11th Joint Conference of
Taiwan and Japan on
Medical Products Regulation

Regulation for Regenerative Medicinal Products

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Outline

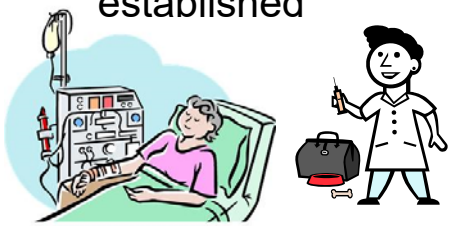
- The Act on the Safety of Regenerative Medicine (Safety Act)
- The Act on Pharmaceuticals and Medical Devices (PMD Act)

Two Acts Regulating Regenerative Medicine
Technology & Product

Regenerative Medicine

Enacted on
25 November 2014

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



Safety Act

The Act on the Safety of Regenerative Medicine

Medical Care or
Academic Research Purpose

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

The Act on Pharmaceuticals and Medical Devices

PMD Act

Commercial Product
Marketing Authorization Purpose

Organizations and Authorities of Regenerative Medicine

MHLW

Health Policy Bureau — R&D Division

Pharmaceutical Safety and Environmental Health Bureau — Medical Device Evaluation Division

Approval Decision, License Execution

Report

PMDA

Office of Cellular and Tissue based Products

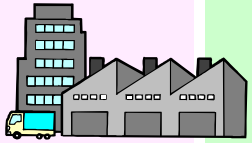
Product Review

Office of Manufacturing Quality and Compliance

Office of Non-clinical and Clinical Compliance

PMD Act

Safety Act



Manufacturing Sites

Cell Processing Facility

GCTP (GMP)

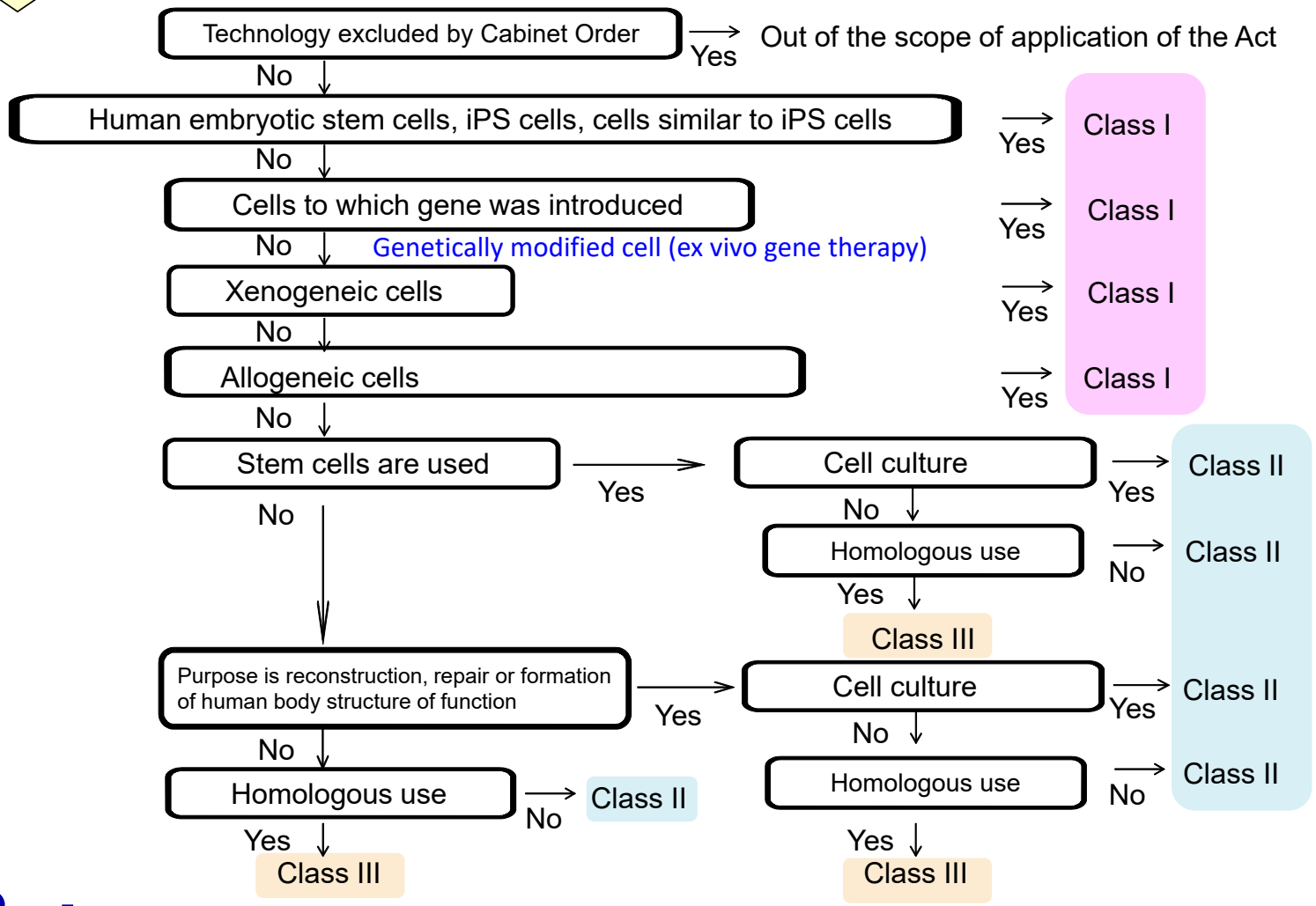
GMP-type facilities/ equipment and quality control requirements

