



Current status and future direction of the regulatory framework for gene therapy in Japan

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MORI Megumu, M.D., Ph.D.

Deputy Director, Medical Device Evaluation Division

Pharmaceutical Safety and Environmental Health Bureau,

Ministry of Health, Labor and Welfare, Japan

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COI : The author have no financial conflicts of interest to disclose concerning the presentation.

Our Strategy

**Report from Advisory Panel
for Promotion of Medical Ventures**

Report from Advisory Panel for Promotion of Medical Ventures (Summary)

Innovation is a “key trigger” for Japan’s economic growth, and venture company is a driving force which is definitely important for the success in innovation. Especially, progress of drugs and medical devices is significant as an investment for the future. This report shows a guiding principle of MHLW’s promotion policy for medical ventures.

※ Medical ventures; Venture companies for drugs, medical devices and cellular and tissue-based products

I. Importance and necessity of promotion of medical ventures

◆ There is a very high growth potential in healthcare.

- Healthcare is a huge growing market all over the world.
- In Japan, it is necessary to respond to problems for extension of healthy life expectancy and building sustainable healthcare system.

◆ Venture companies are at the center of the innovation of drugs and medical devices.

- Many new drugs of the biggest US & EU pharmaceutical companies are come from venture companies.
- Japan’s fundamental research and manufacturing technology is good enough. However, it doesn’t work effectively for development of medical devices etc.

◆ Promotion of medical ventures is necessary right now in Japan.

- Venture companies must play an important role when predicting future R&D trends of medicine .

◆ Three types of Medical ventures



II. Issues with promotion of medical ventures

Features of medical venture projects

Medical ventures have the following business features (and therefore they face many challenges):

(1) High scientific and technological level and high development risk

- Innovating in the medical field requires high levels of science and technology and involves high development risk.

(2) Long period of time to approval and large amount of funding required

- Require a long period for development and need a large amount of capital.

(3) Understanding of and response to medical, pharmaceutical affairs and medical insurance regulations

- Sufficient understanding of pharmaceutical affairs and public insurance is essential to overcome this obstacle to entry.

(4) Difficult to secure talent knowledgeable about these features

- Development of talent requires time and cost. Difficult for new entrepreneurs to emerge or be fostered.

Japan's strengths and weaknesses (Compared to Europe and the U.S.)

Japanese ventures need to consider overseas deployment to raise efficiency of high capital investment

Japan's strengths

-High level of seeds, even by global standards, at universities and research institutes

-Spread of clinical research in hospitals

-SMEs have excellent manufacturing technologies

-Fast approval review process (Ex.: regenerative medicine)

Japan's weaknesses

-Few entrepreneurs and difficult for ventures to secure talent

-Venture funding is scarce and weak support for financial side

-Weak ties with overseas in terms of funding or talent

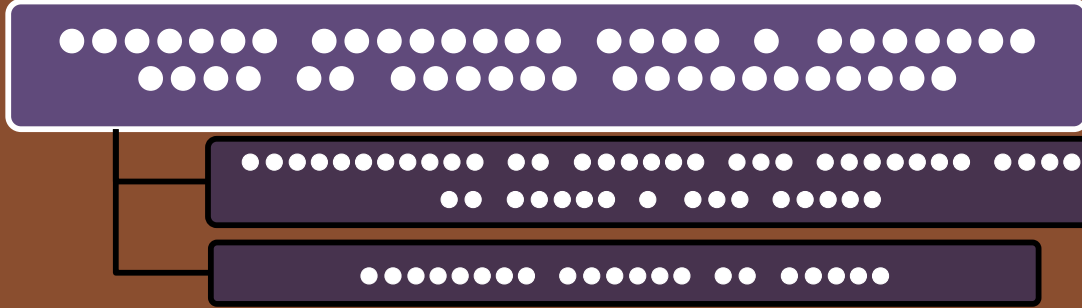
-Medical system does not consider ventures

