November 25, 2020

JPN Kanagawa Prefecture – UK Cell & Gene Therapy Catapult Webinar

Japan's Regulatory Landscape for Cell Therapy and Regenerative Medicine

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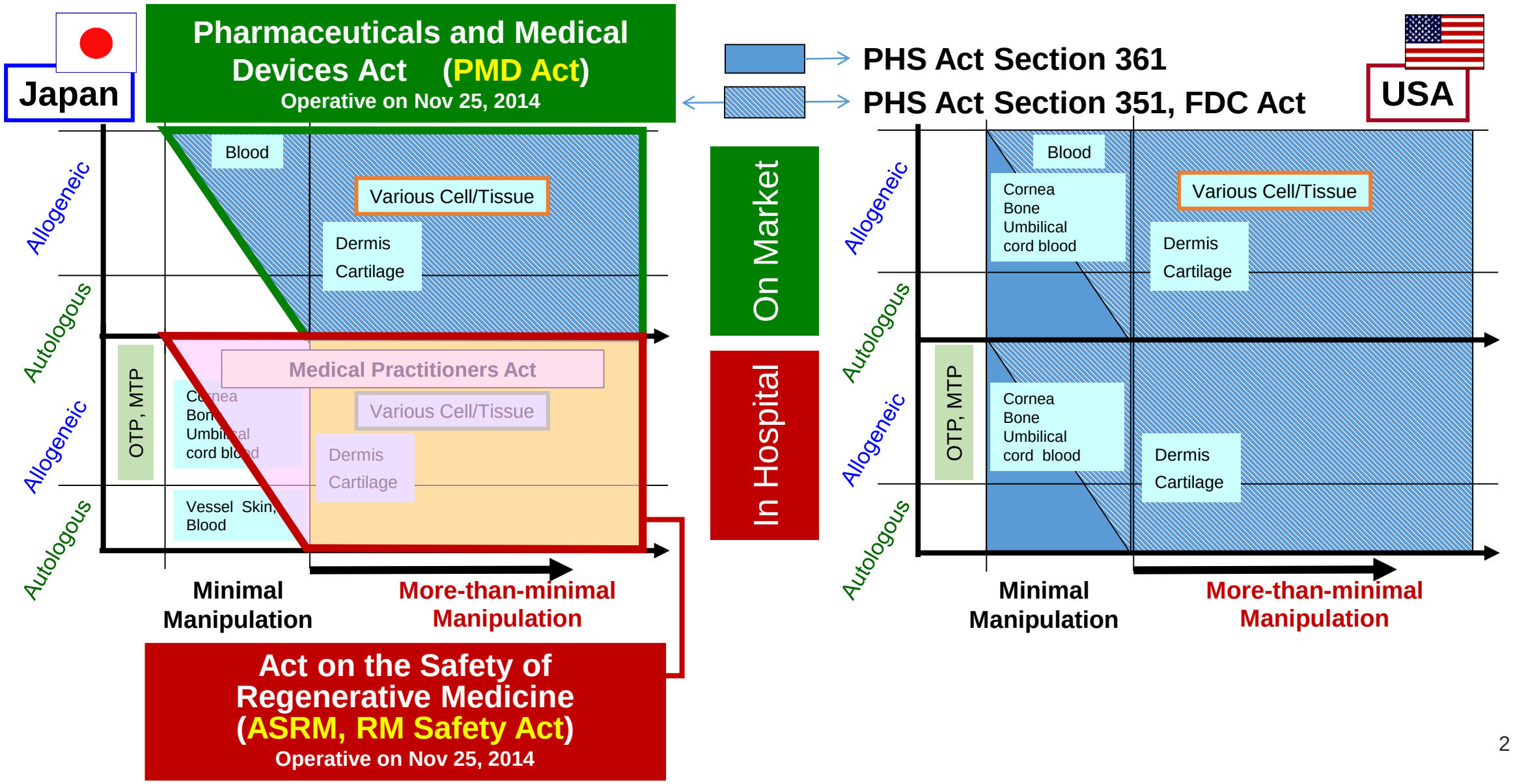
Regulations for CT/RM



