June 4, 2021
Korea

第2回先端再生医療及び先端バイオ医薬品政策審議委員会
The 2nd Regenerative Medicine & Advanced Biological Products Policy Committee

日本における再生医療・細胞治療の提供のための制度
The Regulatory System for the Provision of Regenerative Medicine & Cell Therapy in Japan

佐藤 陽治
国立医薬品食品衛生研究所
再生・細胞医療製品部長

Yoji SATO, Ph.D.
Head, Division of Cell-Based Therapeutic Products
National Institute of Health Sciences, Japan

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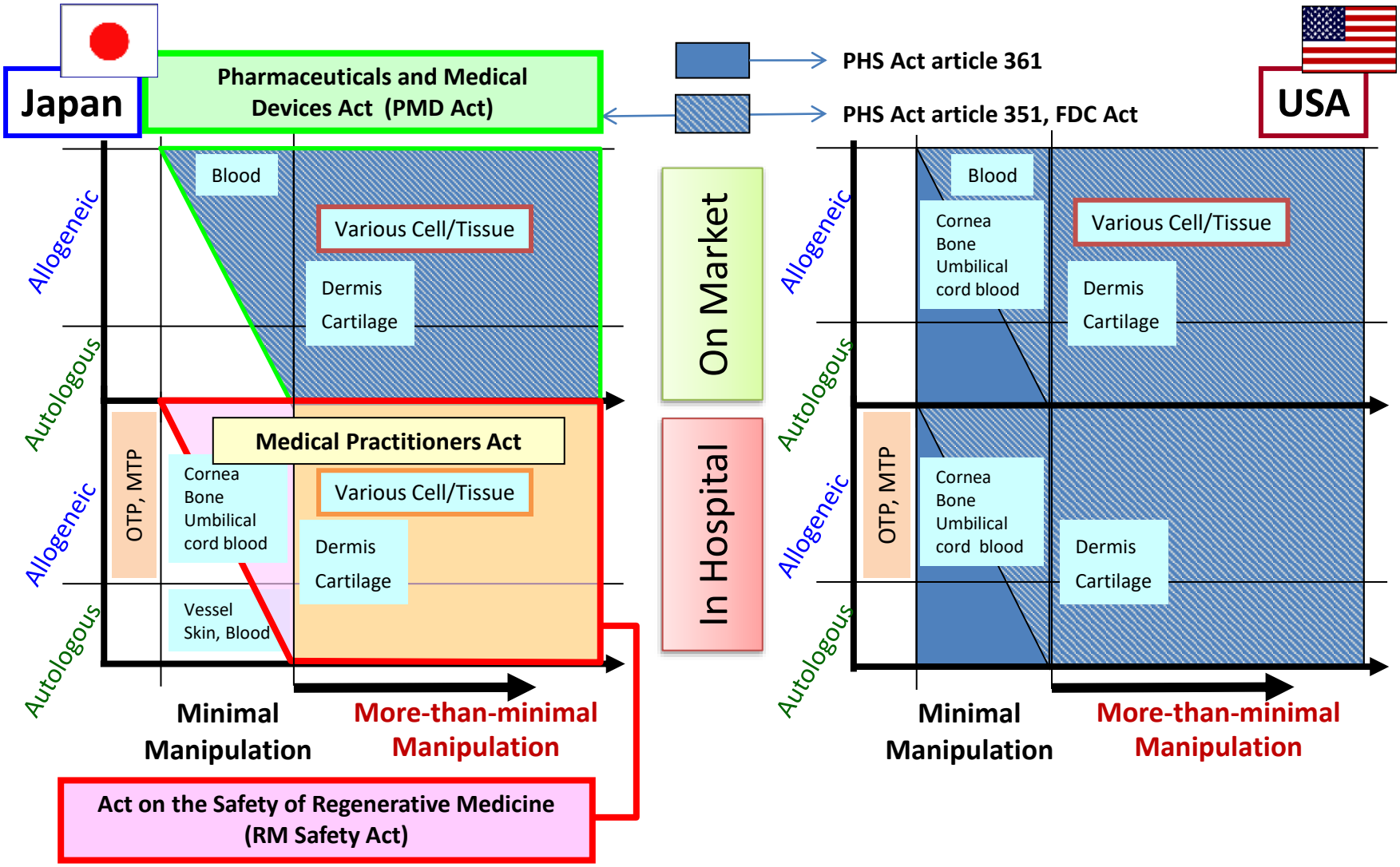
Q1. 再生医療における治療、研究、先進医療など、日本の再生医療の区分とそれぞれの承認(許可）の要件は何ですか?