-Few model cases

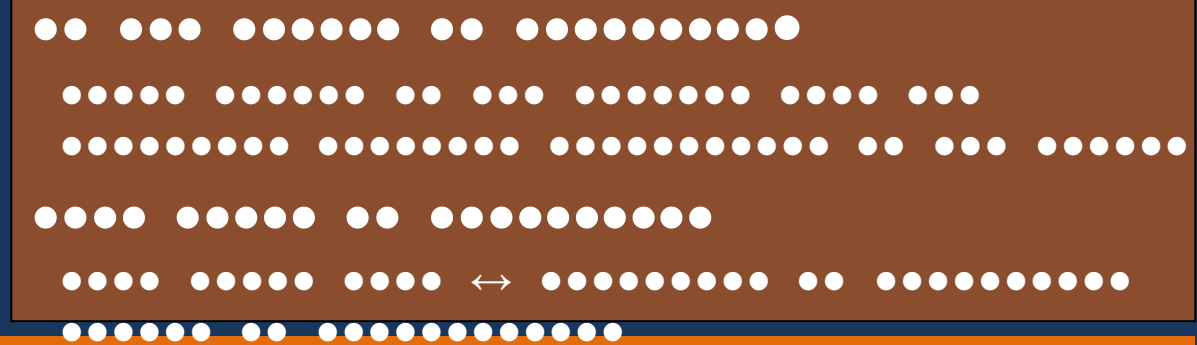
By making use of strengths and overcoming weaknesses, there is great potential for growth and significance in promoting medical ventures.

III. Promotion policy and measures for medical ventures

“The Goal of Policy”



“The Vision of Policy”

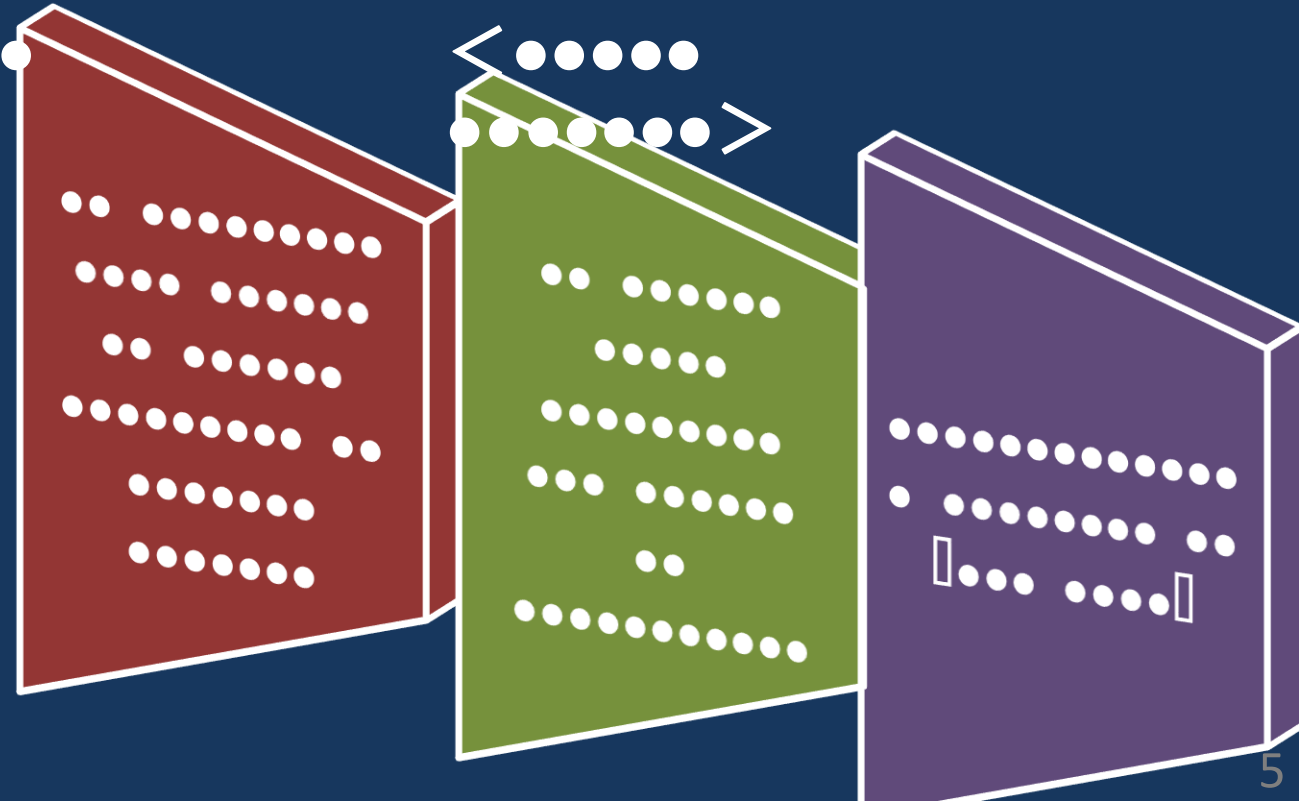


◆ “Three principles” & “Three pillars” of promotion measures

<)
Proper regulation from the venture business point of view Support from MHLW

Promotion measures with a sense of urgency

Support corresponding to the characteristics of each company



Two Acts
Regulating
Regenerative Medical
Technology & Product

New Legislative Framework

- **Revision of the Pharmaceutical Affairs Law:
The Act on Pharmaceuticals and Medical Devices (PMD Act)**
- **The Act on the Safety of Regenerative Medicine**

