Regulatory Aspects of Cell and Gene Therapy Products: The PMDA Perspective

再生医療等製品の実用化促進におけるPMDAの取り組み

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COI開示

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Approved CGPs in Japan

4 somatic cell derived products

7 somatic stem cell derived products

5 *ex vivo* gene therapy products

4 *in vivo* gene therapy products

20

JACE

JACC

TEMCELL HS

HeartSheet

STEMIRAC

Kymriah

Collategene

Nepic

ZOLGENSMA

Aloficel

Ocural

Breyanzi

YESCARTA

Delytact

Sakracy

Abecma

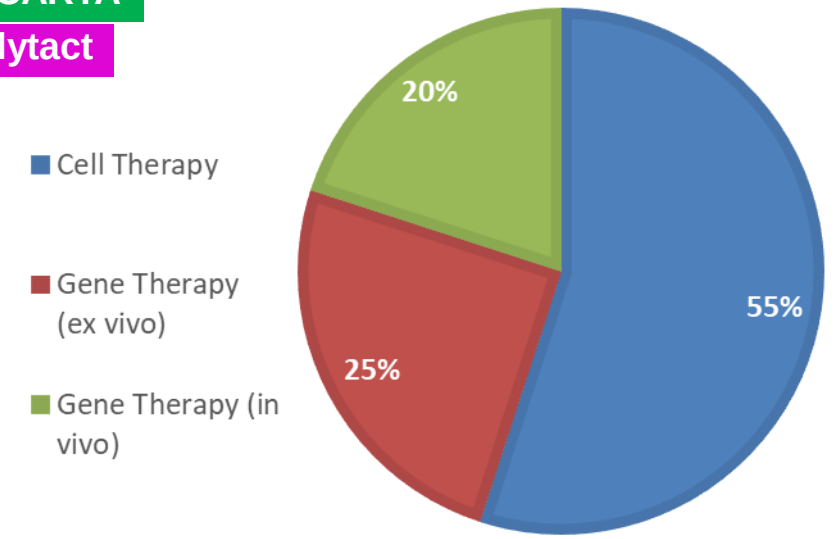
CARVYKTI

LUXTURNA

JACEMIN

Vyznova

2007 2012 2015 2018 2019 2020 2021 2022 2023



Accelerating Approval Pathways for CGPs in Japan

Type	Area	Product Features
Expedited review	Any product categories	In a particular situation requiring expedited review
Priority review		Designated as: 1. Orphan 2. Apparent improvement of medical care and for severe diseases
SAKIGAKE (Forerunner designation)		• Innovative medical products • For serious diseases • Development & NDA in Japan: being world's first or simultaneous with other countries • Prominent effectiveness expected on non-clinical and early phase clinical studies
Conditional and Time-limited Approval	Regenerative Medical Products (Cell, Gene, Tissue-engineering)	• Based on the clinical data from a limited number of patients, efficacy is predicted in a shorter time compared with the conventional process. • Acute-phase adverse reactions etc., can be evaluated for safety in a short period of time.

