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The New Japanese Regulatory Framework for Regenerative Medicine & Cell Therapy

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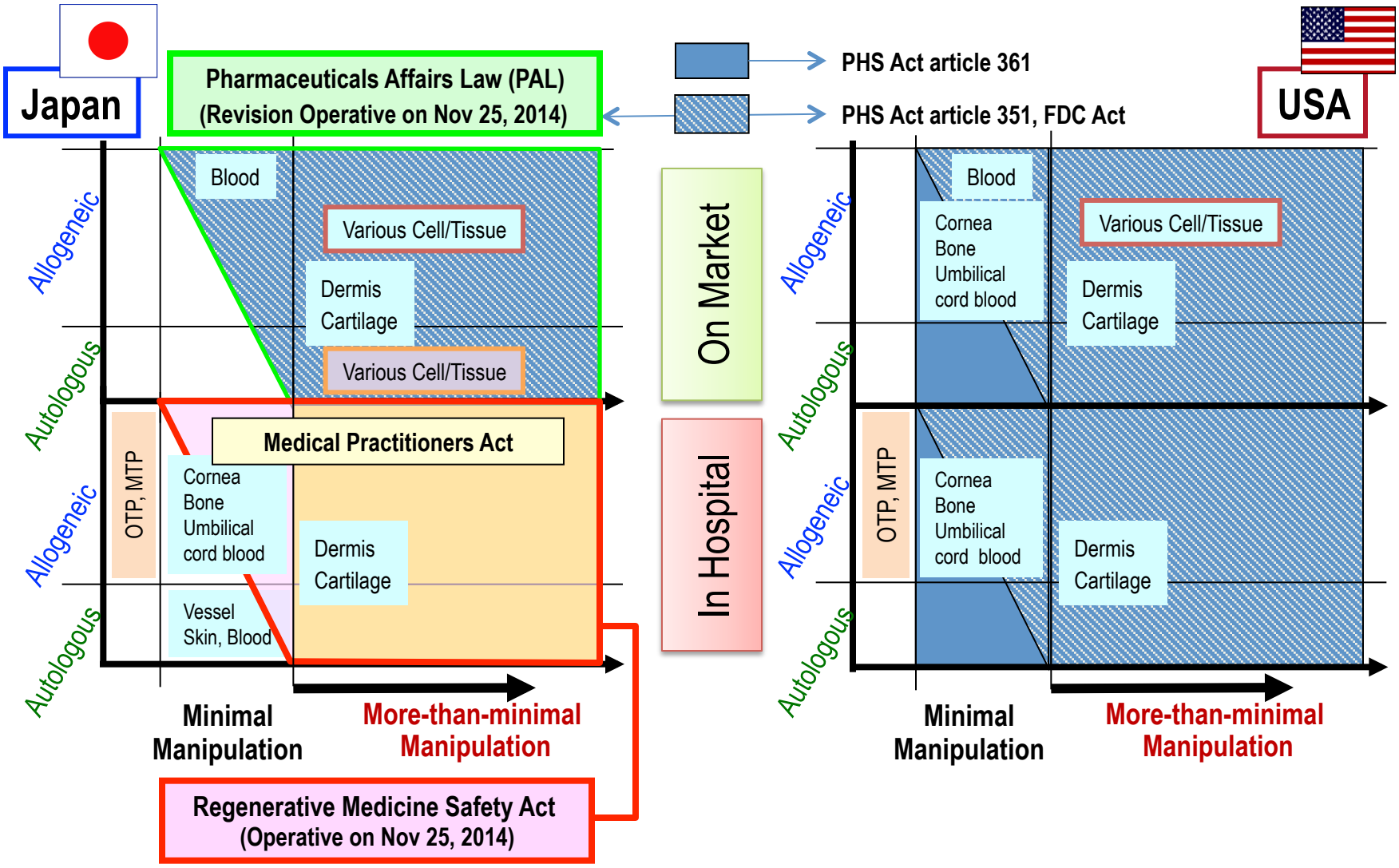
Regulation for Regenerative Medicine/ Cell Therapy



Background for new legislations

1. Legal basis for the guideline to ensure safety of cell therapies is required.
2. Need for collaboration between medical institutions and industry from the early stage of development is growing.