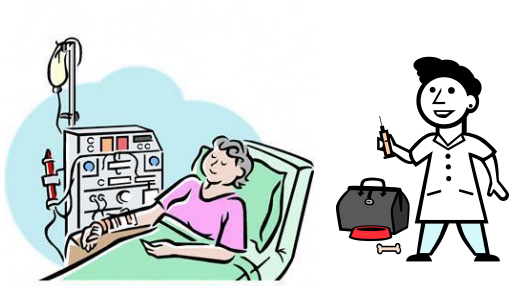
Two Acts Regulating CT/RM

In Hospital

Cell Therapy
Regenerative Medicine

On Market

Medical practices using processed cells, which are not intended for marketing



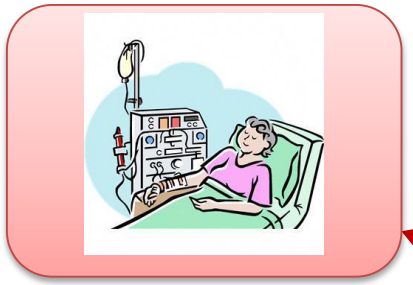
Regenerative Medicine Safety Act (RM Safety Act) *

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

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

* Two laws were enacted on 25 November 2014.

CT/RM using processed cells without MA under the Act on the Safety of Regenerative Medicine (RM Safety Act)



CT/RM as medical practices

Hospitals / Clinics

Plan

Review

Approval

Certified Committee for Regenerative Medicine

II. Enable commissioning cell processing to licensed enterprises

I. Obligate hospitals and clinics to notify MHLW of their 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)

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

Clinical study, private practice
(using processed cells without MA)

Regenerative medical products
(for marketing)

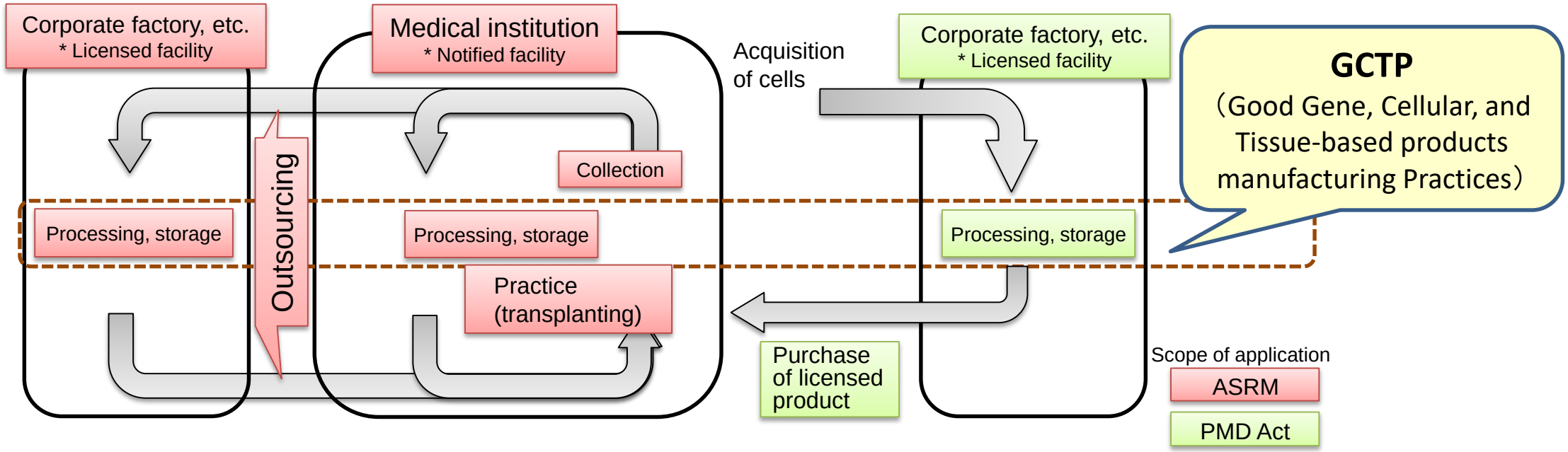
RM Safety Act

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 mandatory.

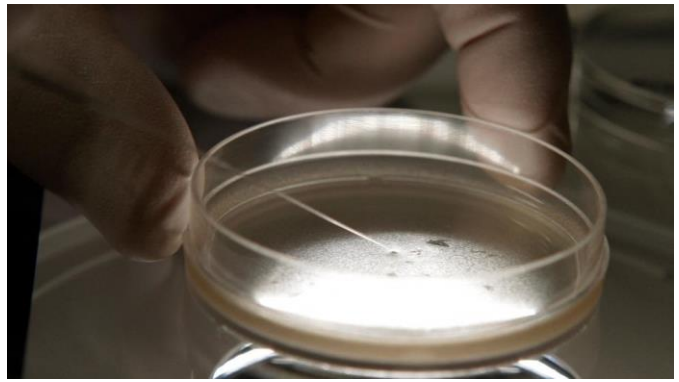
https://www.eurostemcell.org/regenerative-medicine-special-report/access-to-regenerative-medicine/full-article

Stem cell shots linked to outbreak of bacterial infection

At least 12 patients in Florida, Texas and Arizona became infected after getting injections, the Centers for Disease Control and Prevention said.

