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Preparing for Clinical Trials: Development of Cell and Gene Therapy Products in Japan

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Disclosure

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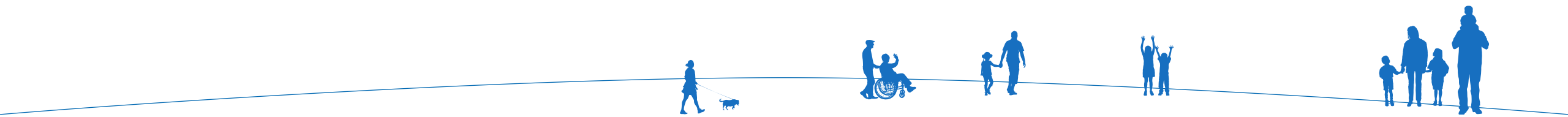
The speaker is affiliated with Pharmaceuticals and Medical Devices Agency.

The views expressed in this presentation are those of the author and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.



Outline

- Preparing for clinical trials
- Preparing for commercialization

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Clinical Trial Notification

Attached documents

1. Statement explaining the scientific justification for sponsoring the proposed clinical trial
2. Protocol of the proposed clinical trial
3. Informed consent and consent form
4. Sample of Case Report Form (CRF)
5. Current investigator's brochure (IB)

Investigation period

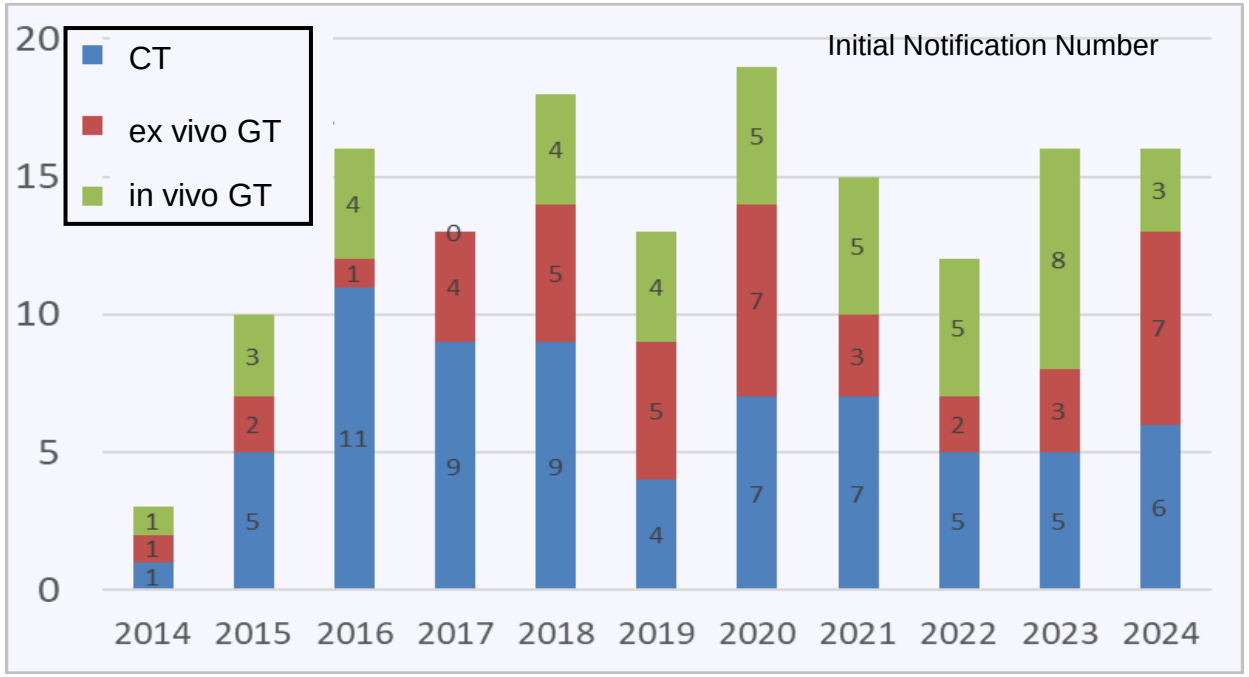
Initial notification: 30 days

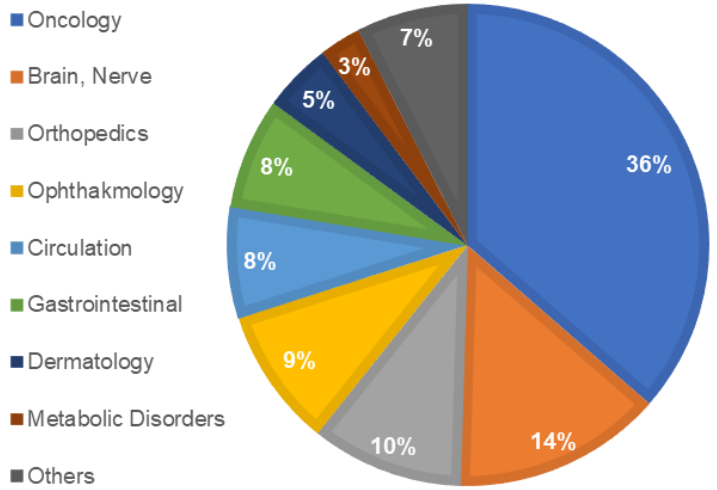
2nd or later notification: 14 days

Clinical Trial Notifications for CGT Products in Japan

FY	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Total
Initial	3 [1]	10 [2]	16 [7]	13 [8]	18 [8]	13 [7]	19 [9]	15 [7]	12 [3]	16 [4]	16 [7]	151 [63]
2nd or later	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	25 [14]	23 [9]	22 [2]	166 [62]