Ministerial Ordinances No.110

Ministerial Ordinances No.93

Safety Act

Risk Classification Regenerative Medical Technology



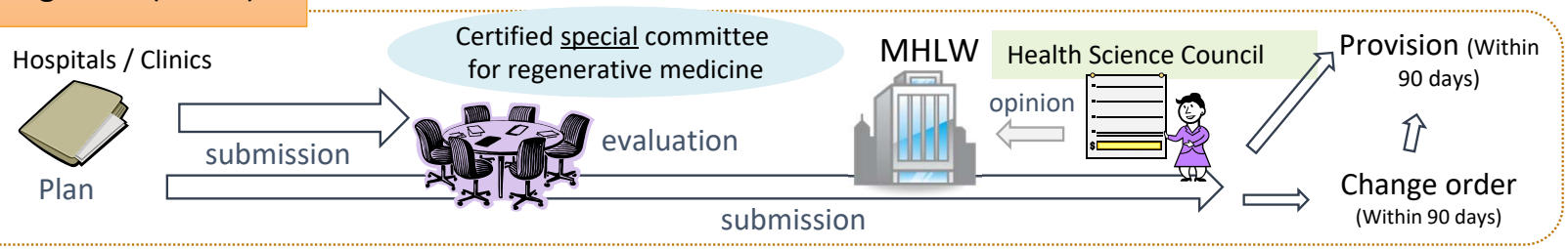
Current Activity

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.