Q1: Please explain the categories of regenerative medicine and cell therapy in Japan, *e.g.,* medical practice/care, clinical research, advanced medical care, *etc.*, and the requirements for approval/permission for each category.

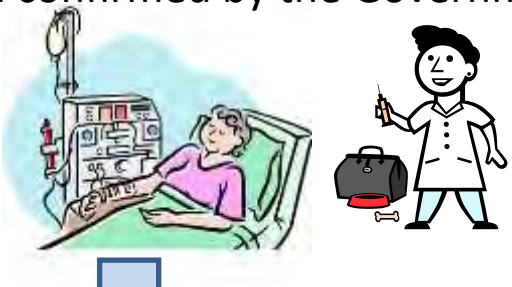
Regulation for regenerative medicine (RM)/cell therapy (CT)



Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

Medical practices using processed cells, whose safety and efficacy have not yet been confirmed by the Government



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)
- Clinical trials of RMPs (commercial)

The Scopes of the Acts in the Fields of GT and RM/CT

In Hospital

Medical Practitioners Act & Medical Care Act

In Vivo Gene Therapies
Using Gene Vector Products

RM Safety Act

Therapies Using
Specified Processed Cells
(Including Genetically Modified Cells)

On Market

PMD Act

- Products for Gene Therapy
  (Gene Vector Products for *in vivo* gene therapy)
- Human-Derived Cell-Processed Products
- Animal-Derived Cell-Processed Products
  (Including Genetically Modified Cells)

"Regenerative Medical Products"

“RM/CT as Medical Care” vs. “Products for RM/CT (& GT)”

	RM/CT as Medical Practices	Products for RM/CT (&GT)
Purpose	Ensuring the safety and validity of **medical treatments AND non-commercial clinical researches** using processed cells	Development, manufacturing & marketing of **regenerative medical products (RMPs = CTPs & GTPs)**
Regulatory Framework	**Medical Practitioners Act & Medical Care Act** **Regenerative Medicine Safety Act (RM Safety Act)** **Ordinance for Enforcement of the Act on the Safety of Regenerative Medicine (MHLW Ordinance No. 110 (2014))**	**Pharmaceuticals and Medical Devices Act (PMD Act)** GLs and Standards for Ensuring the Quality/Safety of Cell-Based Therapeutic Products and Gene Therapy Products
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Advisory	**MHLW Health Science Council** [for Class 1 RM/CT]	
Health Insurance	**NOT covered by public insurance**	**Fully covered by public insurance**

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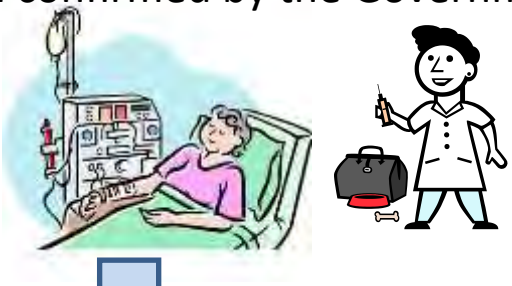

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The Scope of the RM Safety Act

Scope of the Act

includes

- Islet transplantation
- Platelet rich plasma（PRP）

excludes

- Blood transfusion
- Assisted reproductive technology
- Hematopoietic stem cell transplantation
- Processed cells intended for marketing (regenerative medical products)

[Application]

- Restoration, repair, or formation of structures or functions of the human body
- Treatment or prevention of human diseases
  - Organ transplantation
  - Tissue transplantation
  - Blood transnfusion
  - Assisted reproductive technology