New legislation is needed for prompt and safe regenerative medicine.

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

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

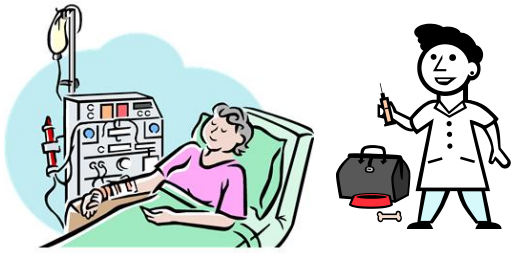
Definition of products for RM/CT and establishment of new framework are needed.

→ **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.

“Provision of RM/CT” vs. “Product for RM/CT”

[#] : ~ Nov. 24, 2014
[*] : Nov. 25, 2014 ~

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

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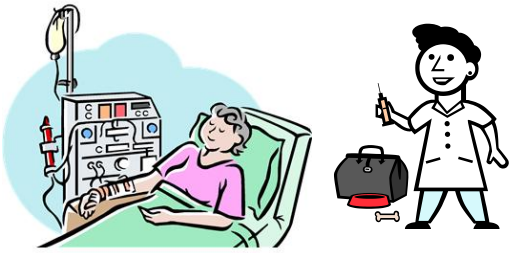

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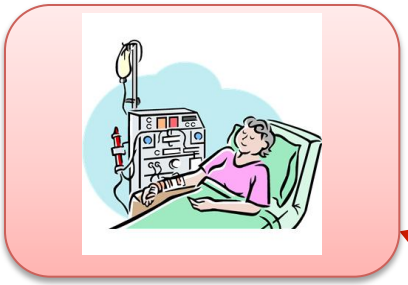
It may be similar to researcher initiated IND application system