Note: The table in brackets in parentheses indicate the number of notifications of “investigator-initiated clinical trials (IIT).
https://www.pmda.go.jp/files/000276137.pdf





Area of disease

（2014～2021）

Points of CTN investigation

Purpose	Prevent the occurrence or spread of hazard to the public
Quality issues	• Biological raw material safety • Quality control (in-process, specification, etc.) • Comparability • Stability
Non-clinical issues	Cell and Tissue-based products • General toxicity • Tumorigenicity • Safety evaluation of non-cellular components and impurities Gene therapy products • Genome integration risk • Carcinogenic risk • Reproductive and developmental toxicity • Immunotoxicity
Clinical issues	• Intended indications and effects • Structure and mechanism • Objectives, details and period • Number of subjects • Target disease • Intended dosage and administration

Regulatory Science Consultation on R&D Strategy

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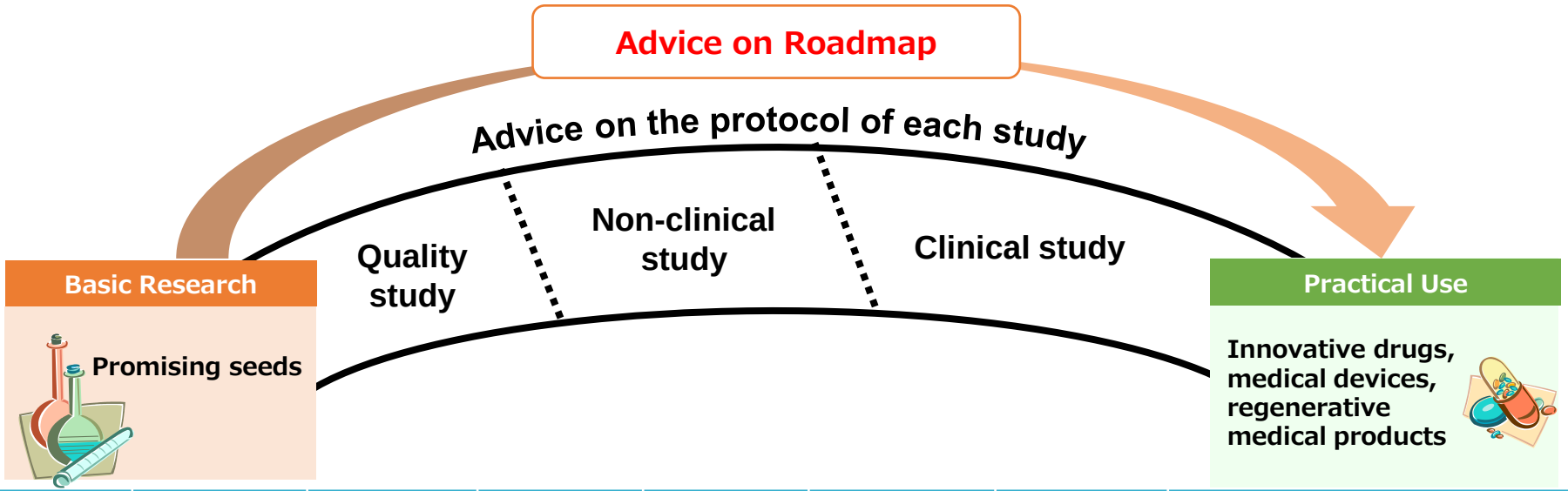
1. Facilitate the development of medical products by developing a more reliable roadmap.
2. Accelerate the clinical trials led by academia.
3. For regenerative medical products, ensure the quality of the products and confirm the nonclinical safety before the clinical trial notification.



FY	2018	2019	2020	2021	2022	2023	Fee
Quality/Non-clinical*1	25 [54]	29 [53]	25 [55]	25 [46]	20 [39]	18 [42]	1,541,600 JPY (14,400 CAD) 154,100 JPY (1,440 CAD)*2
Clinical	5	11	13	16	7	6	874,000 JPY (8,200 CAD) 87,400 JPY (820 CAD) *2
Total	59	64	68	62	46	48	

*1: If consultation is held over multiple days, the fee for one consultation will be charged for up to three consultations. The figures in brackets indicate the total number of these sessions.
*2: Universities/research institutions and start-up companies that meet the requirements specified separately.

