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Scientific Workshop at the 2021 ASH Annual Meeting
The Regulatory Drug Approval Process: Getting to the Finish Line

Japan's Regulatory System for Cell-Based Therapeutic Products

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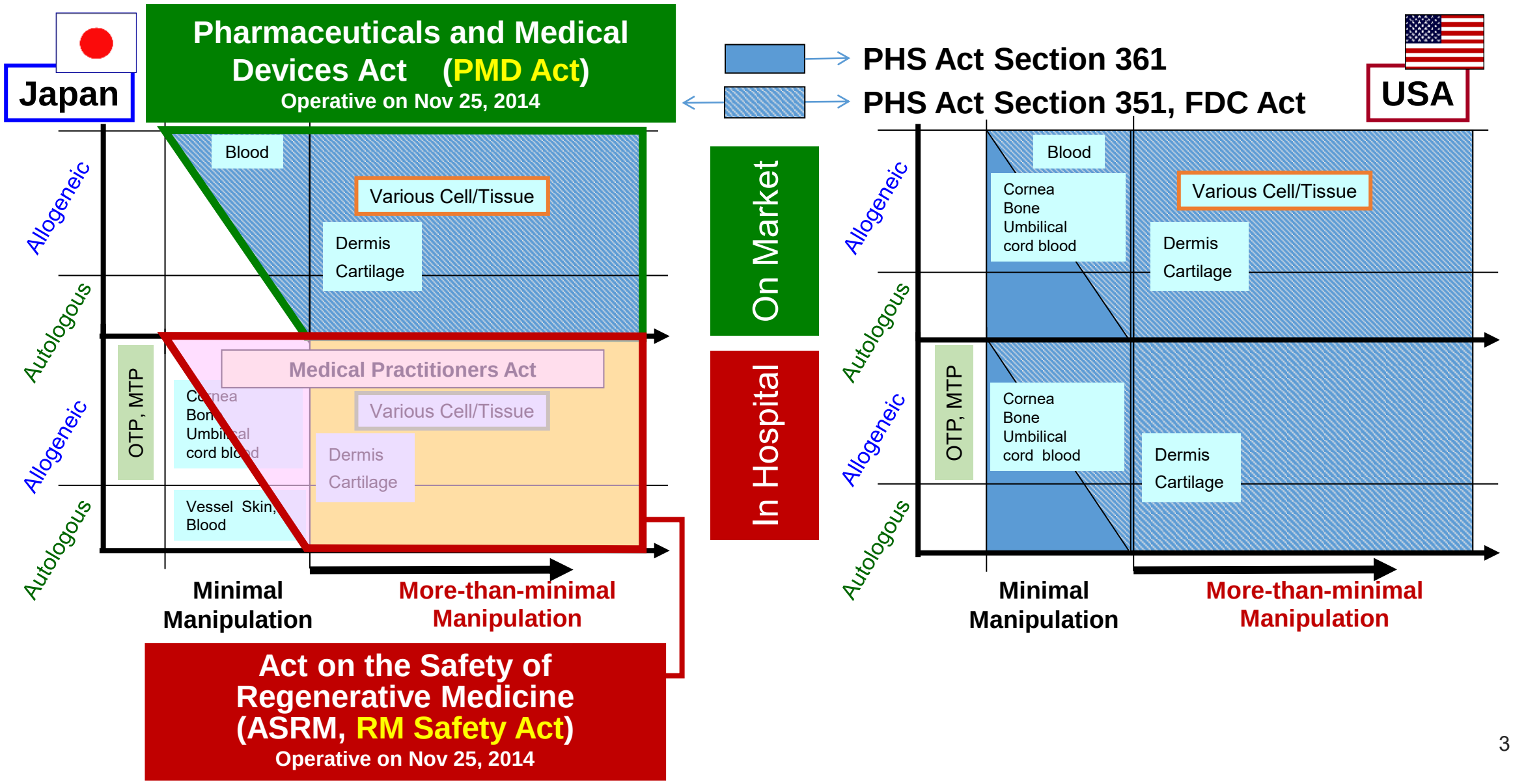
DISCLAIMER:

The views and opinions expressed in this presentation are those of the presenter and do not necessarily represent official policy or position of the Japan National Institute of Health Sciences or the Japan Ministry of Health, Labour & Welfare. Also, the presenter has no COI to disclose in connection with this presentation.