Overview of the RM Safety Act



Provision of regenerative medicine

Hospitals / Clinics

Certified Committee for Regenerative Medicine

II. Enable commissioning cell processing to licensed enterprises

Cell processing

I. Obligate hospitals and clinics to submit plans

Certification

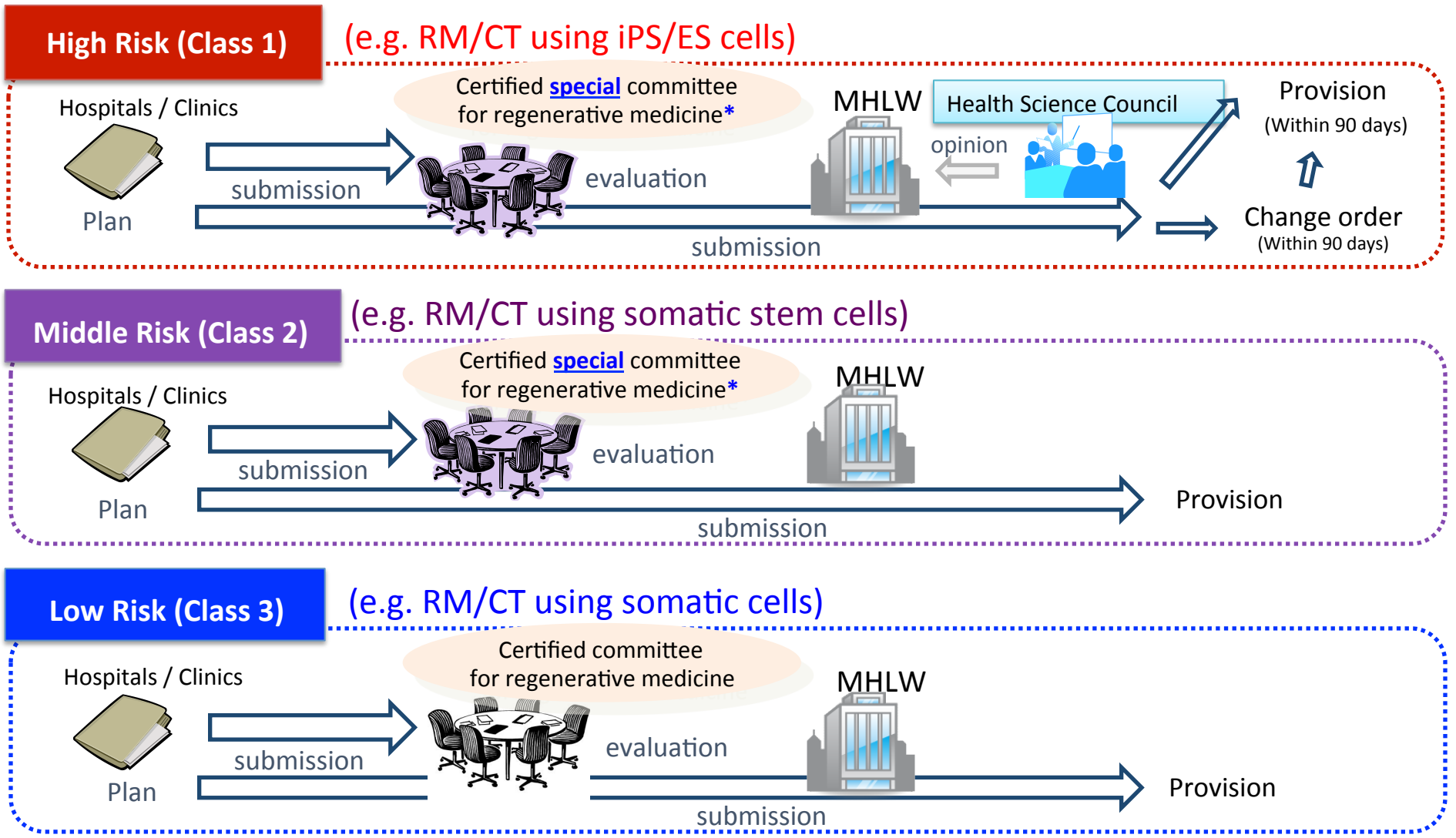
Cell processors

III. Obligate CPCs to notify or obtain licence

Notification (Hospitals / Clinics) or
Application for a license (Firms)

Minister of Health

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)

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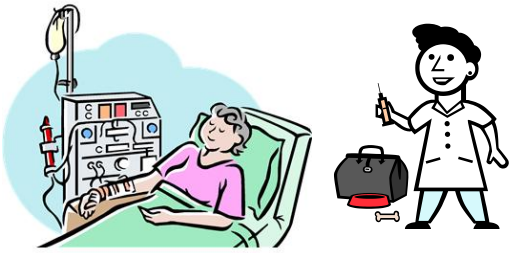

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Company driven IND and product approval system

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

- **In PMD Act, "regenerative medical products (RMPs)"** are defined as processed human cells that are intended to be used

  1) for either

  (1) the restoration, repair, or formation of structures or functions of the human body or

  (2) the treatment or prevention of human diseases,

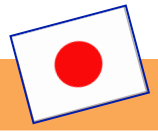
  or

  2) for gene therapy

≈ Cellular and Tissue-Based Products (and Gene Therapy Products) 

≈ Advanced Therapy Medicinal Products (ATMPs) [Regulation (EC) No 1394/2007]

Early Access Schemes of ICH 3 Parties

US 	EU 	JAPAN 
Priority Review		Priority review
Accelerated approval for serious or life-threatening illnesses	Conditional MA MA under exceptional circumstances	Conditional approval for Oncology drug, Orphan drug Conditional & time-limited approval for RM products
Break through therapy & Fast Track designation		Forerunner Review Assignment

Various agencies have various approaches to accommodate patient access though they have certain similarity.