These two acts were enacted on 25 November 2014

Other related governmental policy:

- **Healthcare and Medical Strategy Promotion Act (2014.5)**
- **Japan Medical Research Development Institution Act (2014.5)**

Two acts regulating regenerative medicine & cell therapy

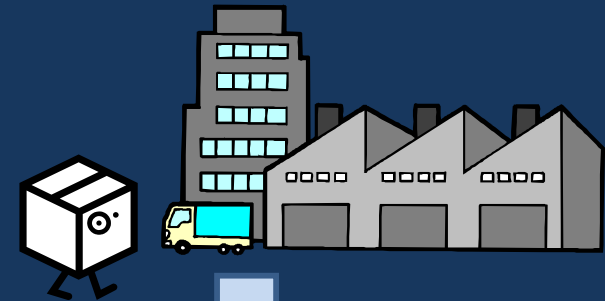
MHLW
process

Regenerative
Medicine

PMDA process

All **medical technologies** using processed cells which safety and efficacy have not yet been established

Production and marketing of regenerative and cellular therapeutic **products** by firms



The Act on the Safety of
Regenerative Medicine (ASRM)

Medical Care or
Academic Research Purpose

The Act on Pharmaceuticals and
Medical Devices (PMD Act)

Commercial Product
Marketing Authorization Purpose

Outsourcing Cell Culturing and Processing under the Act on the Safety of Regenerative Medicine (ASRM and PMD Act)

Clinical study, private practice

Regenerative medical products

ASRM

PMD Act (Revised PAL)

Corporate factory, etc.
* Licensed facility

Medical institution
* Notified facility

Corporate factory, etc.
* Licensed facility

Processing, storage

Processing, storage

Processing, storage

Outsourcing

Collection

Practice (transplanting)

Acquisition of cells

Purchase of licensed product

Scope of application

ASRM

PMD Act

The Act on Pharmaceuticals and Medical Devices (PMD Act)

regenerative medicine products in the PMD Act

Former Pharmaceutical
Affairs Law (PAL)

Drug

Device

PMD Act
(Revised PAL)

Drug

Regenerative
Medical
Products

Device

◆ Additions for regenerative medicine products

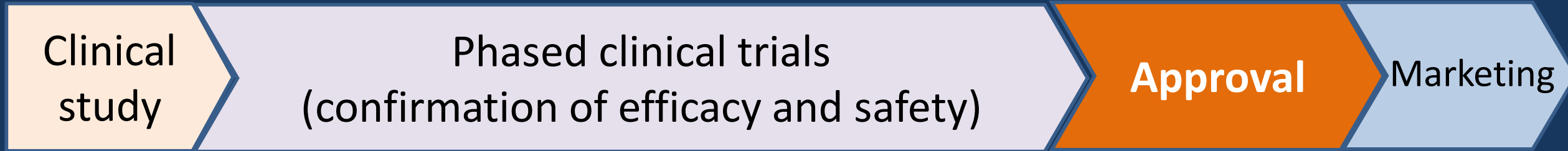
- Definition and independent chapter for regenerative medicine products
- Introduction of conditional/time limited approval system

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 medicine products]



Enhancing the R&D of Regenerative Medicines

SAKIGAKE Designation System

MHLW assigns and supports the world's first products currently being developed with high expectation on a trial basis since 2015.

Assignment criteria

- Prominent effectiveness and dire medical needs for the therapy
- Technological innovativeness
- World's first submission for approval in the future (incl. simultaneous submissions)

Priorities and advantages

1. Prioritized consultation

[Waiting time: 2 months → 1 month]

2. Substantialized pre-submission assessment and 3. Prioritized review

4. Review partner [PMDA manager as a concierge]

5. Substantial post-marketing safety measures

[Extension of re-examination period]

Strategy of SAKIGAKE

Lead the world in the practical application of innovative medical products



Accelerate R&D through supporting each stage

Strengthen the structure of PMDA

(consultation, review, safety measures in terms of quality and quantity)

Promotion of Regulatory Science

(Developing guidelines/assessment for the state-of-the-art technology)