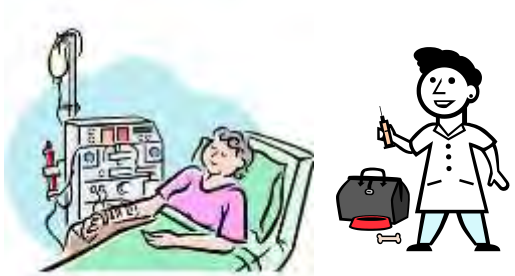
Regulations for RM/CT



Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

Medical practices using specified processed cells
without marketing authorization



Manufacturing and marketing of
products for RM/CT by firms

Act on the Safety of Regenerative Medicine (RM Safety Act)

- Medical treatments using processed cells
- Clinical researches using processed cells (non-commercial)

Pharmaceuticals & Medical Devices Act (PMD Act)

- Regenerative medical products (RMPs=CTP/GTPs)
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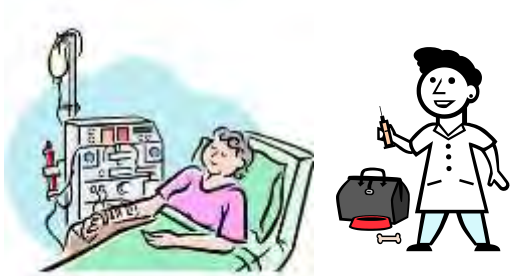

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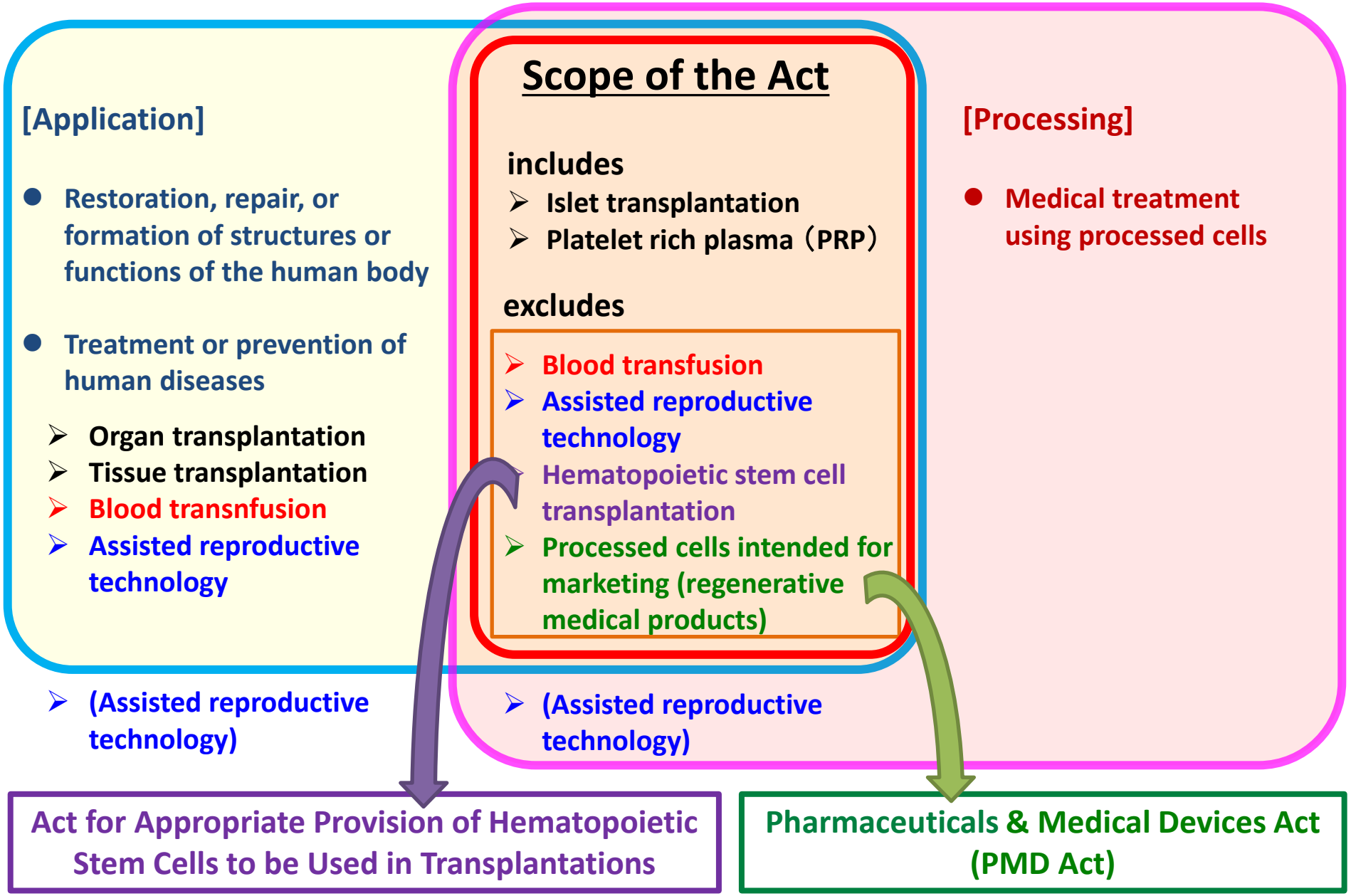
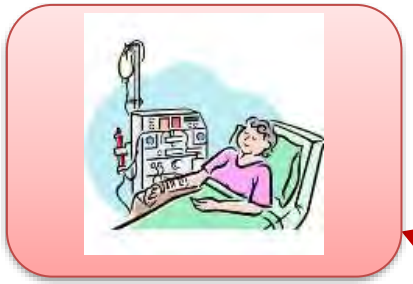
The Scope of the RM Safety Act