The Pharmaceuticals and Medical Devices Act (PMD Act)

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

Difficult to collect and evaluate the data for the efficacy of RMPs in a short time due to heterogeneity of cells

To secure timely provision of safe RM/CT, a new regulatory framework is needed

Expedited approval system for RMPs

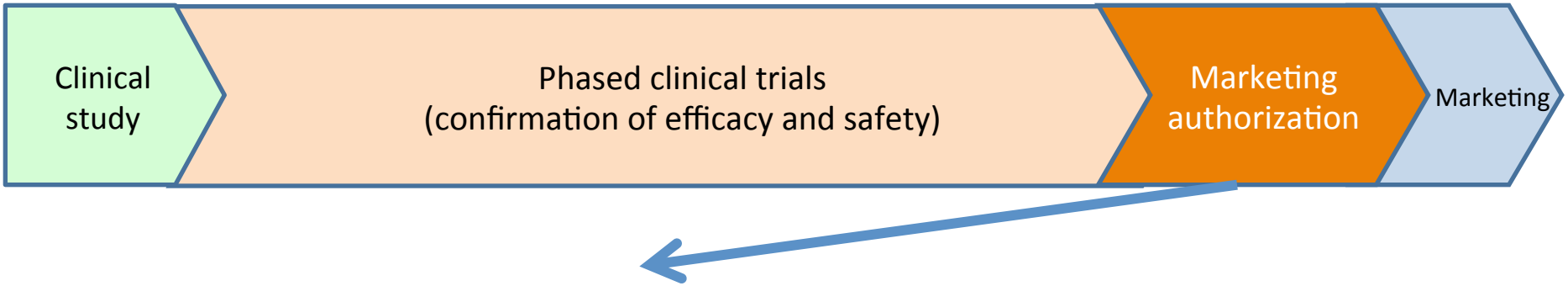
After the safety is confirmed and the data predict likely efficacy,
the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.

Expedited approval system under PMD Act

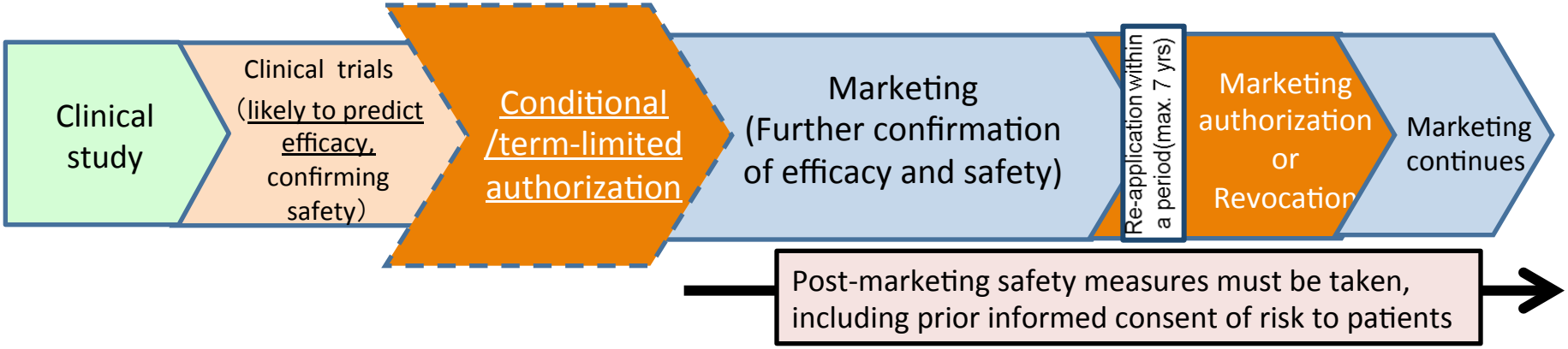
< Drawback of traditional PAL approval system >