SAKIGAKE Assignment for RM products

(Feb. 2016(#1-3), Feb.2017(#4-6))

	Name	Proposed indication	Sponsor
#1	STR01 (Autologous bone marrow-derived mesenchymal stem cell)	Nerve syndrome and dysfunction caused by spinal cord injury	NIPRO Medical Co., Ltd. / Sapporo Medical Univ.
#2	G47Δ (Growth-controlled oncolytic herpes simplex virus type 1)	Malignant glioma	Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo
#3	JRM-001 (autologous cardiac progenitor/stem cells)	Pediatric congenital heart disease (single ventricle physiology)	Japan Regenerative Medicine Co., Ltd. / Okayama University
#4	CLS2702C/D (Oral mucosa-derived esophageal cell sheet)	Extensive endoscopic submucosa dissection (ESD) in esophageal cancer	CellSeed / Tokyo Women's Medical University Hospital
#5	Dopamine neural precursor cell derived from allogenic iPS cell	Parkinson's disease	Sumitomo Dainippon Pharma Co., Ltd. / CiRA, Kyoto University
#6	Pluripotent progenitor cell derived form allogeneic adult bone marrow	Acute brain infarction.	Healios K.K. / Athersys

SAKIGAKE Assignment for RM products

(Mar. 2018(#7-9), Apr. 2019(#10-11))

	Name	Proposed indication	Sponsor
#7	TBI-1301 (cancer antigen(NY-ESO-1) specific TCR Gene-transduced T Lymphocytes (autogenous))	Treatment of synovial sarcoma	Otsuka Pharmaceutical Co., Ltd.
#8	CLBS12 (autogenous CD34+ cells)	Improvement of Severe lower limb ischemia	Caladrius Biosciences, Inc.
#9	AVXS-101 (recombinant AAV containing human SMN (survival motor neuron) gene)	Treatment of spinal muscular atrophy (Type I)	Novartis Pharma K.K.
#10	OBP-301 (gene-modified oncolytic adenovirus)	Unresectable, chemotherapy-intolerant/-resistant locally advanced esophageal cancer	Oncolys BioPharma Inc.
#11	SB623 (adult bone marrow-derived mesenchymal stem cells)	Improvement of motor impairment after traumatic brain injury (Moderate to severe)	SanBio Co., Ltd.

Approved Products
2018-2019
Under The PMD Act

New therapy for spinal cord injuries gets fast-tracked

By MASATOSHI TODA/ Staff Writer

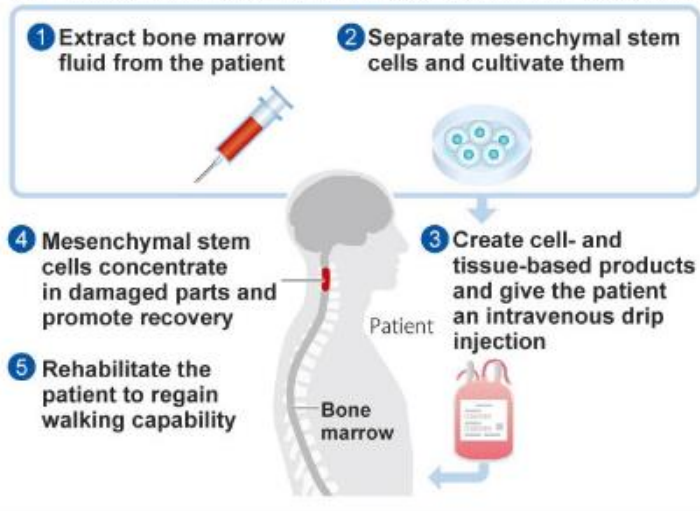
November 22, 2018 at 14:30 JST



Therapy using mesenchymal stem cells for patients with spinal cord injury

Mesenchymal stem cells

Contained in bone marrow and fat and work to replace damaged cells. Can turn into bone, nerve and other cells.



The Asahi Shimbun

Treatment using stem cell regenerative medicine to restore damaged nerve connections in patients with spinal cord injuries, whose only course of treatment is rehabilitation, may be available by year-end.

SAKIGAKE
Designated
Products

Conditional &
Time-Limited
Approval



NOW APPROVED: The first and only CAR-T cell therapy* approved in two indications for B-cell malignancies¹

KYMRIAH CAR-T

*CAR-T, chimeric antigen receptor T-cell.