- (Assisted reproductive technology)

[Processing]

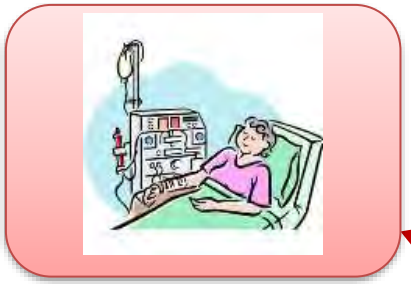
- Medical treatment using processed cells

- (Assisted reproductive technology)

Act for Appropriate Provision of Hematopoietic Stem Cells to be Used in Transplantations

Pharmaceuticals & Medical Devices Act (PMD 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

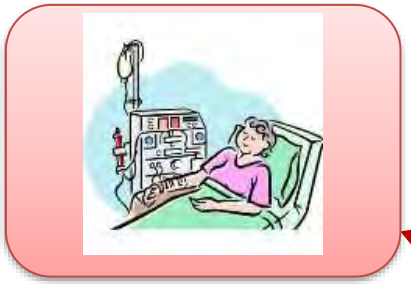
Cell processors

III. Obligate CPFs to notify or obtain licence

Minister of Health

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

Overview of the RM Safety Act



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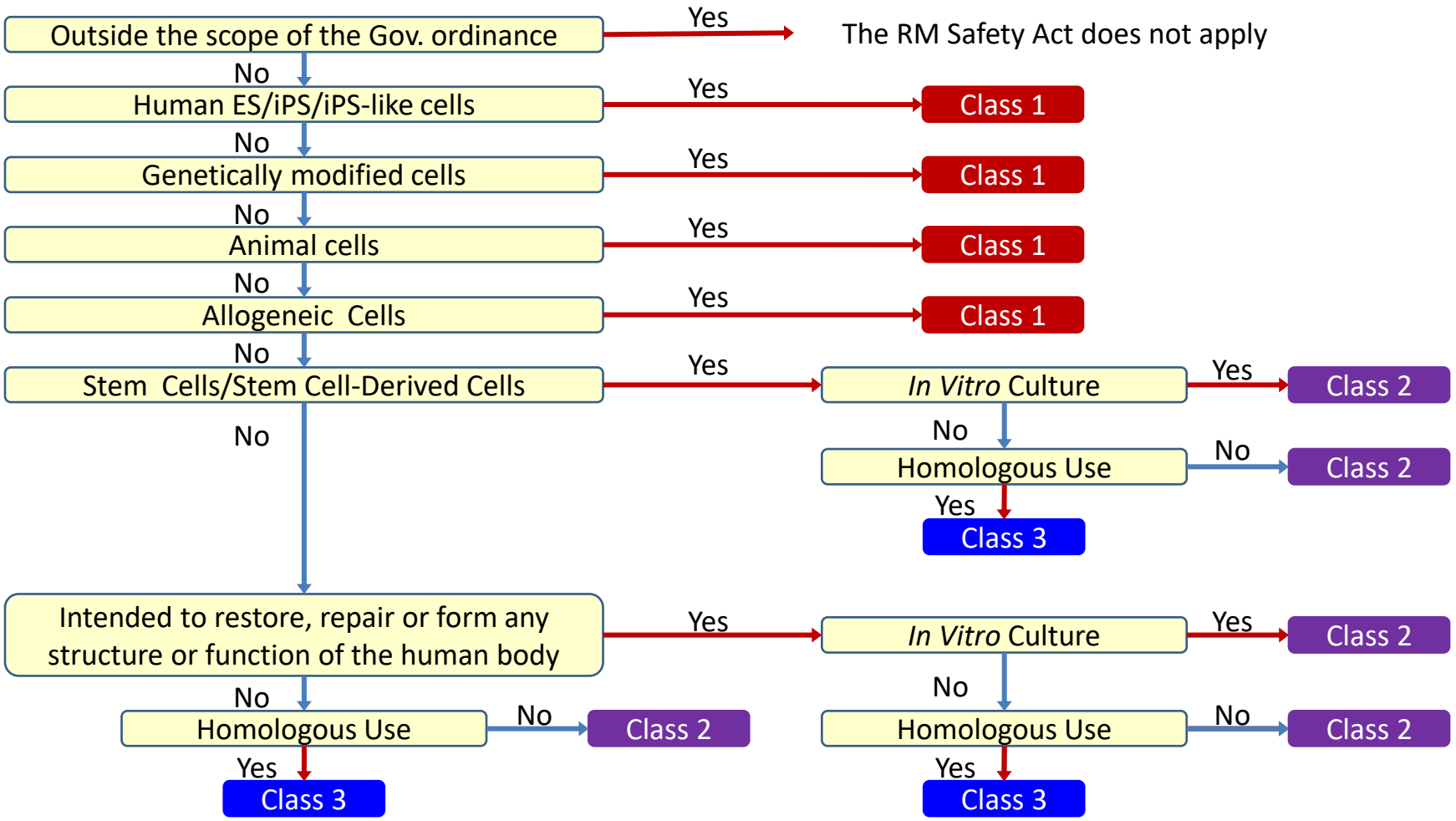
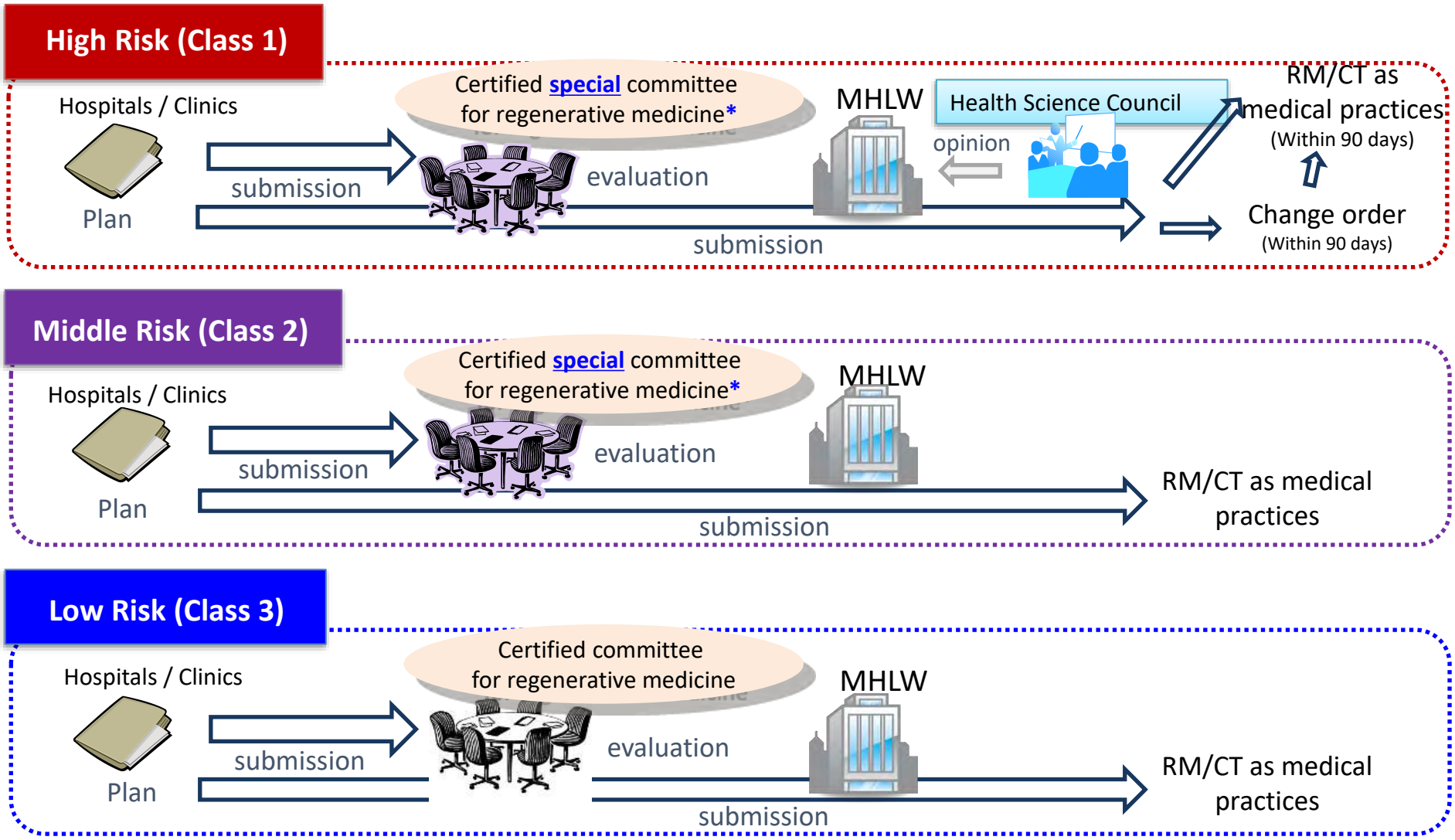
Classification of RM/CT under the RM Safety Act

