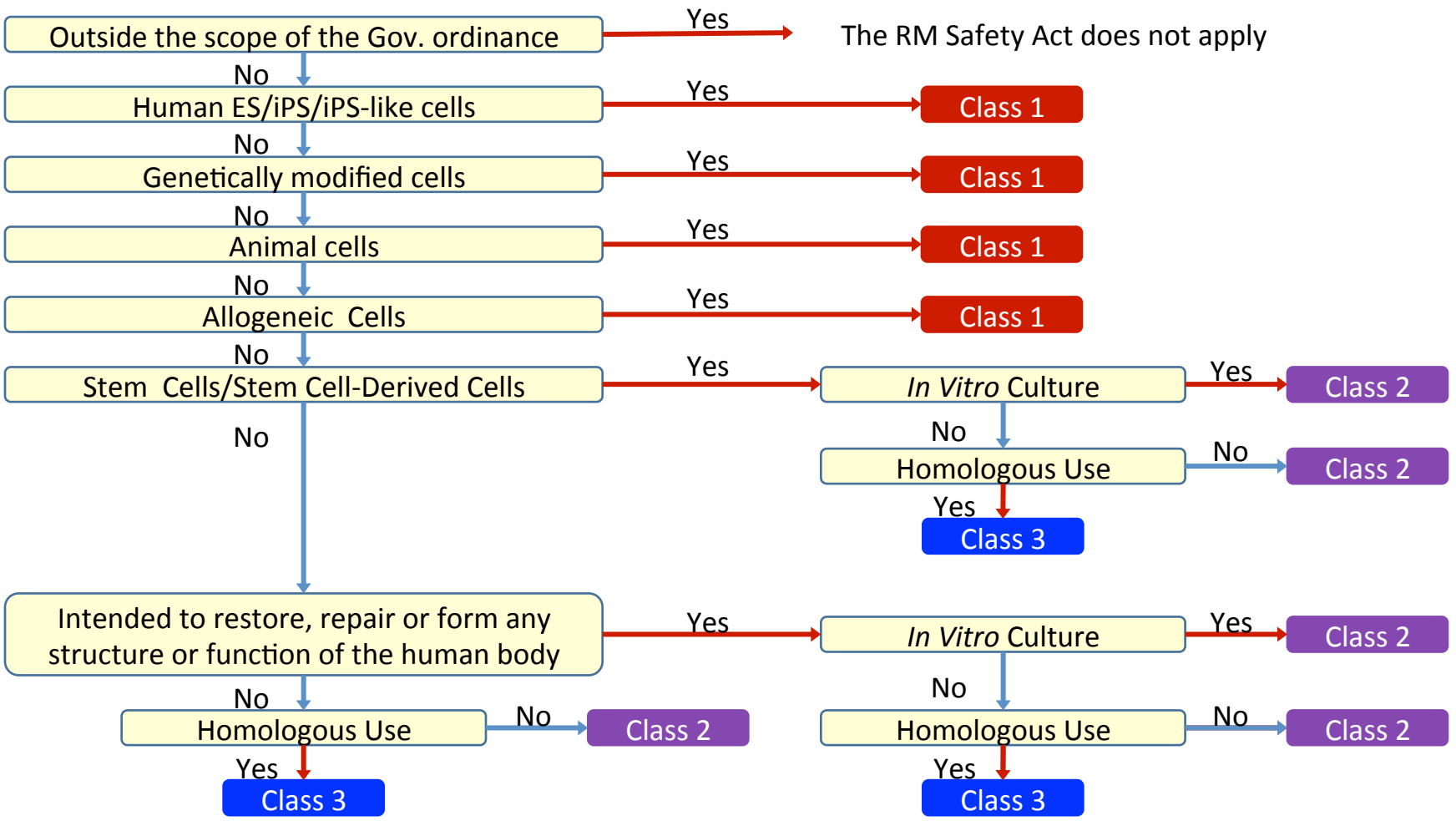
III. Obligate CPFs to notify or obtain licence