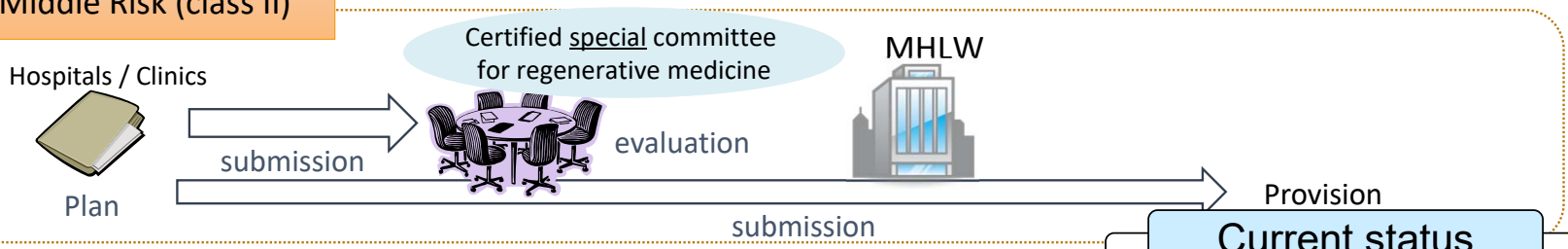
Safety Act

Rules for Hospitals and Clinics

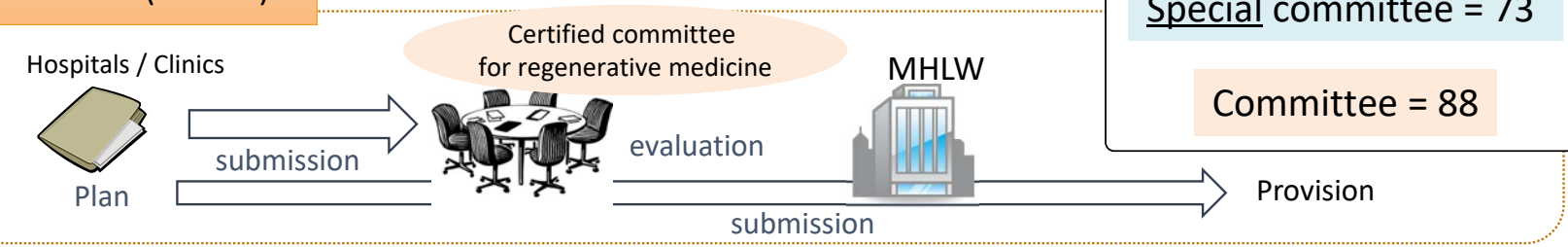
High Risk (class I)



Middle Risk (class II)



Low Risk (class III)



Current status

Special committee = 73

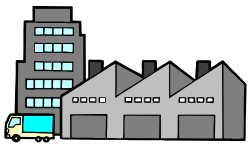
Committee = 88

Current status

	Medical care	Clinical research
High Risk (class I)	7	16
Middle Risk (class II)	1,396	47
Low Risk (class III)	3,840	45