Overview of the RM Safety Act



RM/CT as medical practices

Hospitals / Clinics

Plan

Review

Certified Committee for Regenerative Medicine

Approval

II. Enable commissioning cell processing to licensed enterprises

I. Obligate hospitals and clinics to submit plans

Cell processing

Certification

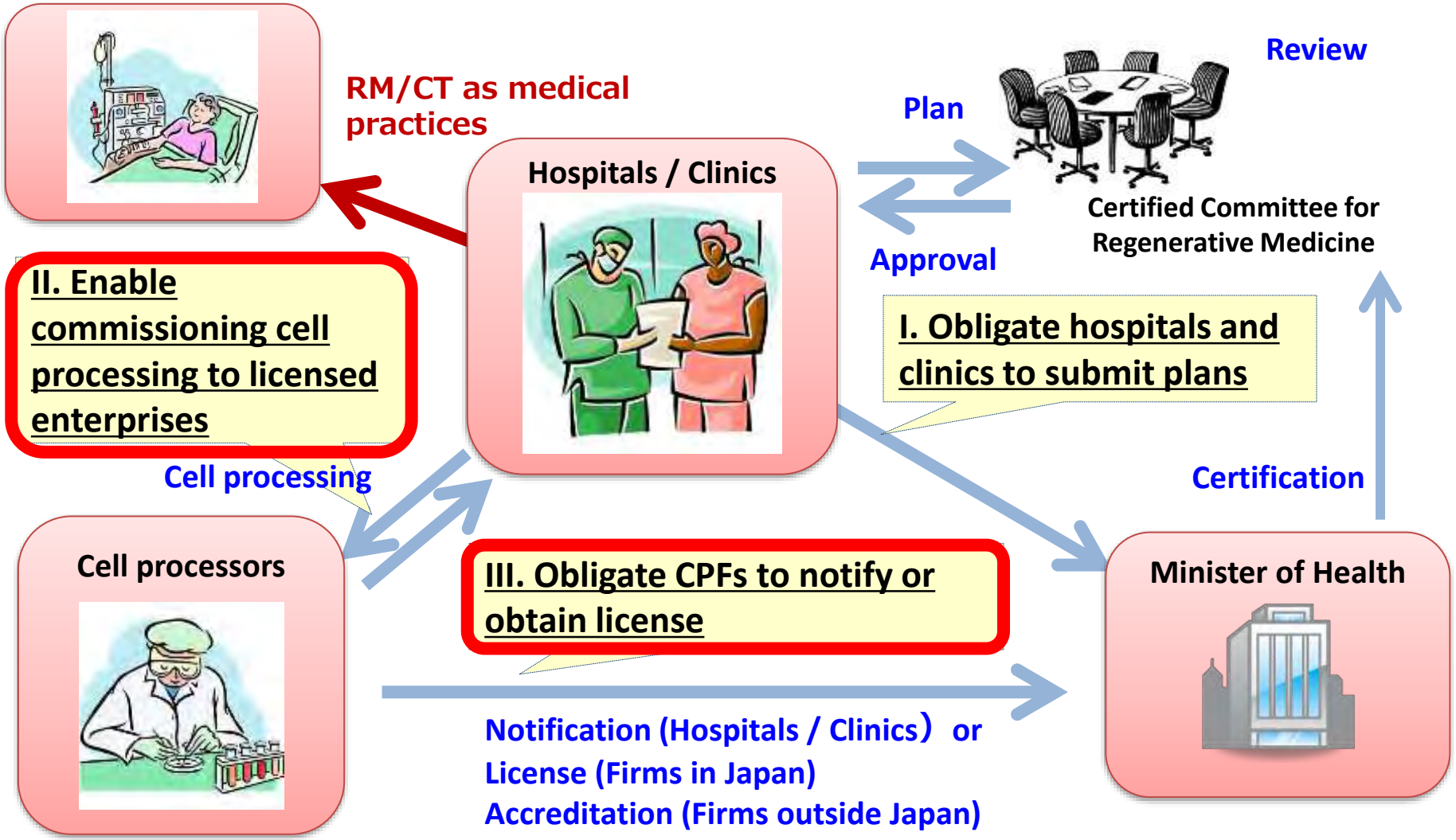
Cell processors

III. Obligate CPFs to notify or obtain license

Minister of Health

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

Overview of the RM Safety Act



The two legislations share common good practices for the quality/manufacturing control of manipulated cells

Out-of-pocket medical treatments
& non-commercial clinical researches
using specified processed cells without MA

Commercial distributions of