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

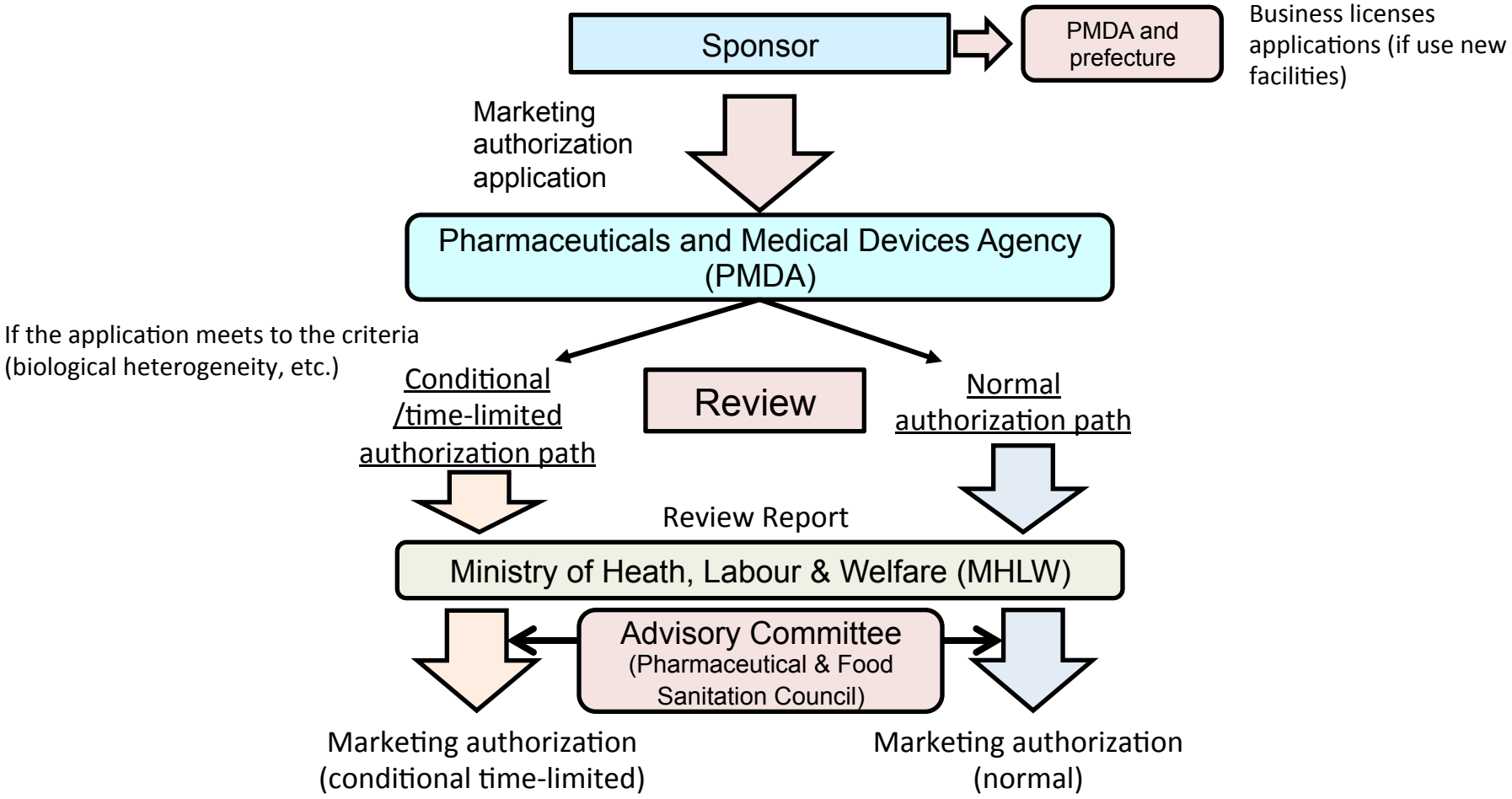
[Traditional approval process]



[New scheme for regenerative medical products]



Review Pathway of RMPs



Ref. Hara A. Sato D. Sahara Y. *Ther. Innov. Regul. Sci. http://dx.doi.org/10.1177/2168479014526877 (2014).*