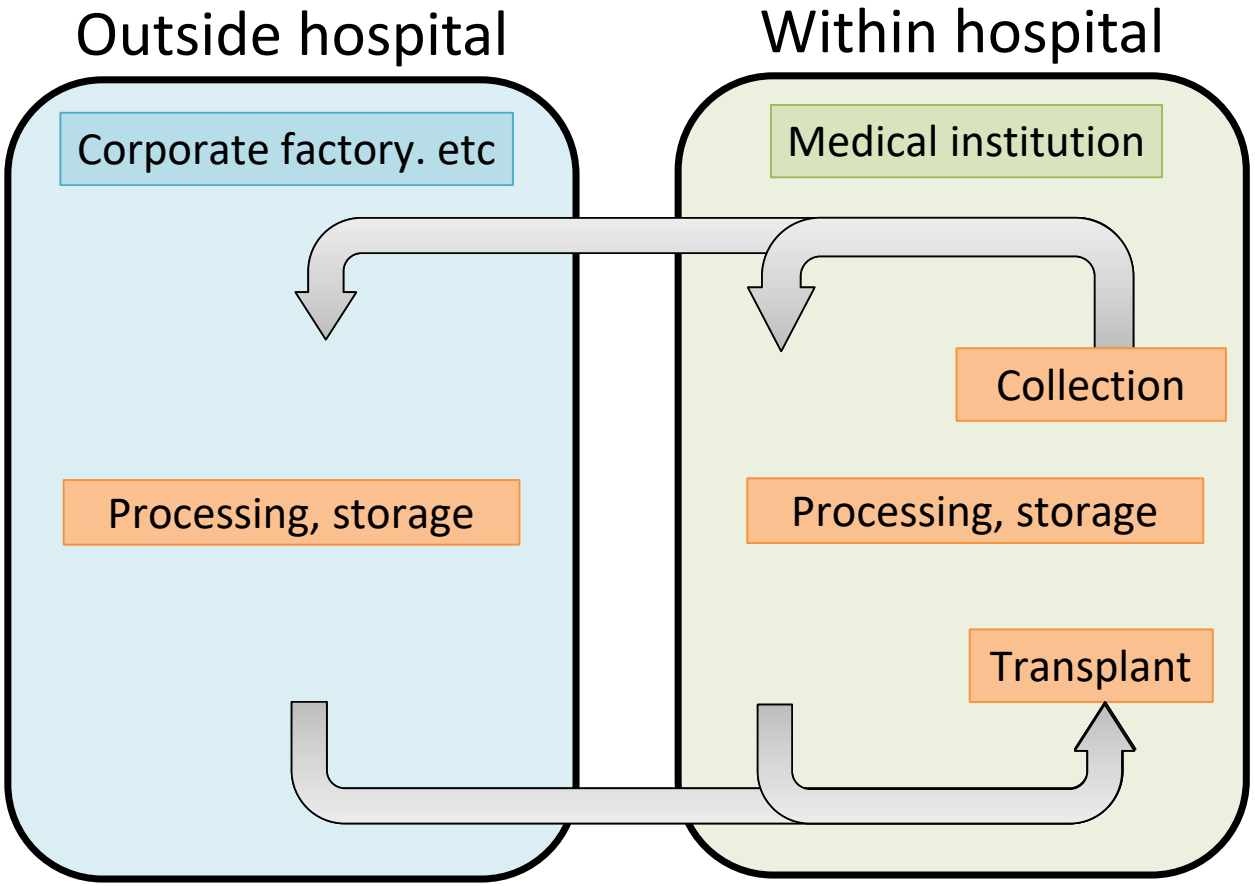
Safety Act

Cell Processing Facility



Licensed (Local)
= 71 sites

Accreditation (Overseas)
= 11 site (Korea)
= 1sites (China)
= 2 sites (Taiwan)
= 1 site (Austria)



Notified
= 3,431 sites

Medical Institutions

Outline

- The Act on the Safety of Regenerative Medicine (Safety Act)
- The Act on Pharmaceuticals and Medical Devices (PMD Act)

Approved Regenerative Medical Products in Japan (1)