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)

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“Standards for the Provision of Regenerative Medicine & Cell Therapy” [in MHLW Ordinance No. 110 (2014)]

1. Requirements concerning the number of personnel and facilities to be possessed by hospitals or clinics that provide regenerative medicine & cell therapy (RM/CT).

2. Requirements concerning the method of obtaining cells used for RM/CT and the method of manufacturing and quality control of specified cell processed products

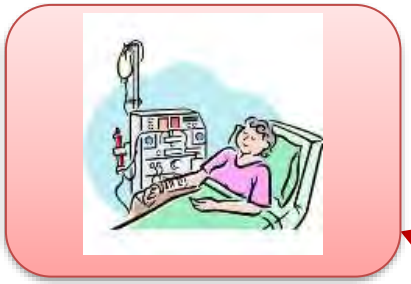
3. In addition to what is listed above, requirements concerning measures to ensure the safety of technologies for RM/CT.

4. Requirements concerning the method of compensation for health damage to a person who provides cells used for regenerative medicine, etc. and a person who receives RM/CT.

5. Other requirements necessary for the provision of RM/CT.

Regenerative medicine & cell therapy (RM/CT) under the RM Safety Act shall be provided in accordance with the Standards for the Provision of Regenerative Medicine & Cell Therapy.

Overview of the RM Safety Act



RM/CT as medical practices

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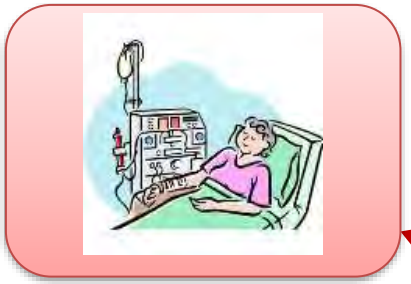

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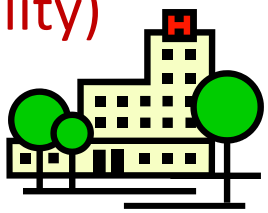
Notification or Manufacturing Business License

- Hospital in-house CPF (Cell Processing Facility)
  - ✓ Notification of facility and equipment



- CPF outside the hospital

  If physicians commission cell processing to a CPF outside the hospital, license or accreditation by MHLW is required.

  - ✓ Manufacturing Business License for Local manufacturing sites
  - ✓ Manufacturing Business Accreditation for Foreign manufacturing sites

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

Both types of CPFs need to be compliant with GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice = GMP for regenerative medical products)

Q2. 事前審査なしに患者と病院間の同意によって実施される自由診療の場合、危険性に対する恐れはないのでしょうか

Q2: Is there any risk of medical treatment being carried out at the discretion of medical practitioners only with the consent of the patient and hospital and without prior review ?

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.

