独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulatory Update of Regenerative Medicine in Japan

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7th India-Japan Medical Products Regulatory Symposium

Outline

- The Act on the Safety of Regenerative Medicine

- The Act on Pharmaceuticals and Medical Devices

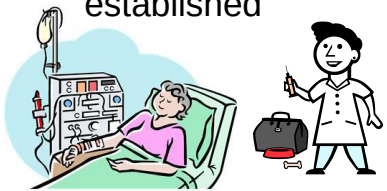
Dual Regulation of Regenerative Medicine in Japan

Technology & Product

Regenerative Medicine

Enacted on
25 November 2014

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

Safety Act

The Act on the Safety of Regenerative Medicine

Medical Care or
Academic Research Purpose

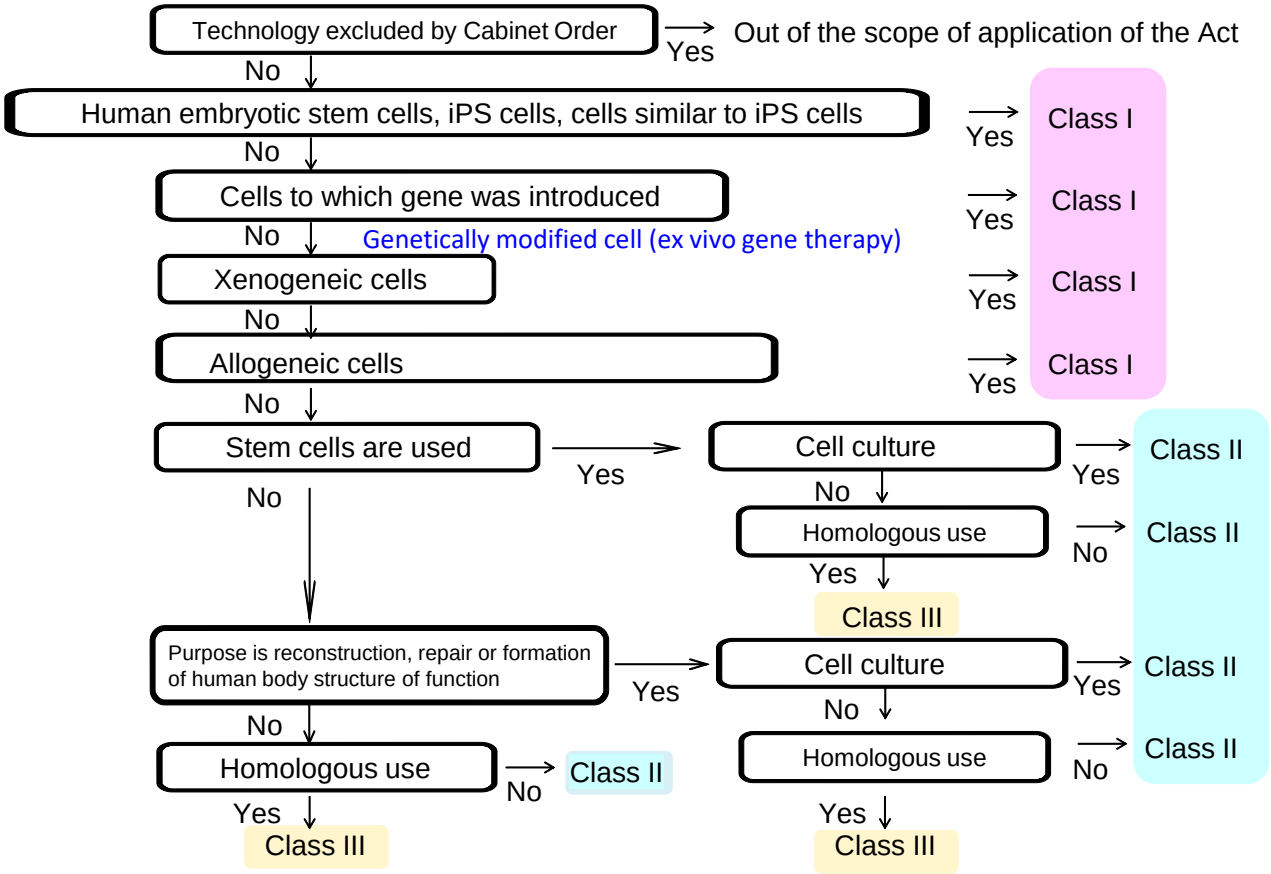
The Act on Pharmaceuticals and Medical Devices