PMD Act

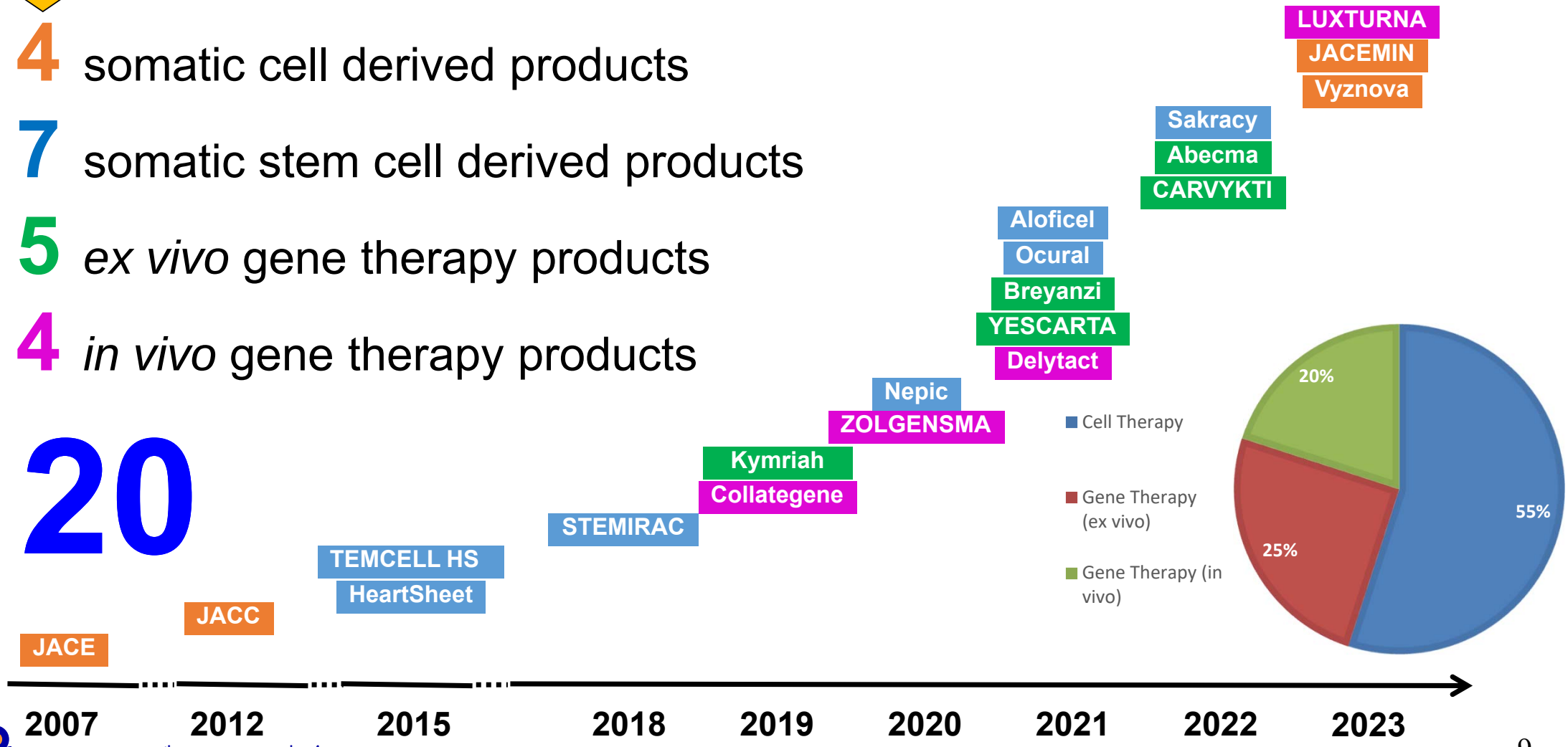
4 somatic cell derived products

7 somatic stem cell derived products

5 *ex vivo* gene therapy products

4 *in vivo* gene therapy products

20



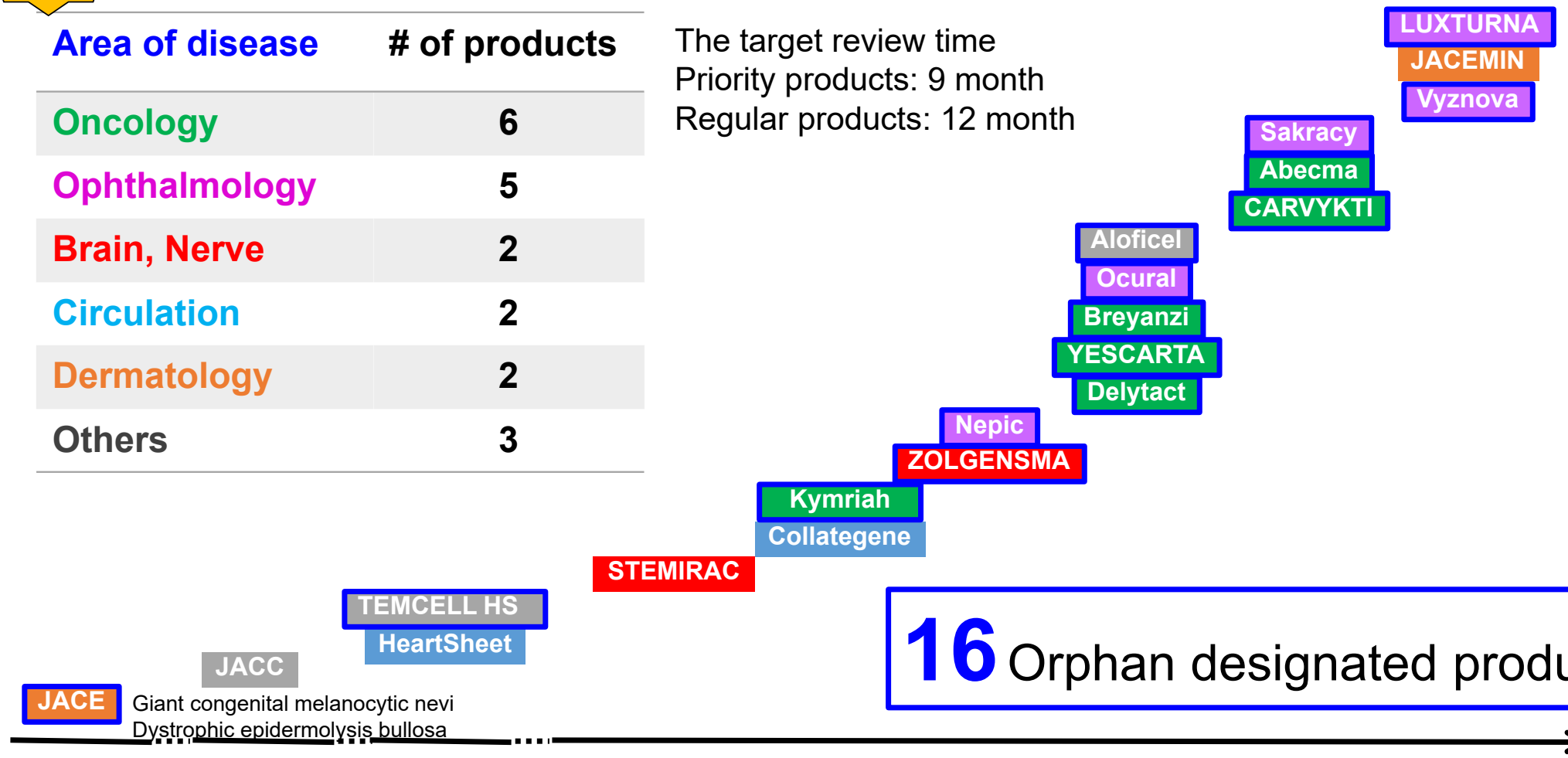
(As of 31 August 2023)