Medical practitioners who conduct **cell therapy without notifying the authorities can be arrested** by the Government **in order to prevent future adverse events.**

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

Q3. 再生医療の治療、研究、先進医療に対する患者の費用負担は、それぞれどのように行われていますか?（保険収載の比率、患者負担額の割合など)

Q3: How much do patients pay for regenerative medicine as a medical treatment, clinical research, or advanced medical treatment? (Percentage of insurance coverage, percentage of patient contribution, *etc.*)

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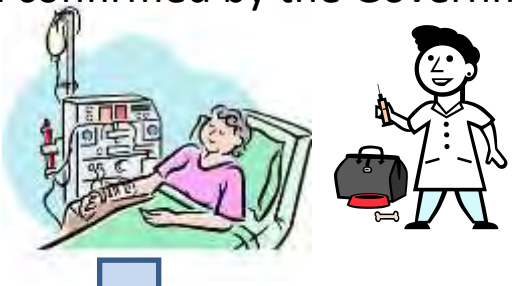

Manufacturing and marketing of **products for RM/CT** by firms

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

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

Public insurance NOT applied

Funded by research grant

Pharmaceuticals & Medical Devices Act (PMD Act)

- Regenerative medical products (RMPs=CTP/GTPs)
- Clinical trials of RMPs (commercial)

Public insurance fully applied

Self- (or research grant-) funded

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Public insurance NOT applied → **Exception**

Funded by research grant

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- Clinical trials of RMPs (commercial)

Public insurance fully applied

Self- (or research grant-) funded

→ Exception

“Advanced Medical Treatment”

- In Japan, medical treatment that is not covered by public medical insurance is not allowed to be combined with medical treatment covered by public medical insurance, and the patient must pay the full amount for both treatments when conducted at the same time.

- However, for new treatments and surgeries for intractable diseases, etc., which are studied and developed at specific university hospitals, etc., once information on efficacy and safety is accumulated, certain institutional criteria are set for each medical treatment.

- Medical treatment at an insured medical institution that meets the criteria is designated as “Advanced Medical Treatment" by the Ministry of Health, Labor and Welfare, and is allowed to be combined with medical treatment covered by public medical insurance.

- Advanced medical treatment is considered to be a treatment or surgery that is still in the process of being evaluated to be covered by public medical insurance.

“Advanced Medical Treatment”

Example:

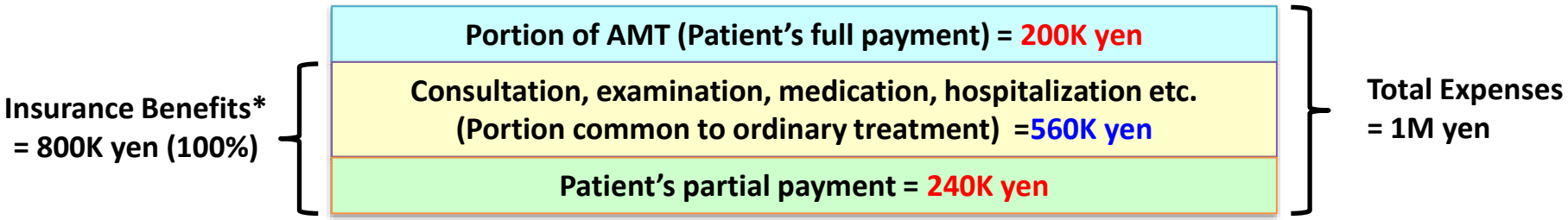
Total medical expenses are 1 million yen, of which 200,000 yen is for advanced medical treatment.

1. The patient is responsible for the entire 200,000 yen for the advanced medical treatment.
2. The portion common to ordinary treatment (consultation, examination, medication, hospitalization fee*) is the portion that is covered by public medical insurance.

Insurance benefits* = 800,000 yen (100%)

70% (560,000 yen) is paid by public medical insurance.

30% (240,000 yen) is the patient’s partial payment.



* **The high-cost medical care system** can be applied to the patient’s partial payment, which is the difference between the insurance benefits and the actual payment by public medical insurance.

Q4. 保険収載ができてない施術(自由診療、保険未適用の治療)の場合、高費用の再生医療施術に対する患者の医療へのアプローチの公平性が問題化されるかと思いますが、これらに対して、例えば、公益ファンドや民間レベルの基金助成などを通してサポートした事例があるのでしょうか、または、他のやり方で、何か解決策があるのでしょうか?