PMD Act

Commercial Product
Marketing Authorization Purpose

Risk Classification Regenerative Medical Technology

Safety Act



Class	Medical Care	Clinical Research
I (High risk)	7	16
II (Middle risk)	1,571	43
III (Low risk)	3,898	42

(As of 1 December 2023)

Current Activity

WG has been establish to review the Safety act, and studies are being conducted.
in vivo gene therapy is currently out of scope. *in vivo* gene therapy is also under consideration for inclusion in the scope of Safety act.

Approved Plans (Class I, Clinical Research)

Safety Act

iPS cells

Health Condition(s) or Problem(s) Studied	Hospital/Clinic	Trial ID
Aplastic anemia with platelet transfusion refractoriness due to anti-platelet alloantibo	Kyoto University Hospital	jRCTa050190117
Bullous keratopathy	Keio University	jRCTa031210199
Damage of articular cartilage of the Knee	Kyoto University Hospital	jRCTa050190104
Limbal stem-cell deficiency	Osaka University Graduate School of Medicine	jRCTa050190084
Recurrent or advanced head and neck cancer	Chiba University Hospital	jRCTa030220741
Retinitis pigmentosa	Kobe City Eye Hospital	jRCTa050200027
RPE impaired disease	Kobe City Eye Hospital	jRCTa050210178 jRCTa050200122
Severe heart failure patients with NYHA class III or higher (HFrEF by dilated cardiomyopathy)	Keio University School of Medicine	jRCTa032200189
Spinal cord injury at subacute stage	Keio University School of Medicine	jRCTa031190228

Autologous cells to which gene was introduced

Health Condition(s) or Problem(s) Studied	Hospital/Clinic	Trial ID
CD19 positive acute lymphoblastic leukemia	Nagoya University Graduate School of Medicine	jRCTa040190099
Familial LCAT deficiency	Chiba university	jRCTa030190230

Allogeneic cells

Health Condition(s) or Problem(s) Studied	Hospital/Clinic	Trial ID
Bullous keratopathy	Kyoto Prefectural University of Medicine	jRCTa050190118
Cartilage defects associated with osteoarthritis of the knee	Tokai University	jRCTa030190242
Cerebral palsy	Kochi Medical School Hospital	jRCTa060200017 jRCTa060200018
Decompensated liver cirrhosis patients who will receive liver transplantation	Hiroshima University	jRCTa060190036 jRCTa030230316
EBV associated lymphoproliferative disorder after allogeneic stem cell transplantation	Nagoya University Graduate School of Medicine	jRCTa040190110
Hematological disorders applicable to cord blood transplantation	Aichi Medical University	jRCTa040190133
Idiopathic peripheral ulcer and cGVHD related corneal ulcer	Keio University	jRCTa030220167
Insulin-dependent diabetes mellitus	Shinshu University School of Medicine	jRCTa030190164
Persistent viral infection after hematopoietic cell transplantation	Tokyo Medical and Dental University	jRCTa030190229
Refractory chronic skin ulcer	Keio University School of Medicine	jRCTa030200053
Refractory cutaneous ulcers	Research Institute for Radiation Biology and Medicine(RIRBM), Hiroshima University	jRCTa060210018