Approved Regenerative Medical Products in Japan (2)

PMD Act

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

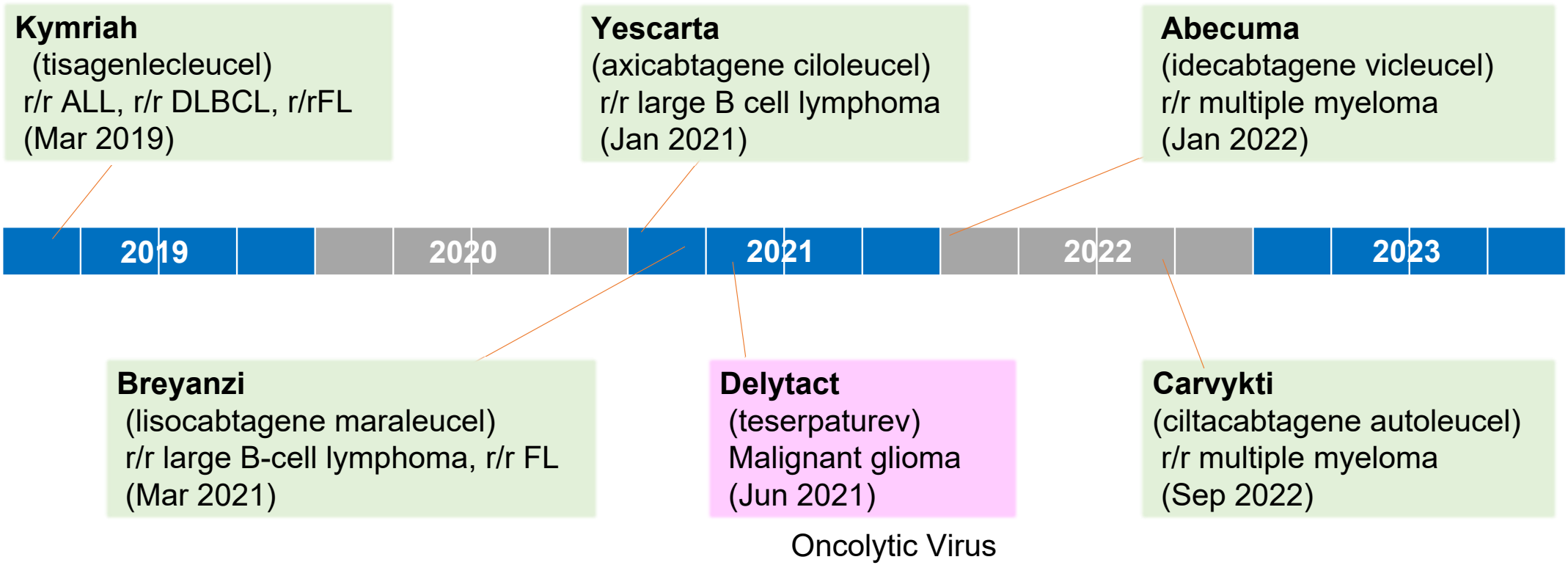


16 Orphan designated products

PMD Act

Oncology Area

Five CAR-T products have been approved by the PMDA since 2019



PMD Act

Ophthalmology Area

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)