regenerative medical products
& their clinical trials

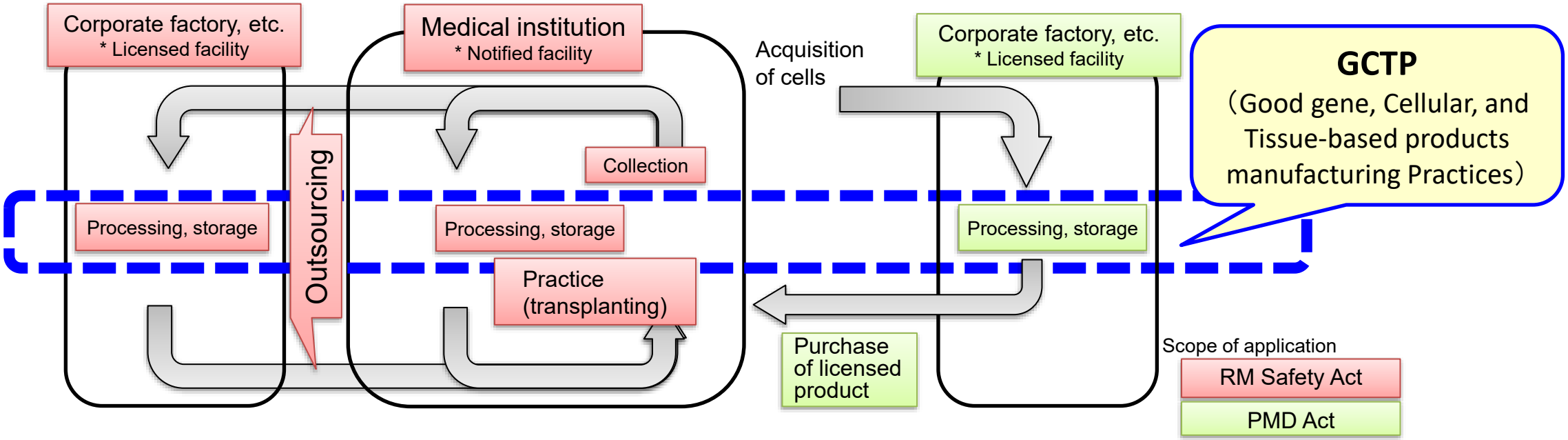
RM Safety Act

The safety, etc., of regenerative medicine provided as a medical service is ensured by stipulating the practical procedures of, for instance, sampling, standards for medical institutions that provide regenerative medicine and standards for facilities that culture and process cells.

PMD Act

The efficacy and safety of regenerative medical products are ensured by stipulating standards for manufactory of regenerative medical products.

* Outsourcing of cell culturing and processing carried out under the responsibility of physicians based on the Regenerative Medicine Safety Assurance Act is exempt from the application of the Pharmaceutical and Medical Device Act.