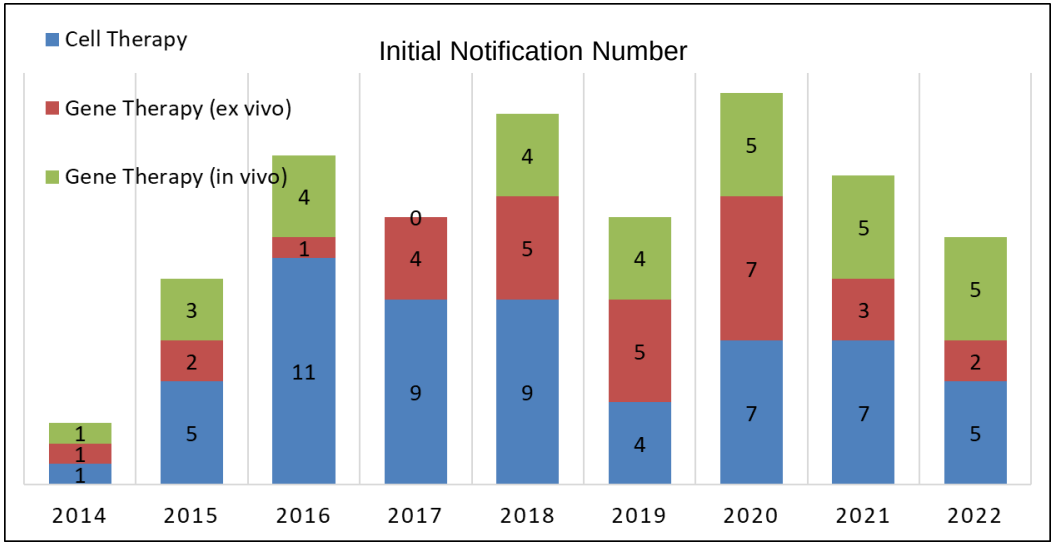
Source: https://jrct.niph.go.jp/search
Search condition: Clinical Research for Regenerative Medicine (Class I)

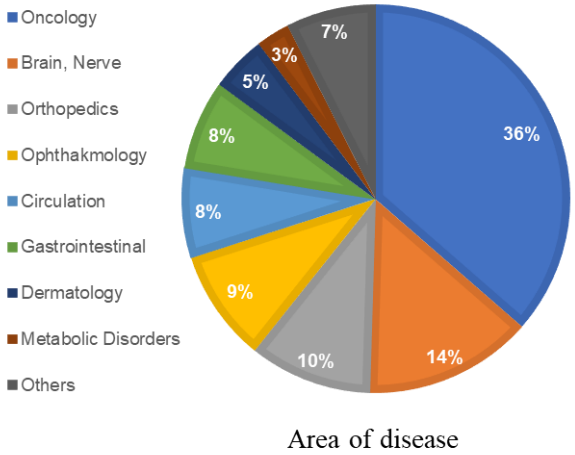
INDs Reviewed by PMDA

PMD Act

Notification	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Initial	3 [1]	10 [2]	16 [7]	13 [8]	18 [8]	13 [7]	19 [9]	15 [7]	12 [3]	119 [51]
2nd or later	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	25 [14]	121 [51]

Note: The table in brackets in parentheses indicate the number of notifications of “investigator-initiated clinical trials (IIT).





Area of disease

Approved RMPs in Japan

PMD Act

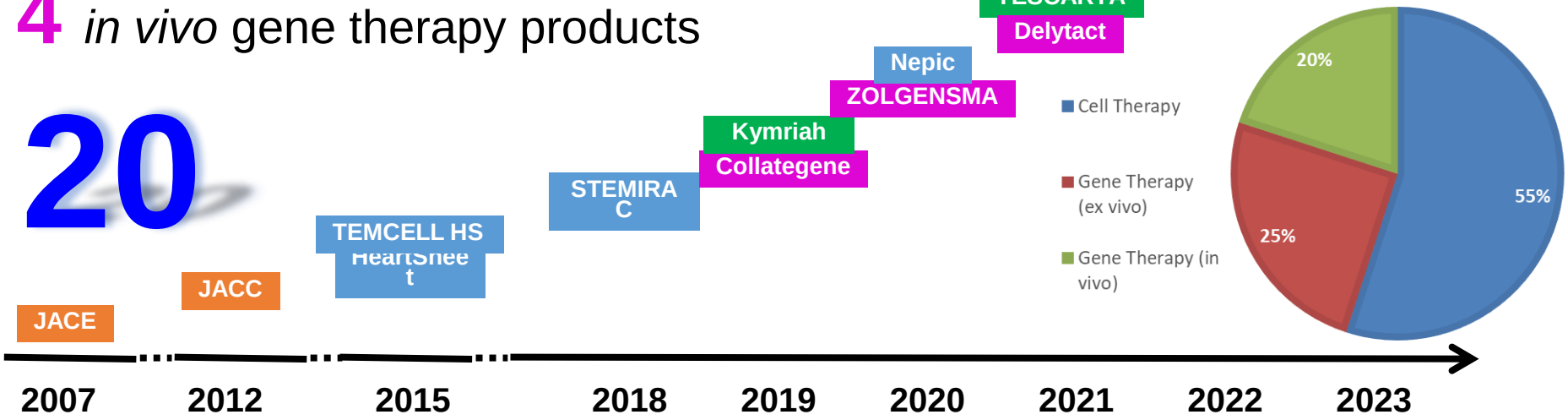
4 somatic cell derived products

7 somatic stem cell derived products

5 *ex vivo* gene therapy products

4 *in vivo* gene therapy products

20



(As of 1 June 2024)