Q4. In the case of medical practices that are not covered by insurance (treatment at the discretion of the physician, treatment not covered by insurance), the fairness of the patient's approach to medical care for high-cost regenerative medicine procedures may be an issue. Is there any support for these through, for example, public interest funds, private funding, or any other means?

“Advanced Medical Treatment Rider”

provided by **private insurance companies**

1. There is **NO** private insurance **for medical care not covered by public insurance**, because no authority guarantees its safety and efficacy.

2. There is **NO** private insurance **that ONLY covers advanced medical treatment.**

3. **Advanced medical treatment rider** can be added **to private medical insurance and cancer insurance.**

4. Advanced medical care rider cannot be added to the other kinds of life insurance such as death benefits and individual annuities.

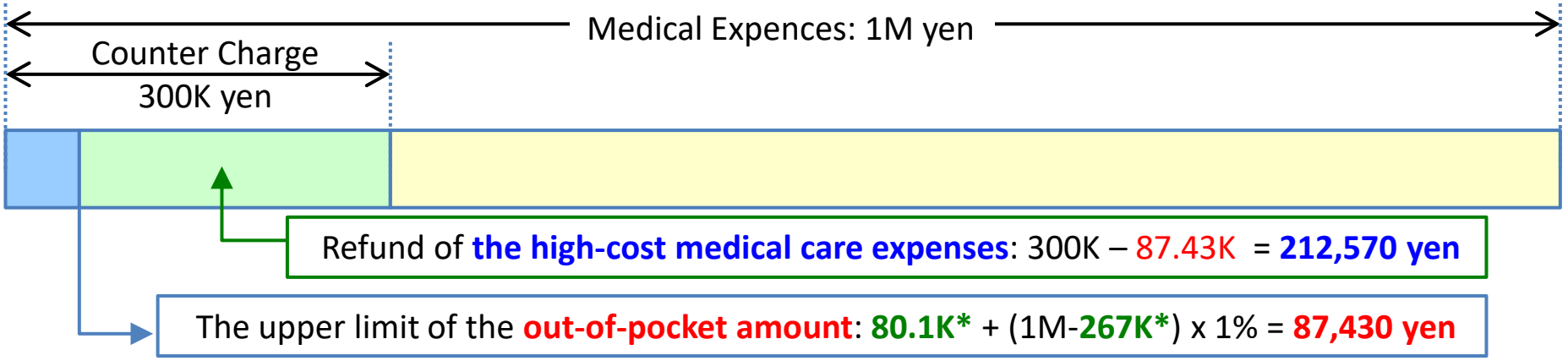
“High-Cost Medical Care System”

for medical care covered by public insurance

The high-cost medical care system is a system for paying the amount of money paid at the counter of a medical institution or pharmacy that exceeds the maximum amount for a month (from the beginning to the end of the month). This does not include the cost of food and other expenses incurred during hospitalization.

Example: 70 years old or older, annual income of approximately 3.7M-7.7M yen (→ 30% payment*)

In the case of a medical expense of 1M yen, the counter charge (30%) would be 300K yen.



212,570 yen will be paid as high-cost medical care expenses, and **the out-of-pocket amount will be 87,430 yen**. *** The amount (10-30%) depends on age and income.**

Q5. その他、韓国の再生医療施術について許可する際、
留意点やアドバイスしておきたいところは何でしょうか?

Q5. What are points to consider when approving the
provision of regenerative medicine in Korea?

nature

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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.

Helene Clinic, for example, had an in-house committee that approved some of its therapies, including a treatment for atherosclerosis. A representative for the company says that this therapy was never given to patients and Helene now uses an independent, third-party committee. The in-house committee was disbanded in March, according to the health ministry. The ALS treatment and several other therapies offered by Avenue Cell Clinic were approved by a committee that includes a staff physician. The clinic did not respond to questions about this.