Specials & Hospital Exemption

	Specials	Hospital Exemption
Legal basis	Art. 5 (1) of Directive 2001/83/EC (Compassionate use on a named patient basis)	Art. 28 (2) ATMP regulation amending art. 3 of Dir. 2001/83/EC
Authorisation	No product licence but manufacturer licence	
Qualified Person	NO	
Scope	Any medicinal product including ATMPs	ATMPs only
Purpose	For special (clinical) needs of an individual patient	For an individual patient
Use	No restriction	Hospital
Movement	YES, possible export/import	NO, preparation and use within the same Member State
Evolution	Stopped once marketing authorisation obtained	*Nothing is said*

Evidence for the efficacy is NOT required.

https://www.eurostemcell.org/regenerative-medicine-special-report/access-to-regenerative-medicine/full-article

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Protection of the Public Health through the RM Safety Act (since 2014)

6 arrested over unauthorized stem cell therapy using cord blood

KYODO NEWS August 27, 2017

MATSUYAMA, Japan – Police on Sunday arrested a doctor and five others suspected of involvement in unauthorized stem cell therapies using blood from umbilical cords and placenta after childbirth.

The doctor who heads a clinic in Tokyo and people involved in cord blood sales are suspected to have administered cord blood to seven patients to treat cancer and as a beauty treatment. Each treatment is said to have cost 3 million to 4 million yen ($27,400-$36,600).

While hopes are high over the use of cord blood in the field of regenerative medicine to treat a number of diseases as it contains stem cells, the health ministry is concerned over the spread of costly medical services provided without clear scientific evidence and without ensuring sufficient safety.

The arrests were the first of anyone suspected of violating a law on regenerative medicine that came into force in 2014. The transplantation of cells could involve the risk of graft rejection and infection.

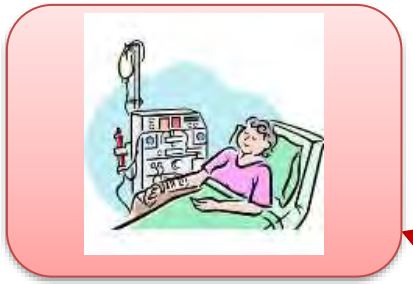
Medical institutions using stem cells are required to submit treatment plans beforehand for review by the health ministry, except for treating designated diseases such as leukemia.

The six suspects allegedly conducted the treatments without notifying the authorities.

In order to prevent future adverse events, the Government can arrest medical practitioners who conduct **cell therapy without notifying the authorities.**

https://english.kyodonews.net/news/2017/08/5d0a5ee3cba3-update1-6-arrested-over-unauthorized-stem-cell-therapy-using-cord-blood.html

Overview of the RM Safety Act



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nature

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nature › news feature › article

NEWS FEATURE | 25 September 2019 | Correction 10 October 2019

The potent effects of Japan's stem-cell policies

A five-year regulatory free-for-all in regenerative medicine has given the industry a boost. But patients might be paying the price.

David Cyranoski

"In addition to the questions about evidence and efficacy, **there are also concerns about the qualifications and independence of the committees that approve such treatments** for inclusion in the registry. The health ministry requires that these committees comprise five to eight people, and include specialists in cell biology, regenerative medicine, clinical research and cell culture. It also requires input from lawyers, bioethicists and biostatisticians. But **rules about conflicts of interest on the committee have been lax**.

…The ministry instituted policies in April to prevent such conflicts. But **even with fully independent committees, clinics can shop around for the answer they want**.

…**The government is considering extra fixes, such as requiring training to make the committee system better**."

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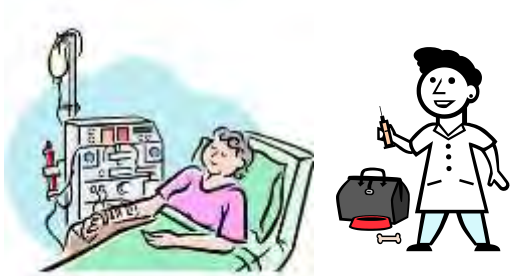