Accelerating Approval Pathways for RMPs in Japan

PMD Act

	Priority review (Orphan)	SAKIGAKE	Conditional & Time-limited Approval
Abecma	✓		
Breyanzi	✓		
CARVYKTI	✓		
Delytact	✓	✓	✓
Kymriah	✓		
YESCARTA	✓		
LUXTRNA	✓		
Nepic	✓		
Ocural	✓		
Sakracy	✓		
Vyznova	✓		
STEMIRAC		✓	✓
ZOLGENSMA	✓	✓	
Collategene			✓
HeartSheet			✓
JACE	✓GCMN*, EB**		
JACEMIN			
Aloficel	✓		
JACC			
TEMCELL	✓		

Area of disease	# of products
Oncology	6
Ophthalmology	5
Brain, Nerve	2
Circulation	2
Dermatology	2
Others	3

The target review time
Priority products: 9 month
Regular products: 12 month

*GCMN: Giant congenital melanocytic nevi
**EB: Dystrophic epidermolysis bullosa

(As of 1 June 2024)

Oncology Area

PMD Act

Kymriah
(tisagenlecleucel)
r/r ALL, r/r DLBCL, r/rFL
(Mar 2019)

Yescarta
(axicabtagene ciloleucel)
r/r large B cell lymphoma
(Jan 2021)

Abecuma
(idecabtagene vicleucel)
r/r multiple myeloma
(Jan 2022)

Breyanzi
(lisocabtagene maraleucel)
r/r large B-cell lymphoma, r/r FL
(Mar 2021)

Delytact
(teserpaturev)
Malignant glioma
(Jun 2021)

Carvykti
(ciltacabtagene autoleucel)
r/r multiple myeloma
(Sep 2022)

Oncolytic Virus

Ophthalmology Area

PMD Act

Epithelial cell sheet for limbal stem cell deficiency (LSCD), a rare and intractable corneal epithelial disease

https://www.jpte.co.jp/business/regenerative/

Nepic
(Human (autologous) corneal limbus-derived corneal epithelial cell sheet)
(Mar 2020)

https://www.jpte.co.jp/business/regenerative

Ocural
(Human (autologous) oral mucosa-derived epithelial cell sheet)
(Jun 2021)

http://hirosaki-li.co.jp/products_sakracy.html

Sakracy
(Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate)
(Jan 2022)

Aketa et al., The Ocular Surface. 29, 220-225 (2023)

2020 | 2021 | 2022 | 2023

Vyznova
(Human (allogenic) corneal endothelium-derived endothelial cell injection)
(Mar 2023)

LUXTURNA
(voretigene neparvovec)
Confirmed biallelic RPE65 Mutation-associated retinal dystrophy
(Jun 2023)

Endothelial cell injection for Bullous Keratopathy, a rare and intractable corneal endothelial disease