Minister of Health

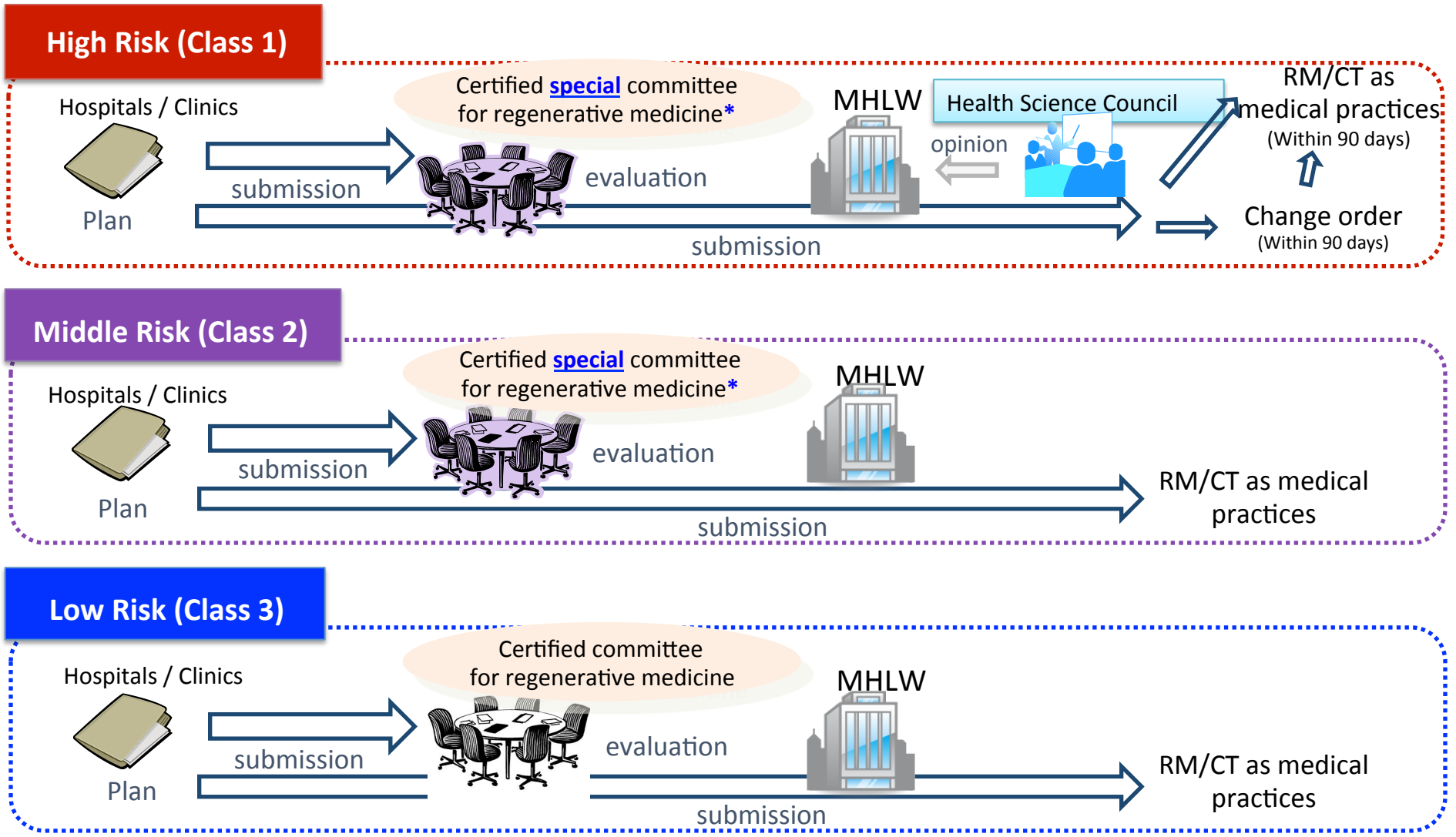
Notification (Hospitals / Clinics) or License (Firms in Japan) Accreditation (Firms outside Japan)

Classification of RM/CT under the RM Safety Act

Class 1, High Risk; Class 2, Middle Risk; Class 3, Low Risk.



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

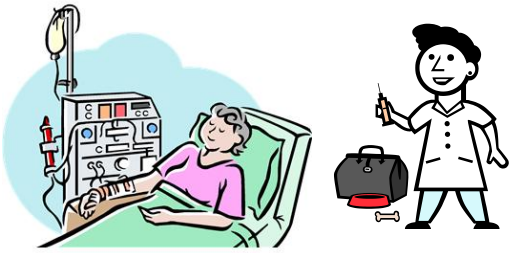


*Certified special committee for regenerative medicine is required to have highly specialized screening expertise and third-party characteristics (roughly 10 to 15 certified special committees for regenerative medicine across the country)

Two Acts Regulating RM/CT

Regenerative Medicine
Cell Therapy

Medical practices using processed cells, whose safety and efficacy have not yet been established



Production and marketing of **products for RM/CT** by firms

Regenerative Medicine Safety Act (RM Safety Act) *

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Company driven IND and product approval system