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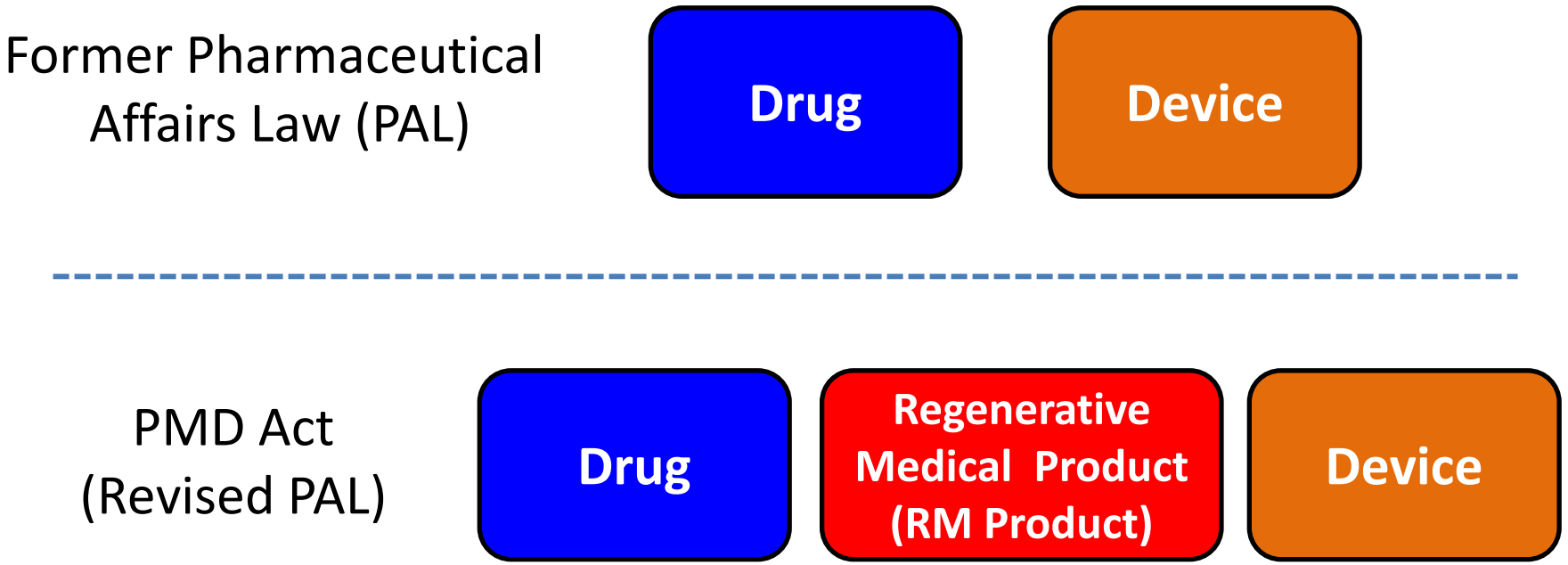
Regenerative Medical Products in the PMD Act



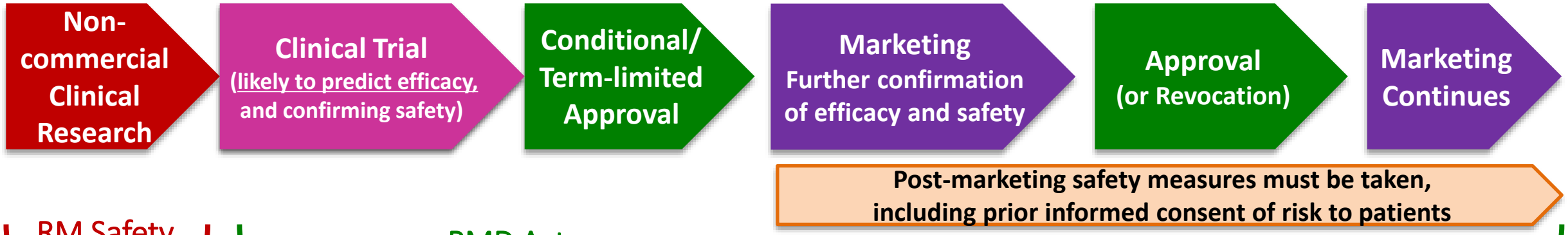
◆ **Additions for regenerative medicine products**

- Definition and independent chapter for regenerative medicine products
- Introduction of conditional/time limited approval system

Unique Approval Pathway for RM products in the PMD Act

☐ Conventional approval process

☐ Approval process that accommodates early practical application of RM products



- If data from the clinical trial are **likely predict efficacy and confirming safety**, **conditional/term-limited marketing authorization** for RM products might be granted to timely provide the products to patients.
- The PMD Act requires **further confirmation of safety and efficacy during the post-marketing phase**.

RM Products Approved for Manufacturing & Marketing in Japan

[as of November 17, 2021]

14 RM products have been approved under PMD Act

(including 2 in vivo gene therapy products & 1 oncolytic virus product)

- autologous epidermis
- autologous cartilage
- allogeneic MSCs (for GVHD)
- **autologous myoblast sheet (for heart failure)***
- **autologous MSCs (for spinal cord injury) ***
- autologous CAR-T cells
- autologous cultured corneal epithelium
- autologous CAR-T cells
- autologous CAR-T cells
- autologous cultured oral mucosal epithelial cell sheet (for extensive damage to the cornea of both eyes)
- allogeneic MSCs (for complex perianal fistulas of non-active or mildly active luminal Crohn's disease)

- **plasmid vector (for chronic arterial occlusion)***
- AAV vector (for spinal muscular atrophy)
- **oncolytic virus (genetically engineered oncolytic herpes simplex virus type 1 for malignant glioma)***

*conditional & term-limited approval

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*conditional & term-limited approval

Criticism of the conditional/term-limited approval of autologous MSCs for SCI

A stem-cell treatment for spinal-cord injuries will soon be available in Japan.