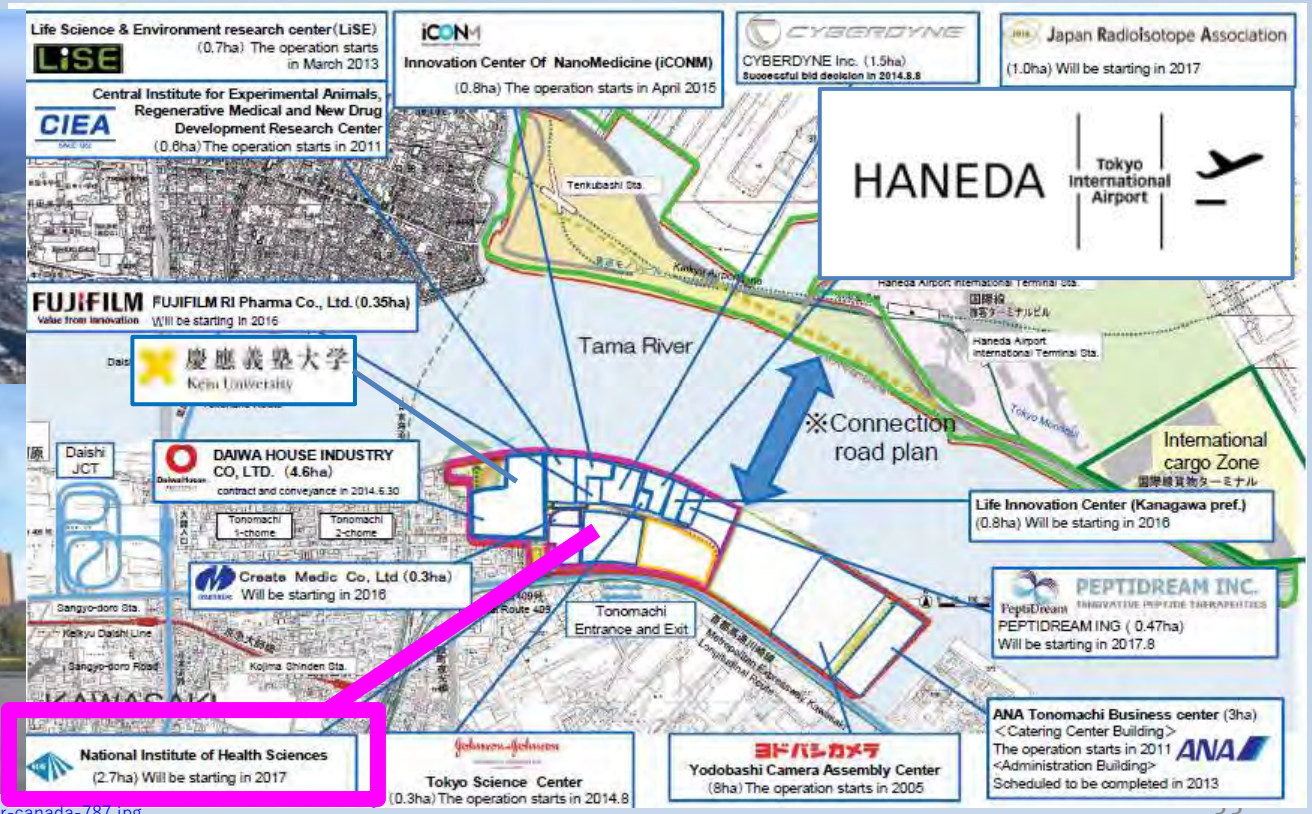
The ministry instituted policies in April to prevent such conflicts. But even with fully independent committees, clinics can shop around for the answer they want. Yoji Sato, who heads the cellular therapeutics unit of Japan's National Institute of Health Sciences in Kawasaki and who sits on two committees himself, says that "committee surfing" is a big problem.

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

Contact Information

Yoji SATO, Ph.D.

Head, Division of Cell-Based Therapeutic Products
National Institute of Health Sciences
3-25-26 Tonomachi, Kawasaki Ward,
Kawasaki City 210-9501, Japan
E-mail: yoji@nihs.go.jp



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