Adeno-associated virus (AAV) vector

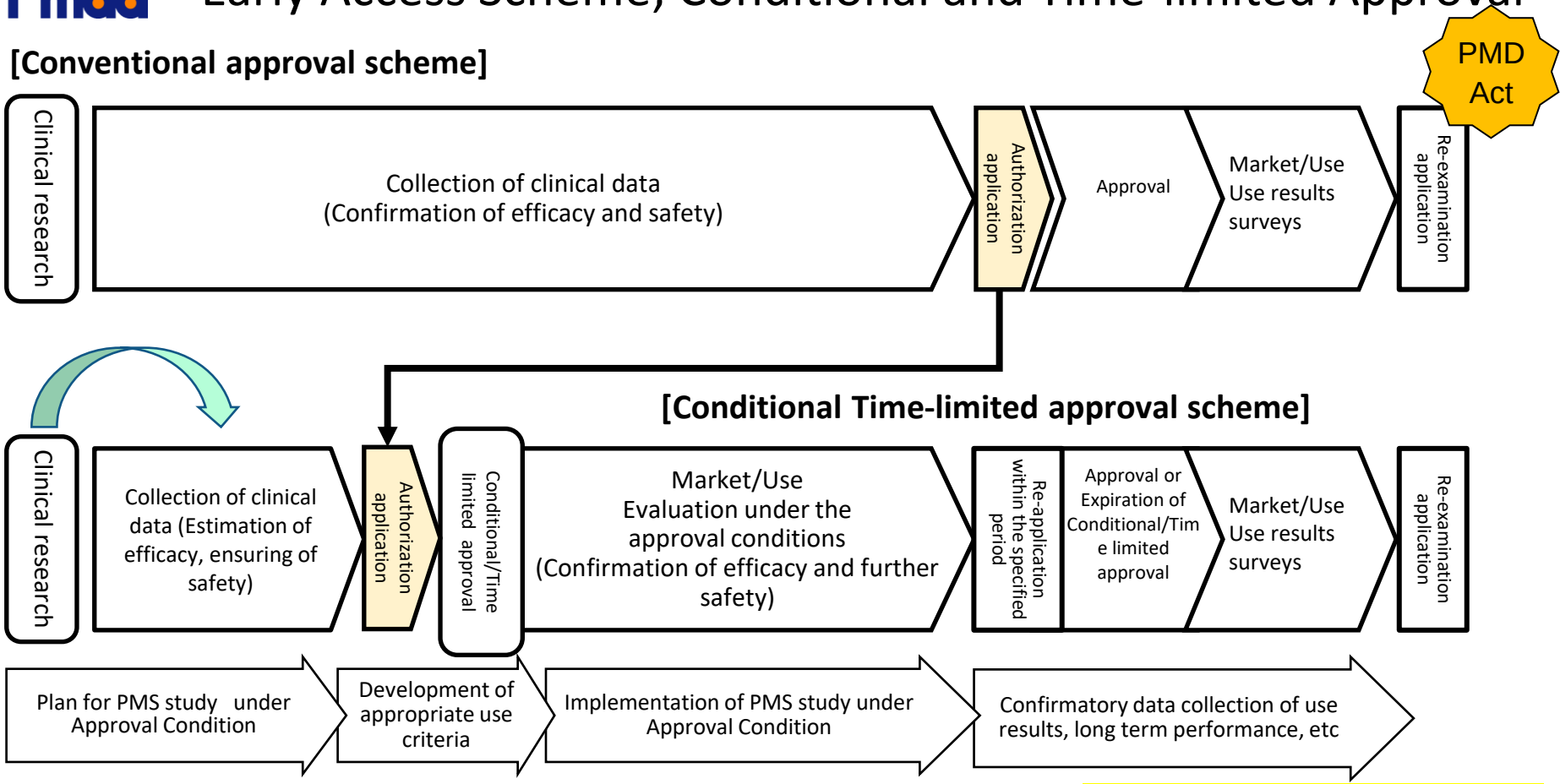
Summary of Approved RMPs in Japan

PMD Act

	Japan Origin (12)	Global (8)
Cell Therapy Products (16)		
Somatic cell derived products (9)	JACE (Skin) JACC (Knee) JACEMIN (Skin) Vyznova (Eye)	Kymriah YESCARTA Breyanzi Amecma CARVYKTI CAR-T
Somatic stem cell derived products (7)	HeartSheet* TEMCELL HS STEMIRAC* Nepic (Eye) Ocural (Eye) Sakracy (Eye)	Aloficel
iPS cell derived products (0)	---	---
Embryonic stem cell derived products (0)	---	---
Gene Therapy Products (4)		
Plasmid vector products (1)	Collategene*	---
Viral vector products (2)	---	ZOLGENSMA LUXTURNA AAV
Others (1)	Delytact*	

*Conditional and Time limited Approval

Early Access Scheme; Conditional and Time-limited Approval



Maruyama et al., Adv Exp Med Biol, 1430, 155-179 (2023)