JAPAN

Stem-cell therapy raises concerns

Independent researchers warn that approval is premature

BY DAVID CYRANOSKI

Japan has approved a stem-cell treatment for spinal-cord injuries — the first such therapy for this kind of injury to receive government approval for use in patients.

"This is an unprecedented revolution in science and medicine, which will open a new era of health care," says neurologist Hidetoshi Tsuboi, head of the Translational Research Informatics Center, a Japanese government organization in Kobe that has been giving advice and support to the project for more than a decade.

But ten specialists in stem-cell science or spinal-cord injuries, who were approached for comment by *Nature* and were not involved in the work or its commercialization, say the approval is premature, because there is insufficient evidence that the treatment works. Many of them say the approval for the therapy, which is unproven and unnecessarily risky, was based on a small, poorly designed clinical trial.

They say that the trial's flaws — including that it was not double-blinded — make it difficult to assess long-term efficacy, because it is hard to rule out whether patients might have recovered naturally. And, although the cells used — which are extracted from a patient's bone marrow and known as mesenchymal stem cells (MSCs) — are thought to be safe, the infusion of stem cells into the blood has been connected with dangerous blood clots in the lungs. And all medical procedures carry risks, which makes them hard to justify unless they are proven to be beneficial.

"This approval is an unfortunate step away from everything researchers have learned over the past 70 years about how to conduct a valid clinical trial," says James Guest, a neurosurgeon at the Miami Project to Cure Paralysis at the University of Miami in Florida.

One architect of the treatment, neurosurgeon Osamu Honmou of Sapporo Medical University in Japan, says he plans to publish a scientific paper that will discuss the clinical trial and safety issues. "I think it is very safe," [he says he did not run a double-blinded study because Japan regulations do not require it. "The most important point is that the efficacy is dramatic and definitive," adds Fukushima.

The unpublished results describe a trial of 13 people who had experienced spinal-cord injuries in the past 40 days. The team found that infusions of MSCs, which had been multiplied in the lab after they were extracted, helped the injured volunteers to regain some of the sensation and movement they had lost.

EARLY GREEN LIGHT

On the basis of these results, Japan's health ministry last month gave conditional approval for the treatment, called Stemirac. In the clinical trial, about 30 million to 200 million MSCs were intravenously infused back into patients' [all days after their injury to help repair the] damage. The team can market and sell the therapy as long as they collect data from the participants over the next seven years that show that it works. People could start paying

"This approval is an unfortunate step away from everything researchers have learned over the past 70 years about how to conduct a valid clinical trial,"
James Guest, spinal cord injury researcher

"This trial, as designed, cannot reveal efficacy,"
Bruce Dobkin, spinal cord injury researcher

"I do not think it is morally justified to charge patients for an unproven therapy that has risks,"
Arnold Kriegstein, stem cell researcher

Nature 565, 535–536; 2019 and Nature 565, 544–545; 2019.

Criticism of the conditional/term-limited approval of autologous MSCs for SCI

Stem-cell therapy

MHLW's response to the Criticism

"cannot accept your criticism of our approval of stem-cell treatment for spinal-cord injuries"

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James Guest, spinal cord injury researcher

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"But **in this therapy**, known as Stemirac, stem cells from the patient's bone marrow are cultured externally and then returned to the patient (in sub-acute phase). **A double-blind study is therefore structurally impossible, and performing a sham operation on a control group would raise ethical issues**."

"I do not think it is morally justified to charge patients for an unproven therapy that has risks,"
Arnold Kriegstein, stem cell researcher

"However, under the terms of the country's conditional and time-limited approval for regenerative medical products, such products are granted marketing authorization only when efficacy can be demonstrated in post-marketing studies within a specified period. And, **because Stemirac is covered by national health insurance, patient payments are fixed at a feasible level**."

Correspondence (Nature 569, 40; 2019)

Likely to Predict Efficacy (Clinical Benefit)

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**.
- Postmarketing studies would usually be studies already underway.
- FDA may **withdraw approval**, if a **postmarketing clinical study fails** to verify clinical benefit; …….