Infection by an unapproved cord blood cell product

Bacterial contamination during the manufacturing



By Associated Press

December 21, 2018

Health officials on Thursday reported an outbreak of bacterial infections in people who got injections of stem cells derived from umbilical cord blood.

At least 12 patients in three states – Florida, Texas and Arizona – became infected after getting injections for problems like joint and back pain, the Centers for Disease Control and Prevention said. All 12 were hospitalized, three of them for a month or longer. None died.

Investigators don't think the contamination occurred at the clinics where the shots were given, because they found bacteria in unopened vials provided by the distributor, Liveyon, based in Yorba Linda, California.

Liveyon voluntarily recalled the stem cells in October.

Protection of the Public Health through the RM Safety Act (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

Two Acts Regulating CT/RM

In Hospital

Cell Therapy
Regenerative Medicine

On Market

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

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

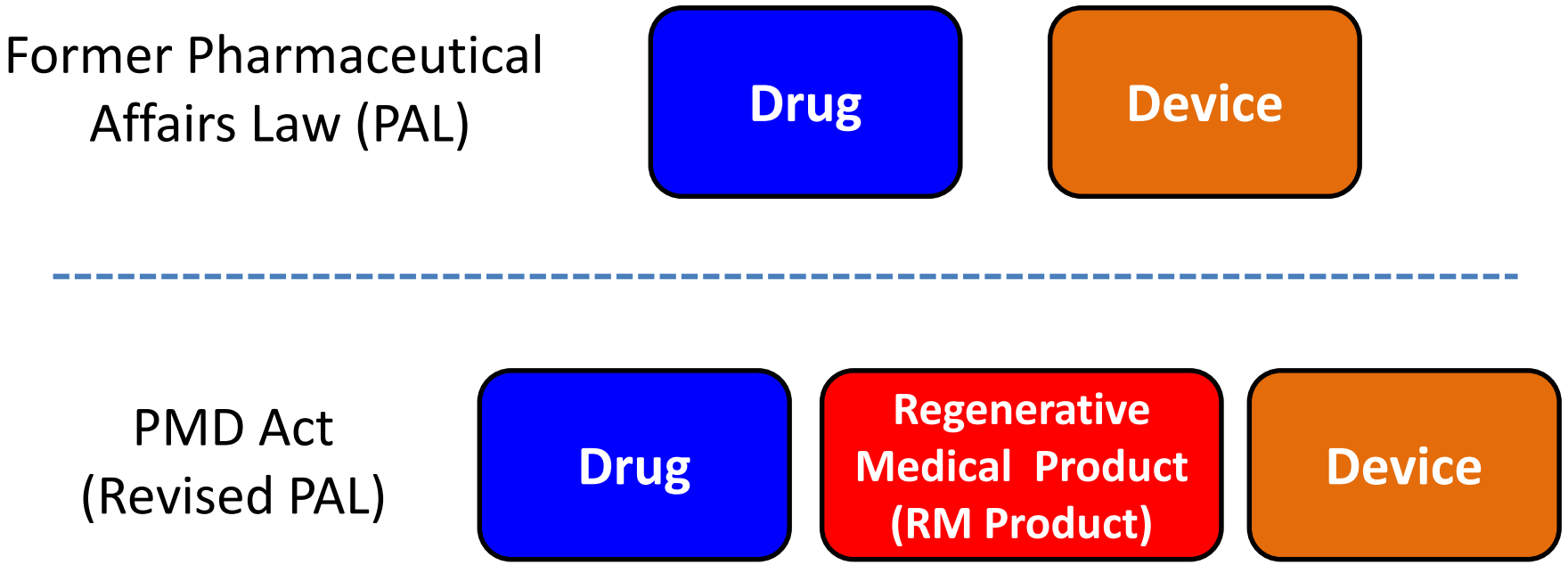
Basically not covered by public insurance