2020 2021 2022 2023

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

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

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

Adeno-associated virus (AAV) vector

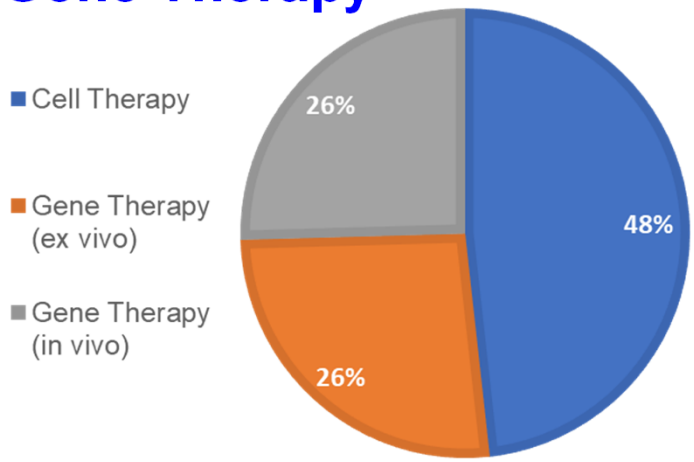
PMD Act

Development Trends; Number of INDs

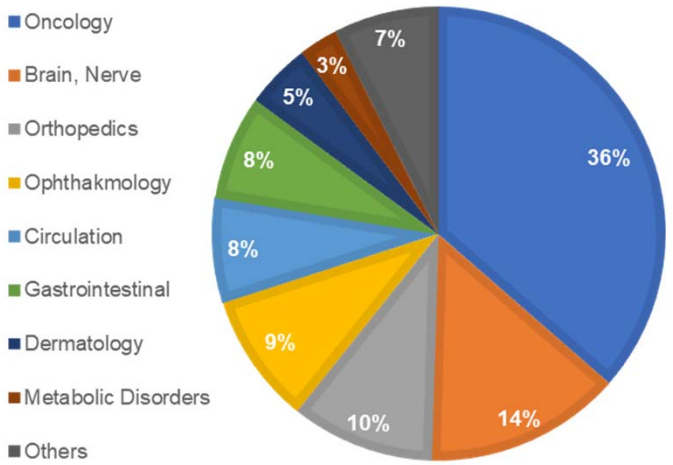
Notification	2014	2015	2016	2017	2018	2019	2020	2021	Total
Initial	3 [1]	10 [2]	16 [7]	13 [8]	18 [8]	13 [7]	19 [9]	15 [7]	107 [49]
2nd or later	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	96 [37]
Protocol change	2	19	52	93	151	206	215	278	1016