Early Access Schemes of US, EU/UK and JP

US	EU & UK	JP
Priority Review	Accelerated Assessment	Priority Review
Accelerated approval for serious or life-threatening illnesses	Conditional marketing authorisation (MA) MA under exceptional circumstances	Conditional approval for Oncology drugs & Orphan drugs Conditional & term-limited approval for RM products
	Hospital Exemption Special Exemption	
Breakthrough therapy & Fast Track designation RMAT (Regenerative Medicine Advanced Therapy) designation	PRIME (PRIority MEdicines) scheme	Forerunner Review Assignment（“SAKIGAKE”）

Each agency has unique approaches, which seem to aim a common goal, to accommodate patient access to medicines.

Thank you for your attention!

Yoji SATO, PhD

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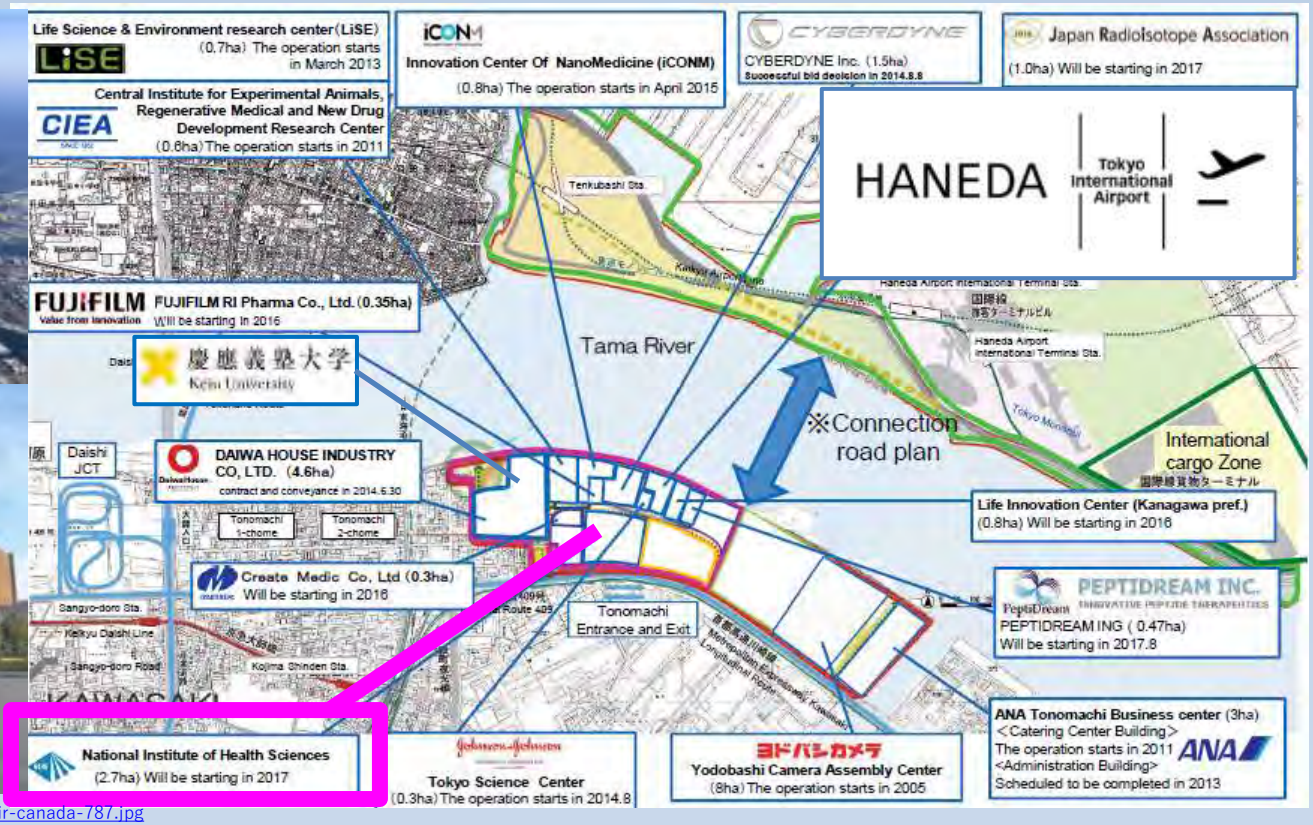

* https://www.oag.com/hubfs/air-canada-787.jpg
** http://www.city.kawasaki.jp/en/page/0000038680.html