Revision of Pharmaceutical Affairs Law (PMD Act)

- **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 the independent chapter for Regenerative Medical Products
  - Introduction of conditional/term-limited approval system

Definition of "Regenerative Medical Products" in Japanese Legislation

In **PMD Act**, **"Regenerative Medical Products (RMPs)"** are defined as

1) processed human cells that are intended to be used for
   (1) the restoration, repair, or formation of structures or functions of the human body (Tissue Engineered Products)
   (2) the treatment or prevention of human diseases (Cell Therapy Products)
2) products for gene expression (Gene Therapy Products)

≈ Cellular and Tissue-Based Products, and Gene Therapy Products 

≈ Advanced Therapy Medicinal Products (ATMPs) 

How to Expedite R&D and Review for RM products

- RM products are designed for unmet needs under the present treatment: limited number of patients are able to avail RM products.
- It is difficult to conduct the controlled study to demonstrate "true end point" of clinical benefit with RM products.
- Source materials affect quality heterogeneity of RM products.

It would take a long time to review RM products if regulators pursue the conventional drug pathway too much.

The Pharmaceuticals and Medical Devices Act (PMD Act)

◆ **A new product category: "**Regenerative Medical Products (RMPs)"

It is difficult to collect and evaluate the data for the efficacy of RMPs in a short time due to heterogeneity of cells.

To ensure timely provision of safe RMPs, a new regulatory framework was expected.

Expedited approval system for RMPs

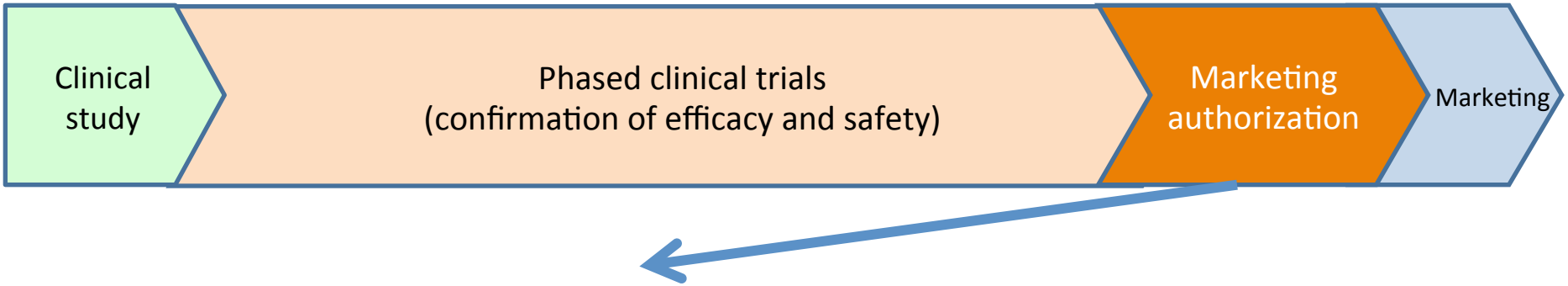
After the safety confirmation and efficacy prediction by the clinical trial data, conditional/term-limited marketing authorization for RMPs will be granted to timely provide the products to patients.

Expedited Approval System for RMPs under PMD Act

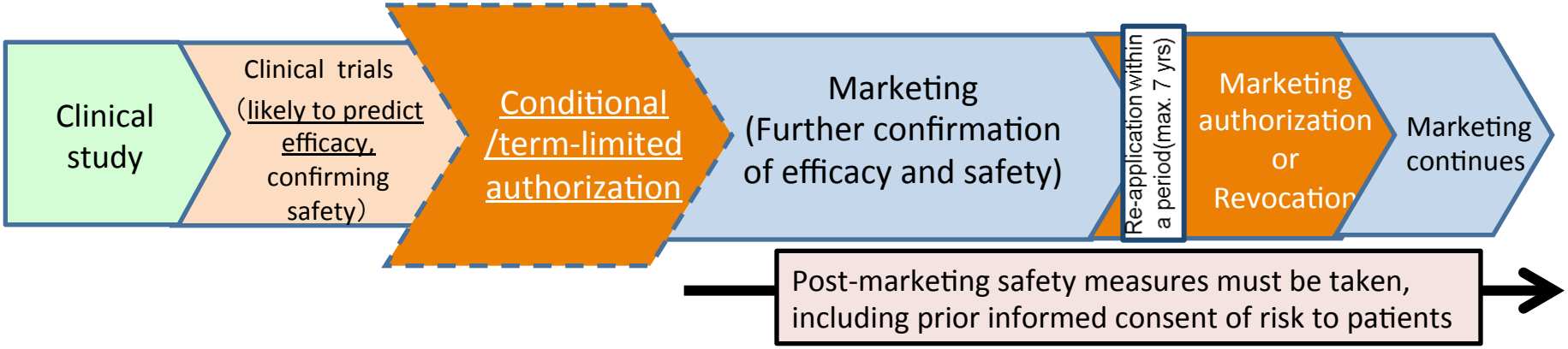
< Drawback of traditional PAL approval system >