Outline of the Condition for Approval and Granted Time-period for PMS Study

PMD Act

Products	HeartSheet	Stemirac	Collategene	Delytact
	Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard	Spinal cord injure	The treatment of ulcers in patients with chronic arterial occlusion	Malignant glioma
Granted time-period	8 years (17/09/2023) (Extend on 20/11/2018 after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council)	7 years (27/12/2025)	5 years (25/03/2024)	7 years (10/06/2028)
Efficacy evaluation				
Primary endpoint	Time to cardiac death (at ≥ 2 years post transplantation)	Cohort I; Patients with AIS Grade A at 6 to 8 weeks (49 ± 7 days) after injury Percentage of patients achieving ≥2 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury Cohort II; Patients with AIS Grade B or C at 6 to 8 weeks (49 ± 7 days) after injury Percentage of patients with AIS Grade B or C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury	The proportion of patients with completely closed ulcer at 12 week later after injection	OS (from the day of diagnosis of malignant glioma to death [from any cause]): For each population of patients with primary glioblastoma and patients with recurrent glioblastoma, conduct a trend score matching so that the Delytact and control groups include the same number of patients (1:1), and perform a log-rank test with the two-sided significance level of 5% on OS in the sample population.
Number of subject				
Product	60	Cohort I; 27 Cohort II; 63	120	Glioblastoma: 250 Grade III malignant glioma: 60 to 100
Control (External)	120	Cohort I; 54 Cohort II; 125	80	Glioblastoma: 500 Grade III malignant glioma: 120 to 200

Benefit and Risk Balance Assessment

PMD Act

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

- Considerations for Conditional and Time-limited Approval of Cell and Gene Therapy Products, PSEHB/MDED Notification No. 0329-3, 2024.
  https://www.pmda.go.jp/files/000267914.pdf
- Guidance on Conditional and Time-limited Approval and Protocol for Post Marketing Study of Stem Cell Therapy Products, PSEHB/MDED Notification No. 0329-4, 2024.
  https://www.pmda.go.jp/files/000267915.pdf

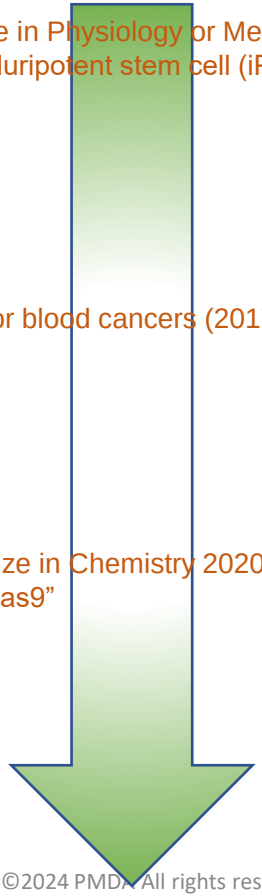
Regulators' Action to Novel Technologies (1)

PMD Act

Nobel Prize in Physiology or Medicine 2012
"Induced pluripotent stem cell (iPSCs)"

CAR-T for blood cancers (2017-)

Nobel Prize in Chemistry 2020
"Crispr-Cas9"



- Current Perspective on Evaluation of **Tumorigenicity** of **Cellular and Tissue-based Products** Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials (20 August 2013)
- Proposal on Basic Principle to **Quality Assurance** of **Cell Therapy (CT) Products** (14 June, 2015)

(PMDA Science Board has started the discussion on gene editing (2018))

- Points to Consider for Ensuring **Quality and Safety** of **Gene Therapy Products** (9 July, 2019)
- Report on Considerations on **Quality and Safety** of **Gene Therapy Products** Using Genome Editing Technology (7 February, 2020)

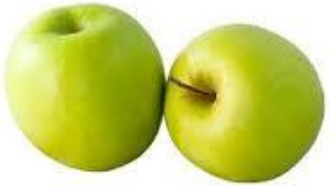
(Discussion on vectors with targeting function has begun(2023))