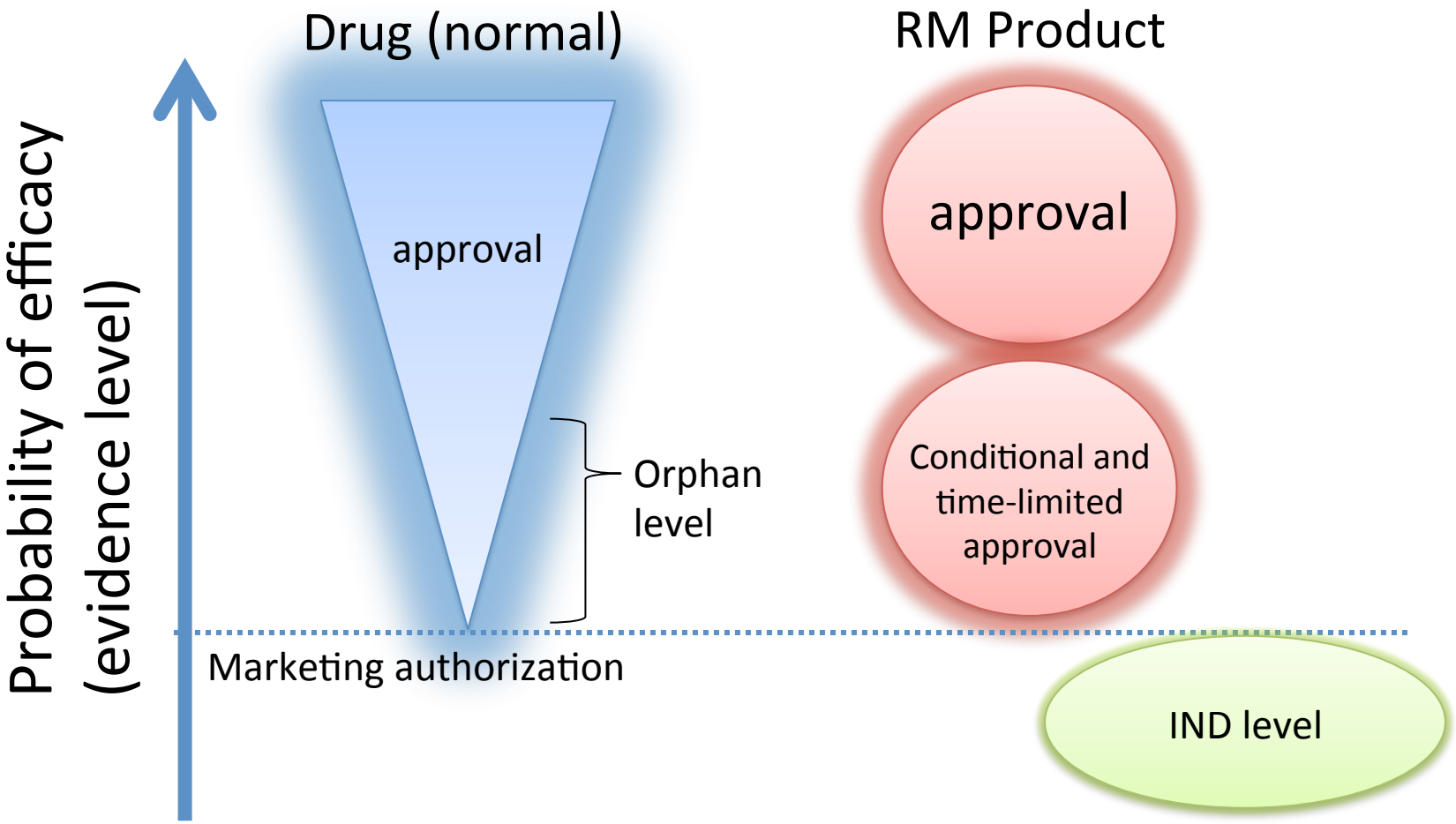
Likely to predict efficacy (clinical benefit)

- 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)

- It applies to certain new drug products in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.
- Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- The drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity..
- Approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit (such as OS).
- Postmarketing studies would usually be studies already underway.
- FDA may withdraw approval, if a postmarketing clinical study fails to verify clinical benefit; ……