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

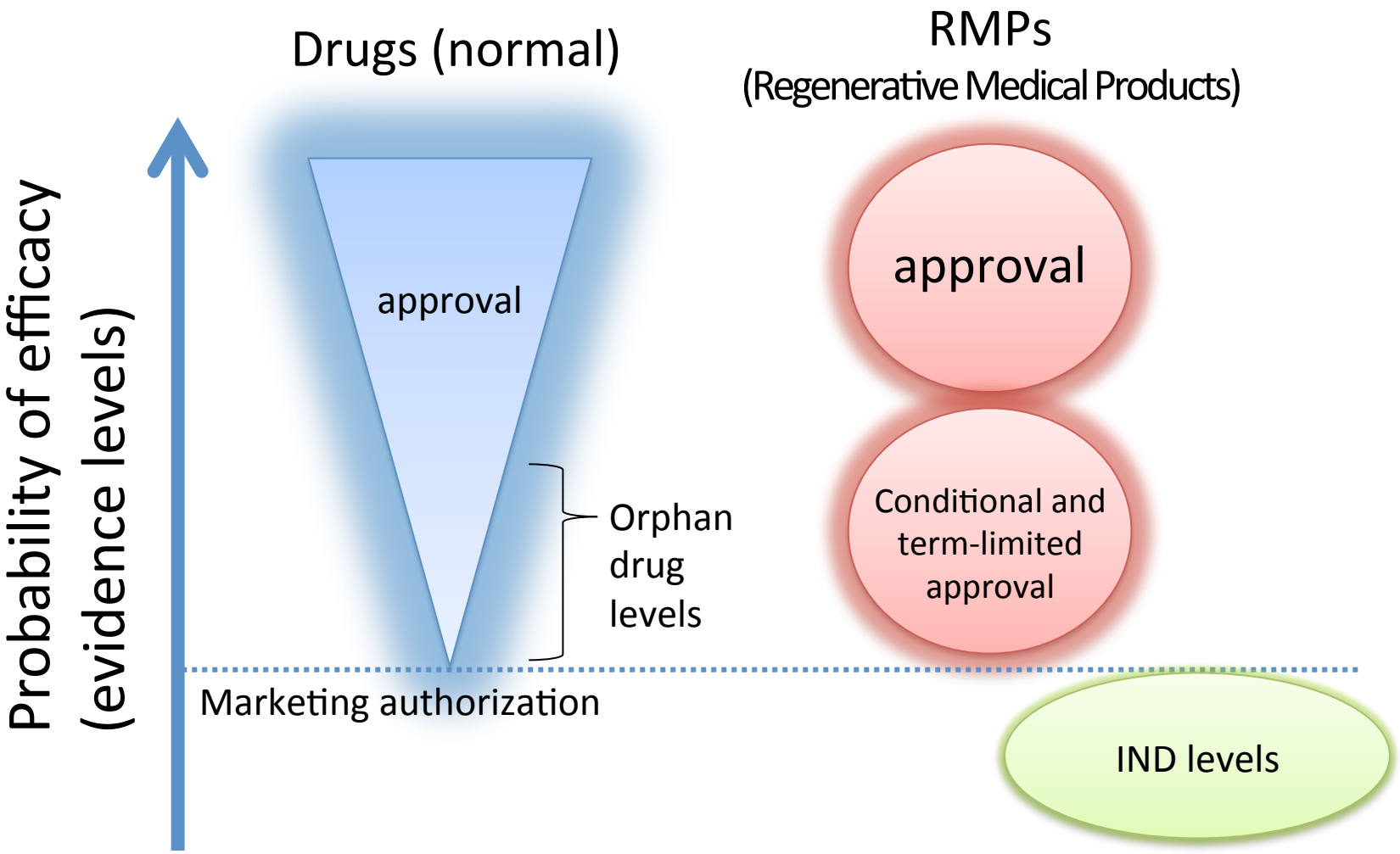
[Traditional approval process]



[New scheme for regenerative medical products]