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

Pharmaceuticals and Medical Devices Act (PMD Act)

Usually fully covered by public insurance

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 in Japan's Legislation

☐ Conventional approval process

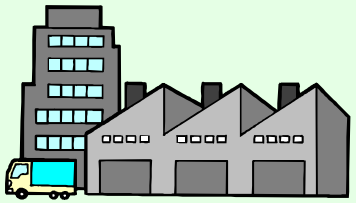
☐ Unique approval process that accommodates early practical application of **RM products**

- 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

9 RM products have been approved under PMD Act
(including **2 products for in vivo gene therapy**)

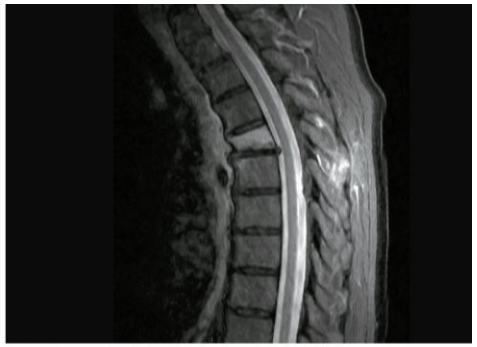
- autologous epidermis
- autologous cartilage
- allogeneic MSCs for GVHD
- autologous myoblast sheet*
- autologous MSCs for spinal cord injury *
- autologous CAR-T cells
- autologous cultured corneal epithelium



- plasmid vector for chronic arterial occlusion *
- AAV vector for spinal muscular atrophy

*conditional & term-limited approval

Criticism of the recent 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 sale to patients.

"This is an unprecedented revolution of science and medicine, which will open a new era of health care," says oncologist Masanori Fukushima, 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 injected intravenously, 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 offer a benefit.

"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 inventor 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 do a double-blinded study because Japan's 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 50 million to 200 million MSCs were intravenously infused back into patients 40 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 recent 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

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MHLW's response to the Criticism

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

"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

"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 JPN

US	EU & UK	JPN
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	
Breakthrough therapy & Fast Track designation RMAT (Regenerative Medicine Advanced Therapy) designation	PRIME (PRIority MEdicines) scheme	Forerunner Review Assignment（“SAKIGAKE”）

Each agency has unique approaches to accommodate patient access to medicines although they have certain similarity.

Unique Approval Pathway in Japan's Legislation

☐ Conventional approval process

Real world data are quite important!

Non-commercial Clinical Research → Clinical Trial (confirmation of efficacy and safety) → Approval → Marketing

☐ New approval process that accommodates early practical application of RM products

Non-commercial Clinical Research → Clinical Trial (likely to predict efficacy, and confirming safety) → Conditional/ Term-limited Approval → Marketing Further confirmation of efficacy and safety → Approval (or Revocation) → Marketing Continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