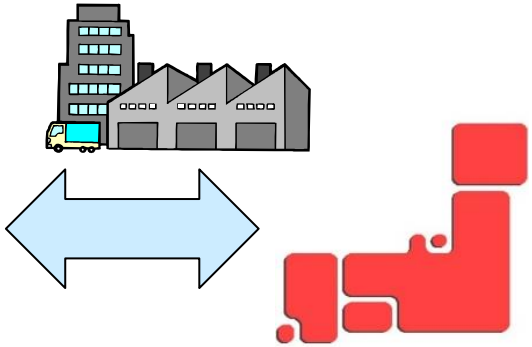
- Points to Consider for **Development** of ***in vivo* Gene Therapy Products** with Target Specific Viral/non-Viral Vector
  (To be publish in 2024)
  https://www.pmda.go.jp/english/rs-sb-std/sb/subcommittees/0031.html

Regulators' Action to Novel Technologies (2)

PMD Act

Comparability





- Comparability of Cell Therapy Products Subject to Changes in Their Manufacturing Process PSEHB/MDED Notification No. 0329-1, 2024.
  https://www.pmda.go.jp/files/000267916.pdf

Summary

- Medical technologies using processed cells are active under the Safety Act.
- 20 RMPs, including 5 *ex vivo* and 4 *in vivo* gene therapy products, have been approved under the PMD Act.
- 4 of 20 RMPs have been approved through comprehensive framework for patient access (conditional and time-limited approval scheme).

  Sponsors are subject to strict PMS study to prepare re-marketing authorization submission with in the granted time-period.
- According to R&D trends, the GLs related to RMPs development have been prepared.

Where to Find Information?

Regenerative Medical Products

1. Regulatory Framework

Regenerative medicine, which is expected to overcome intractable and serious diseases, is expected to play an important role in conventional medicine worldwide. The Japanese government must implement comprehensive policies to promote the development of regenerative medicine, inform the public, and increase public acceptance, and ensure that medical professionals and investigators cooperate with the policies. In this background, two regulatory frameworks for regenerative medicine, "The Act on the Safety of Regenerative Medicine " (ASRM) and the "Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act " (PMD Act), came into effect in November 2014. The ASRM sets out legal regulations not only for research, but also for the daily medical practice of cell therapy, which had previously been under the jurisdiction of the Medical Practitioners' Act and the Medical Care Act .

The PMD Act regulates the commercialization of regenerative medical products. Regenerative medical products in the PMD Act are defined as:

a. Processed (more than minimal manipulation) live human/animal cells that are intended to be used for either
   - reconstruction, repair, or formation of structures or functions of the human body

Review Reports: Regenerative Medical Products

A

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Abecma	idecabtagene vicleucel	January 2022		
Alofisel	darvadstrocel	September 2021		

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B

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Breyanzi Initial Approval	lisocabtagene maraleucel	March 2021		
Breyanzi Partial Change Approval	lisocabtagene maraleucel	December 2022		

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Recent Publication

- Maruyama Y, Noda S, Okudaira S, Sakurai A, Okura N, Honda F. Regulatory Aspects of Cell and Gene Therapy Products: The Japanese Perspective, Adv Exp Med Biol, 1430, 155-179 (2023) https://doi.org/10.1007/978-3-031-34567-8_9
- Maruyama Y, Sakurai A, Noda S, Fujiwara Y, Okura N, Takagi T, Asano J, Honda F. Regulatory Issues: PMDA Review of Sakigake Designation Products: Oncolytic virus therapy with Delytact Injection (teserpaturev) for malignant glioma, The Oncologist, 28(8) 664-670 (2023) https://doi.org/10.1093/oncolo/oyad041
- Aketa N, Kasai M, Noda S, Asano J, Kunieda A, Kawanishi S, Maruyama Y, Honda F. Insights Into the Clinical Development of Regenerative Medical Products Through a Comparison of Three Cell-based Products Recently Approved for Limbal Stem Cell Deficiency. The Ocular Surface, 29, 220-225 (2023) https://doi.org/10.1016/j.jtos.2023.05.008
- Sakurai A, Kanzaki S, Honda F. Japanese pharmaceutical regulations of engineered viral vectors for medical use compared with those in the US and EU. Clinical Pharmacology & Therapeutics (2023) https://doi.org/10.1002/cpt.2788
- Fujiwara Y, Maruyama Y, Honda F. Balancing safety and efficacy with early availability in the regulation of regenerative medicine product. Clin Pharmacol Ther, 109:1182-1185 (2021). https://doi.org/10.1002/cpt.2034

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http://www.pmda.go.jp

http://www.pmda.go.jp/english/index.html