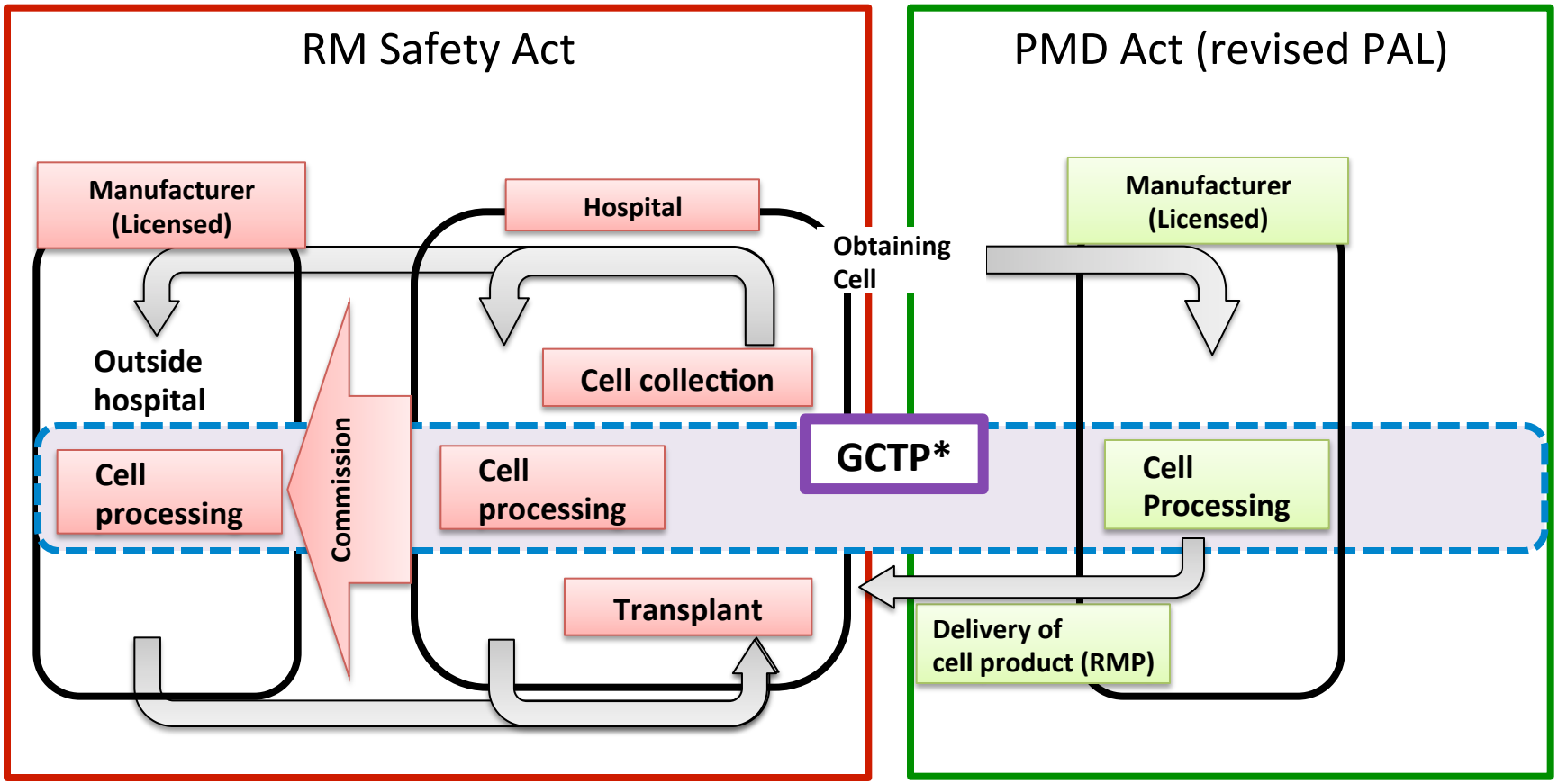
Evidence Levels of Efficacy: Drugs (normal) vs. RMPs



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 (≈ Good Tissue Practice + GMP/QMS))**

GCTP (Good gene, Cell & Tissue Manufacturing Practice)

GCTP is 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 view point of facility,
- but also from the view point of manufacturing operation such as the performance evaluation.

Summary

In line with the commitment of the administration, Japan recently reformed the regulatory framework

- to support and accelerate R&D of regenerative medicine and cell therapy
- to expedite the access to new promising regenerative medicine and cell therapy in a safe and effective manner.

Thank you for your attention

Contact Information

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