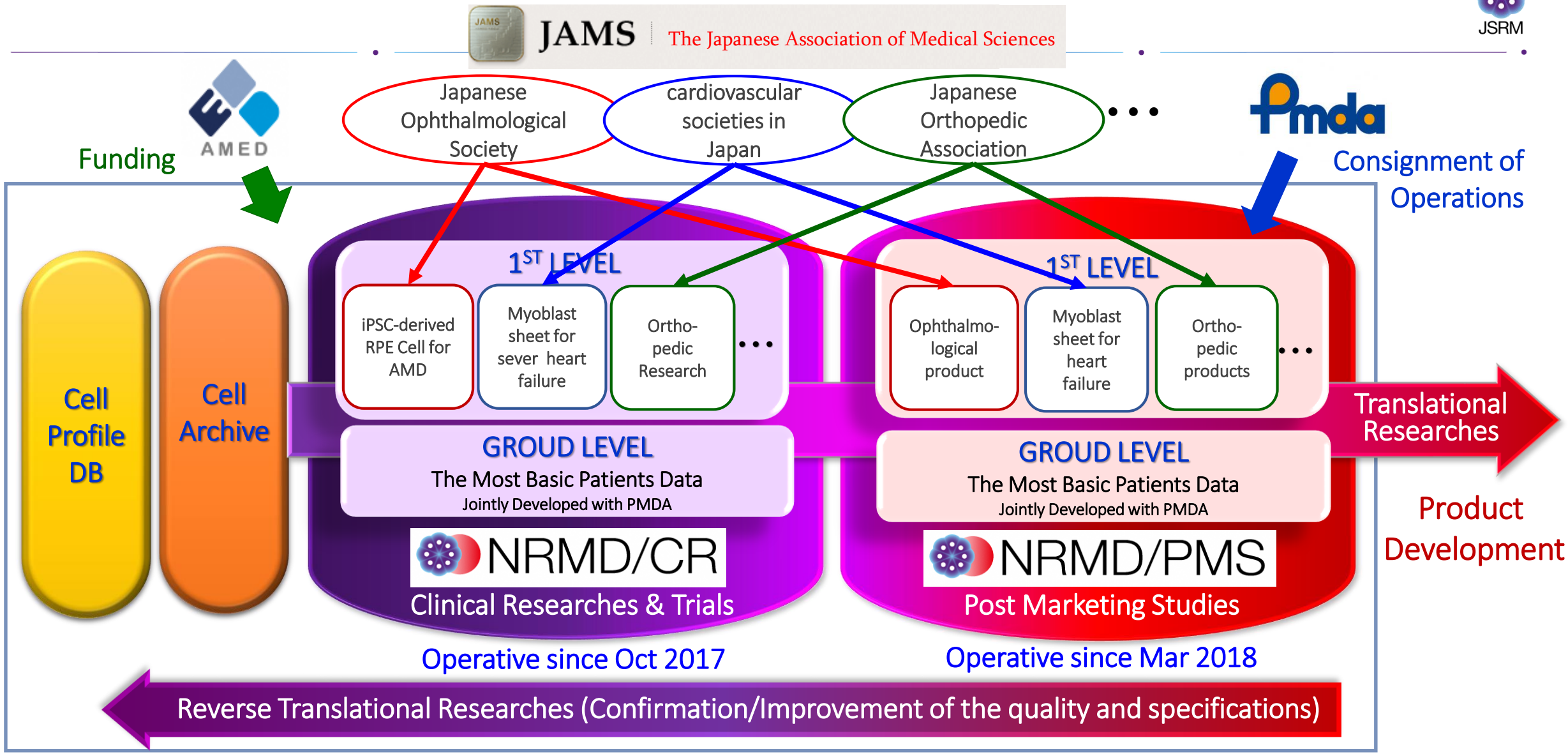
RM Safety Act

PMD Act

Challenge

- 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.

Development of Nation-wide Clinical Research Data Systems (NRMD)



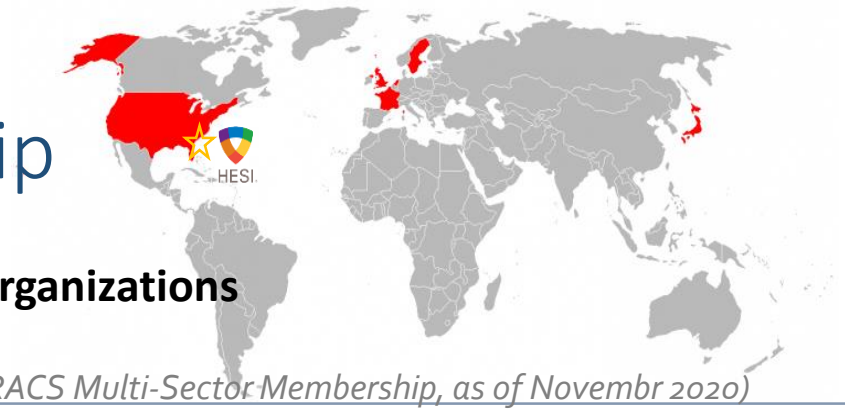
These Databases enables seamless translational/reverse translational researches from clinical investigation to PMS, by acquiring real world data of all clinical cases into the systems with common data quality assurance.

Introduction of
National Regenerative Medicine Database (NRMD)

(Japanese)
https://www.youtube.com/watch?v=s3wdgnYZ-l8

(English)
https://www.youtube.com/watch?v=LVCLVkPzrNQ

HESI CT-TRACS Membership



Committee members and collaborators from > 25 organizations across EU, UK, Japan and USA.