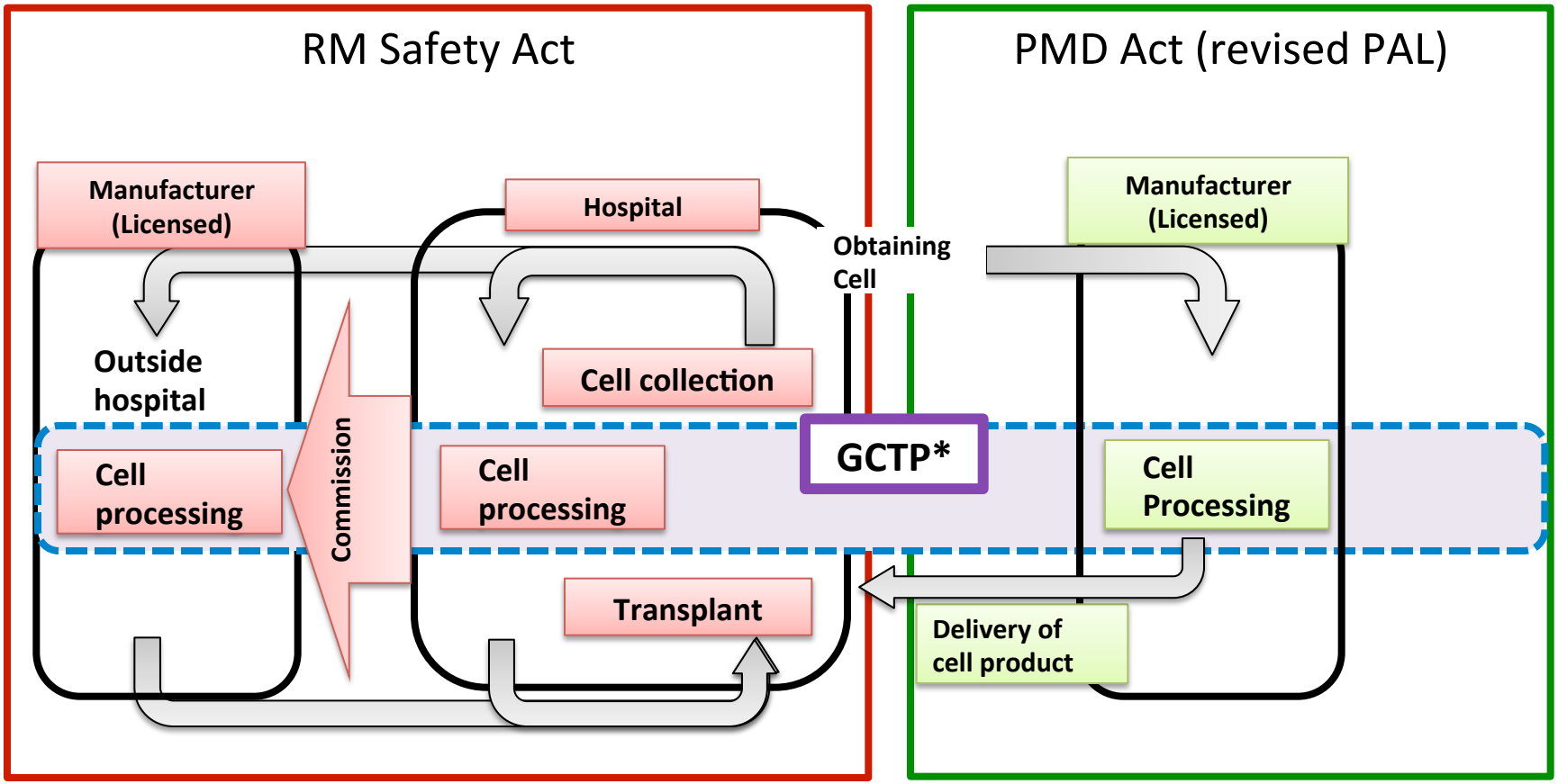
Evidence level of efficacy: Drug (normal) vs. RM Product



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))**

Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act

	Biological device	RM products
Conditional and time limited approval	NA	√
Adverse Drug Reaction Relief Fund	NA	√
Infection Relief Fund	√	√

Private Insurance products will be available for clinical studies under the RM Safety Act

Summary

- In line with the commitment of the administration, Japan is undergoing regulatory reform to support and accelerate R&D of regenerative medicine

- Expedite the access to new promising regenerative medicine in a safe and effective manner

Thank you for your attention

Contact Information

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