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

52% Gene Therapy



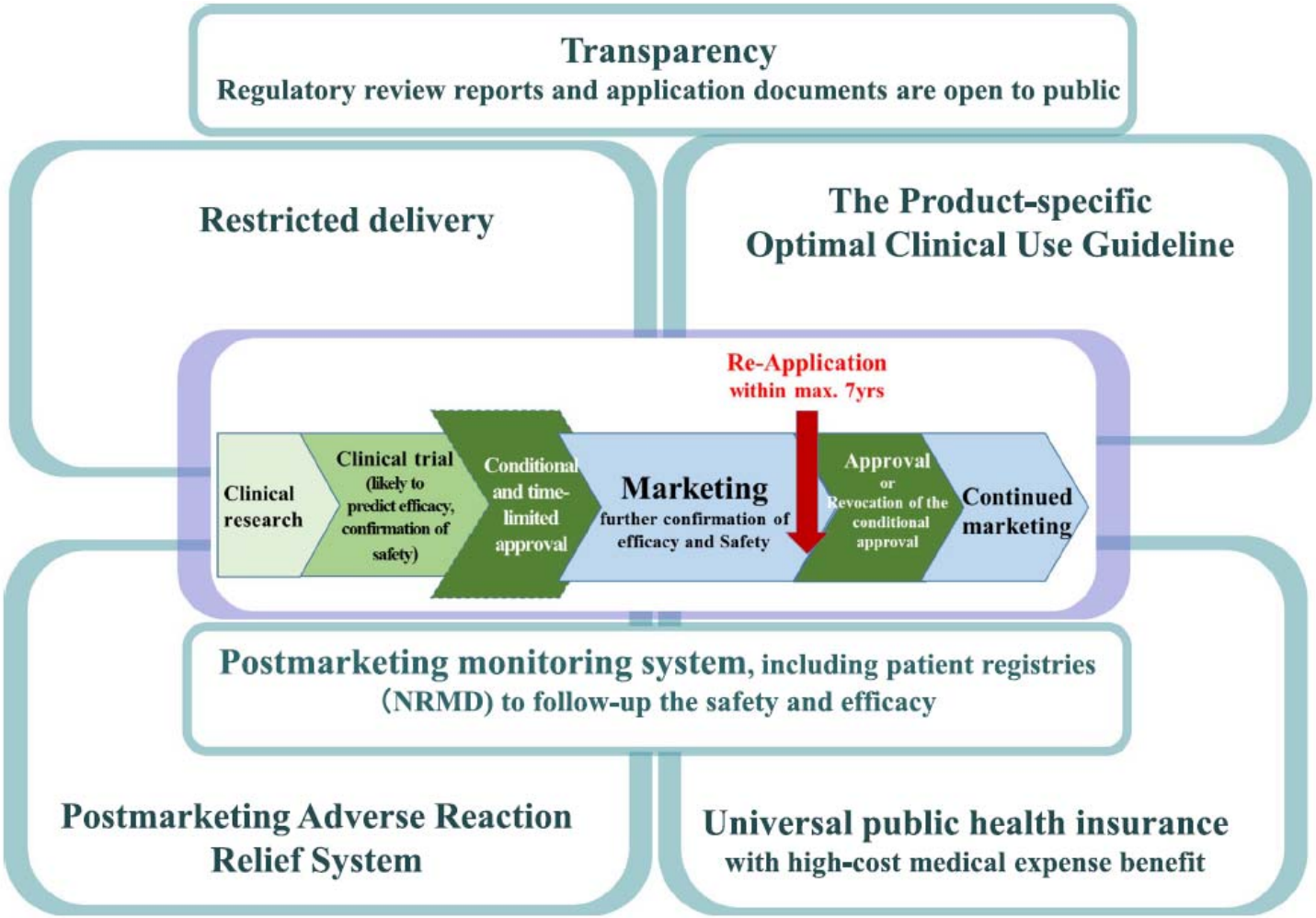
Products categories



Area of disease

PMD Act

Accelerated Access Scheme for RMPs in Japan



Fujiwara et al., *Clinical Pharmacology & Therapeutics* 2021; 109(5), 1182–1185

PMD Act

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

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

Summary

- Safety Act:

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

- PMD Act:

➢ 20 regenerative medical products, including 9 gene therapy products, have been approved under the PMD Act.

➢ 4 of 20 products have been approved through comprehensive framework for patient access (conditional and time-limited approval scheme). Sponsors are subject to strict post-marketing surveillance (PMS) study to prepare re-marketing authorization submission with in the granted time-period.

Where to Find Information?

Home | Reviews | Post-marketing Safety Measures | Relief Services for Adverse Health Effects | Regulatory Science(RS)・Standard Development(JP,GL) | International Activities

Home > Reviews and Related Services > Reviews > Regenerative Medical Products

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Reviews and Related Services

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  - New Drug Review with Electronic Data
  - **Regenerative Medical Products**
  - Advanced Efforts
  - Information for Approved Products
  - Genetically Modified Organisms
- GLP / GCP / GPSP Compliance Assessments
- GMP / QMS / GCTP Inspections
- Assessments to Registered Certification Bodies

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
   - treatment or prevention of human disease

b. Gene therapy (excluding the products that are prophylactic vaccines against infectious diseases).

2. Approved Regenerative Medical Prodcuts

- List of Approved Products
- Review Reports
- Revisions of PRECAUTIONS

Review Reports: Regenerative Medical Products

The following English translations of review reports are intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese originals and the translations, the former shall prevail. PMDA shall not be responsible for any consequence resulting from use of the English versions.

The review reports were selected for translation among those of new regenerative medical products that recently received marketing approval, in consideration of relevant factors including the novelty and priority.

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Abecma	idecabtagene vicleucel	January 2022		
Alofisel	darvadstrocel	September 2021		
Breyanzi	lisocabtagene maraleucel	March 2021		
Carvykti	ciltacabtagene autoleucel	September 2022		
Collategene	beperminogene perplasmid	March 2019		
Delytact	teserpaturev	June 2021		

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, Shinichi N, Asano J, Kunieda A, Kawanishi S, Maruyama Y, Honda F. 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

Thank you for your attention!

Please visit the PMDA website

http://www.pmda.go.jp

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