(CT-TRACS Multi-Sector Membership, as of Novembr 2020)

Regulatory bodies:

FDA

cBG MEB Medicines Evaluation Board

MHRA

Universities/ Research Centers:

King's College London University of London

Memorial Sloan Kettering Cancer Center

University of Liverpool

Imperial College London

UCL

Stanford Cardiovascular Institute

Gov./Consortia/NGO:

CIRM

CATAPULT Cell and Gene Therapy

eatris European infrastructure for translational medicine

FIRM Forum for Innovative Regenerative Medicine

NIBSC

RIVM

NIH National Institutes of Health

NGO Personalized Medicine and Healthcare

NIHS

National Institute for Public Health and the Environment Ministry of Health, Welfare and Sport

PACT Production Assistance for Cellular Therapies National Heart Lung and Blood Program

Developers (Therapies and Tools), CROs:

astellas Leading Light for Life

Athersys

Boehringer Ingelheim

janssen

GE Healthcare

Celsense

FUJIFILM Cellular Dynamics

charles river

CiToxLAB

COVANCE

AstraZeneca

NOVARTIS

Sumitomo Dainippon Pharma

TACONIC

Takeda

VisiCELL MEDICAL

Thank you for your attention!

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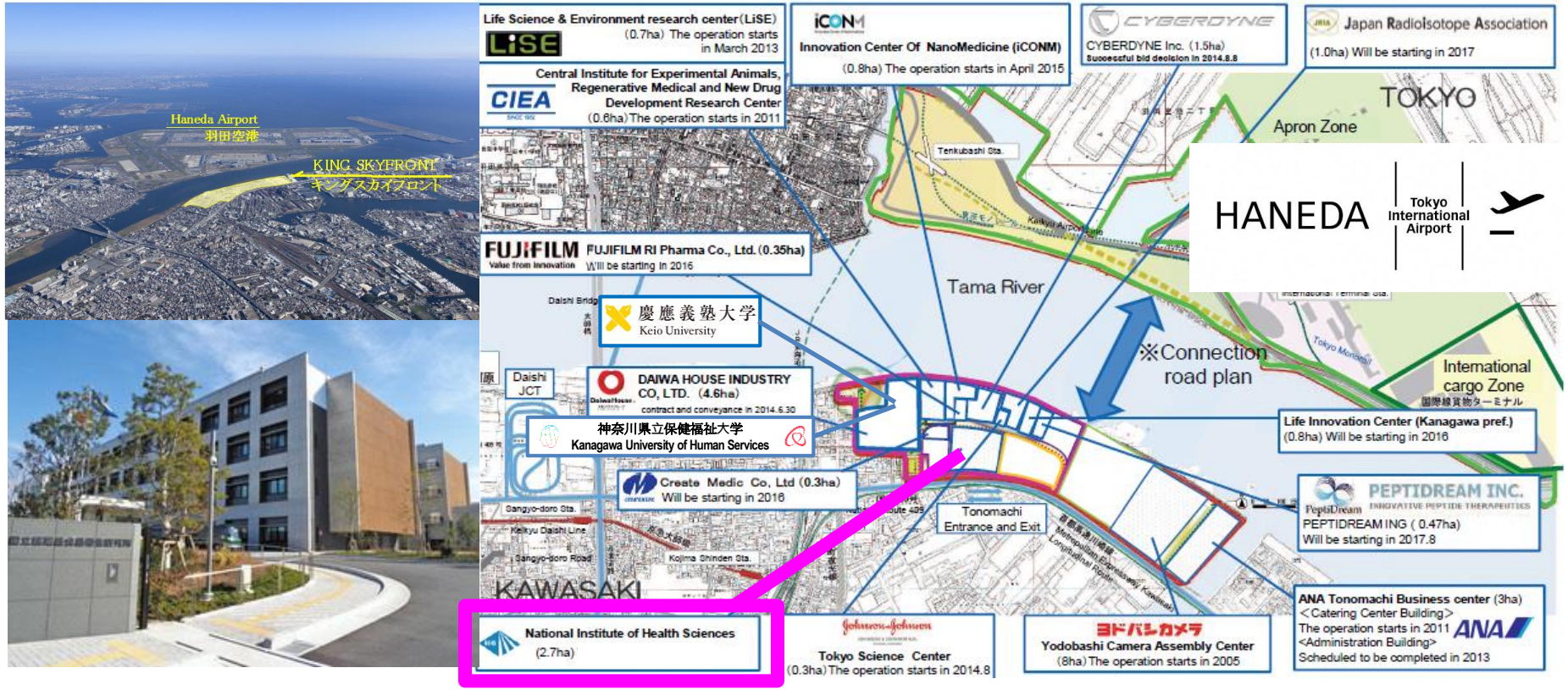

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* https://www.oag.com/hubfs/air-canada-787.jpg
** http://www.city.kawasaki.jp/en/page/0000038680.html