Accelerating Approval Pathways for CGPs in Japan

	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	✓		

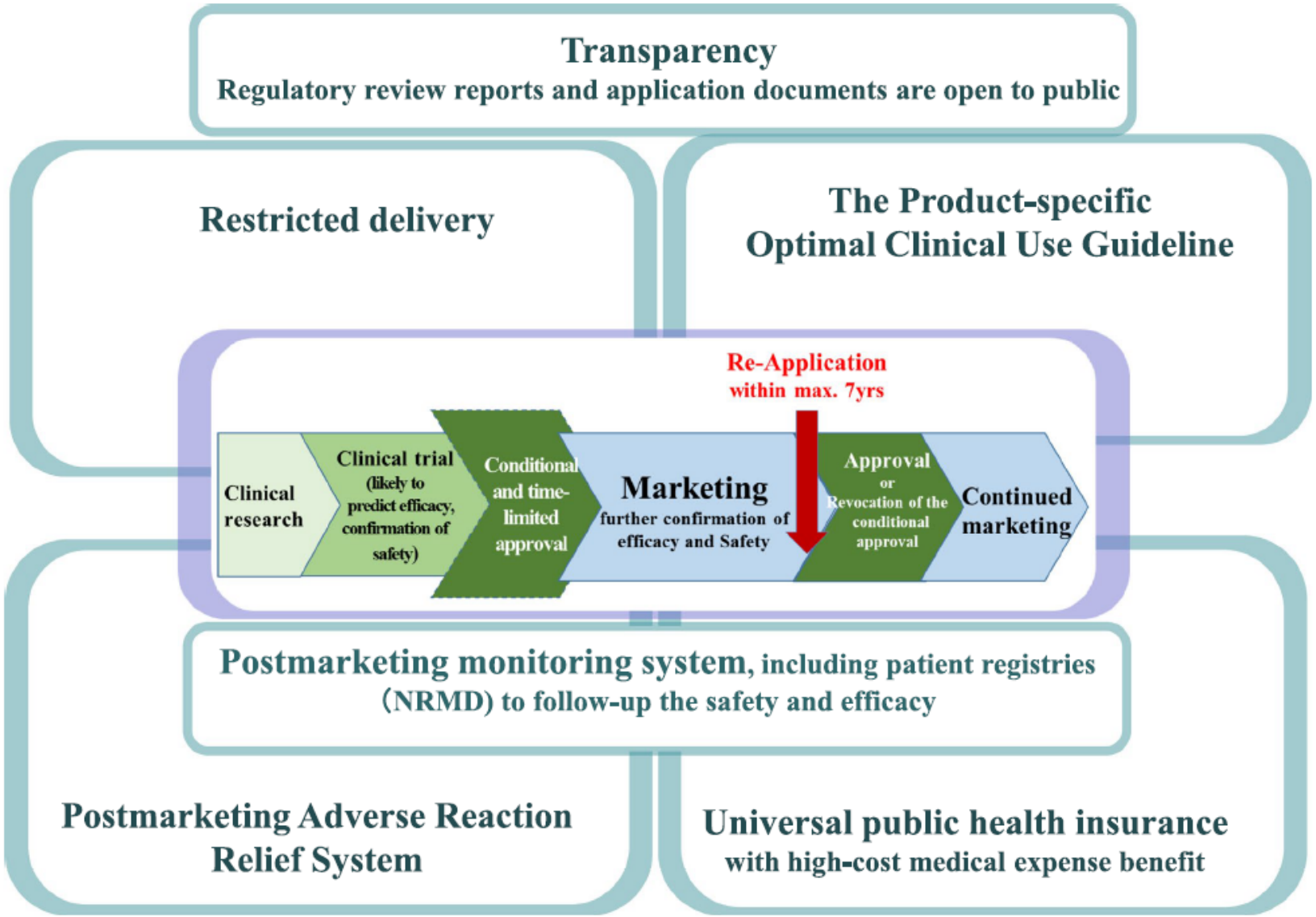
Area of disease	# of products
Oncology	6
Ophthalmology	5
Brain, Nerve	2
Circulation	2
Dermatology	2
Others	3

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

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

(As of 1 March 2024)

Accelerated Access Scheme for RMPs in Japan



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

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

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 in terms of social responsibility for pubic health

U.S. Approved Gene Therapy Products

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiadrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Casgevy (2023)
- Lyfgenia (2023)
- Lenmeldy (2024)

Accelerated drug lag, loss
ドラッグラグ・ロスが加速傾向

Blank: JPN/U.S./EU Approved

U.S./EU Approved

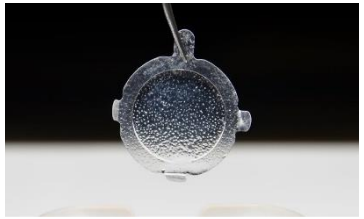
U.S Approved

Ex vivo
In vivo

Example:
Ophthalmology Area

JPN Approved Cell/Tissue-based Products

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



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

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

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

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

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

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

Communications & Outreach (Information Sharing)

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		

Training Materials

Learning Videos (Pmda Channel)

The PMDA-ATC offers you
PMDA and what we do to p

No.	Category
1.	Review
2.	Safety *New!*
3.	Relief
4.	Medical Device
5.	GxP
6.	PMDA Efforts

Learning Videos : Review

(Note) You will be transferred to a
below.

1. Review Teams
2. Application Dossier
3. Review Process
4. Japanese Pharmacopoeia (J
5. Review of Generic Drugs
6. Review of Biosimilars
7. First-in-Human Studies
8. Review of Regenerative Mec
9. Expedited Regulatory Pathw
10. Consultation Service
11. Good Registration Management (GRM)
12. Drug Master File System in Japan
13. Approval review referring Drug Master File
14. Review of Chemistry, Manufacturing and Control (CMC)
15. Review of Over The Counter (OTC) Drugs
16. History of Drug Evaluation using Foreign Clinical Data in Japan
17. Why MRCT?

Summary

- Accelerated pathways are introduced in many countries. Some country operate multiple pathways to offer applicants flexible use.
  早期承認制度が多くの国で導入されている。申請者に柔軟な利用を提案するために、複数の制度が運用されている。
- GCT products are designated to those pathways. Regulators need to consider on how to collaborate for those development, especially multiregional developed products.
  細胞・遺伝子治療用製品はこれらの制度が適用されている。規制当局は、特に複数地域で開発された製品について、開発を協力する方法を検討する必要がある。
- Sharing Japanese knowledge and experience in the regulation of CGT products is important for revitalize development in Japan.
  日本の知識と経験を共有することは、日本での開発を活性化するために重要である。