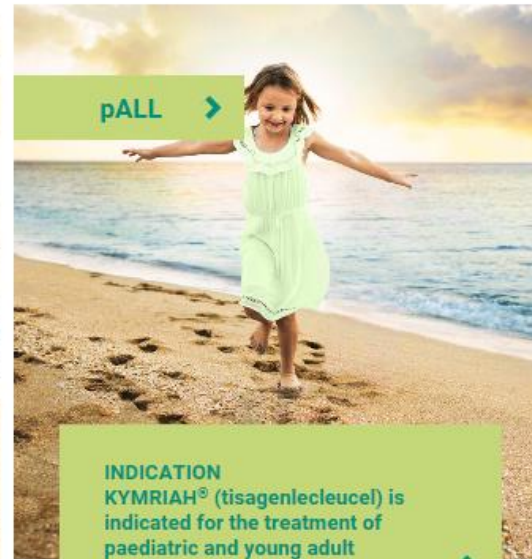
THE TRANSFORMATION OF CANCER TREATMENT IS HERE

Explore how KYMRIAH is transforming the treatment of cancer by selecting an indication below.



DLBCL >

INDICATION
KYMRIAH® (tisagenlecleucel) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.



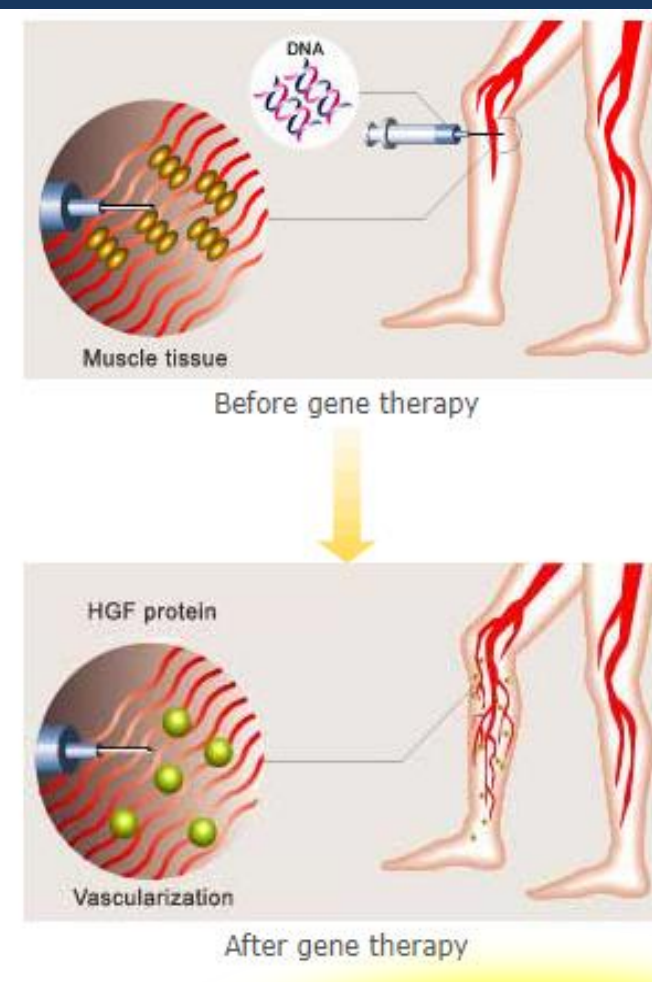
pALL >

INDICATION
KYMRIAH® (tisagenlecleucel) is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

AnGes Obtains Conditional Approval in Japan for HGF Gene Therapy to Treat Critical Limb Ischemia

AnGes, Inc., a biopharmaceutical company focused on developing innovative gene-based medicines for treating serious diseases, announced today that they have obtained conditional approval (“Approval with Conditions and Time Limit”) from the Japanese Ministry of Health, Labour and Welfare (MHLW) for HGF plasmid to treat patients with critical limb ischemia (CLI).

HGF plasmid is the first gene therapy product to be approved in Japan, for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger’s disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. AnGes applied for marketing approval to the MHLW in January 2018 based on positive results from the randomized, placebo-controlled phase three trial and investigator-led clinical study conducted in Japan. HGF plasmid is one of the first gene therapy products to be approved for a non-genetic disease with chronic and progressive symptoms.



**Conditional &
Time-Limited
Approval**

**Indication:
Ulcer healing for Critical Limb Ischemia patient**

Benefit and Risk Balance Assessment

- Discussion of acceptable level of clinical effectiveness vs. patient access to the new therapy
- Weighing acceptable risk against expected benefit
- Based on **Regulatory Sciences**

*Thank you
for your attention*