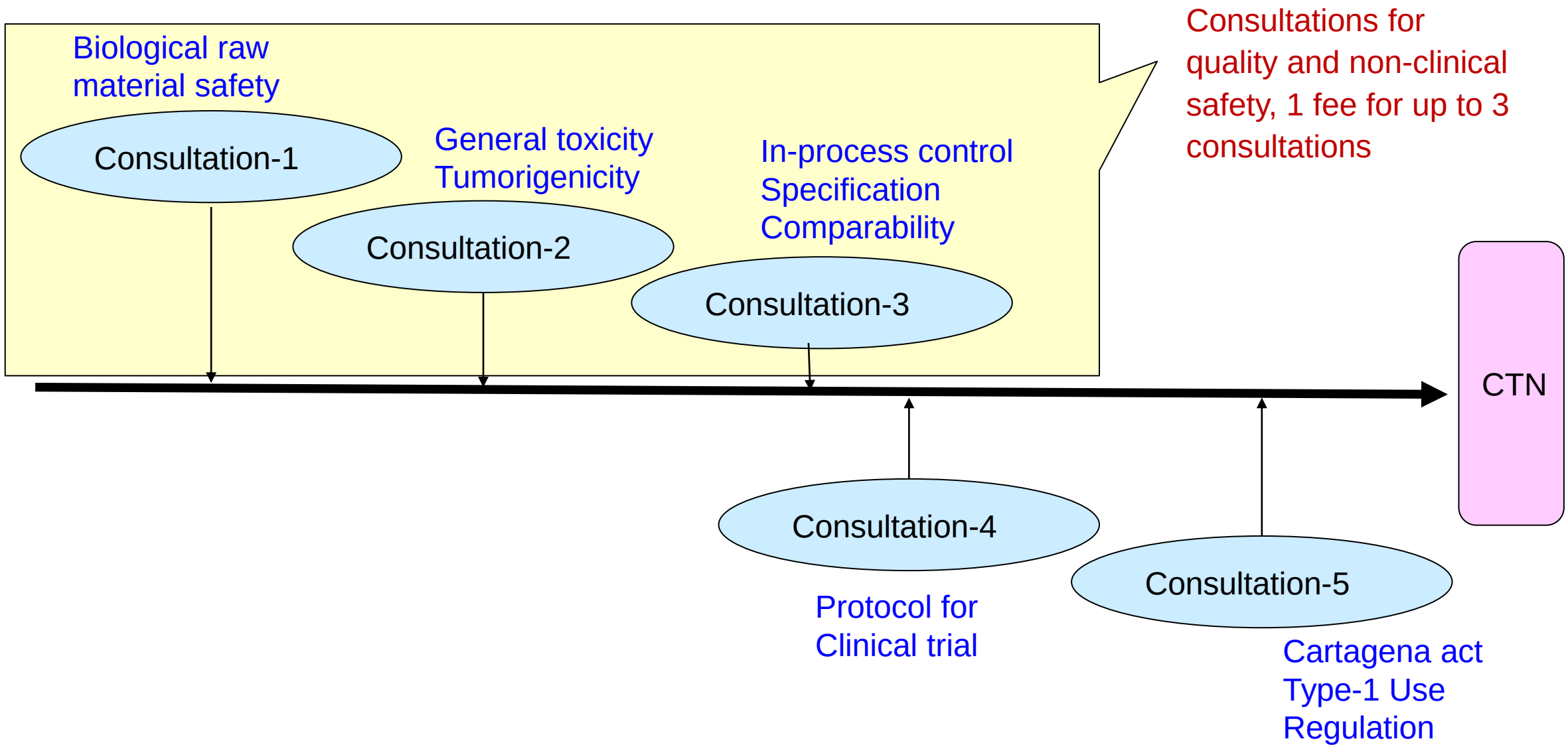
Regulation of GMO/LMO in the Cartagena Act

Type	How to use	Points for review
Type-1 	Deliberate release	Environmental risk assessment (ERA) ＋ Risk assessment for third party
	The Use of GMO without preventive measures against their release into environment	

Review Time Median (months) (Min-Max)	2019 (8 cases)	2020 (6 cases)	2021 (8 cases)	2022 (15 cases)	2023 (5 cases)
Regulatory	**4.7 (2.6-6.6)**	**4.2 (3.6-6.3)**	**3.2 (0.9-4.3)**	**3.3 (1.3-5.3)**	**2.8 (1.1-4.0)**
Applicant	**0.9 (0.1-4.2)**	**2.5 (0.6-4.3)**	**0.2 (0-1.0)**	**1.2 (0-4.9)**	**0.2 (0-3.1)**
Total	**5.9 (3.2-9.9)**	**6.6 (5.1-10.5)**	**3.5 (0.9-4.9)**	**5.0 (1.3-7.5)**	**3.1 (1.2-7.1)**

Years	Improvement of the Cartagena Act Operation
2019	• Published the **standard description** of the Type-1 Use Regulation. • Established the official **consultation** related to the Cartagena Act. *Fee; 2,889,700 JPY=27,000 CAD.
2020	• Published the **specific description** of the Type-1 Use Regulation for AAV, Adenoviral, and Herpes viral vectors.
2021	• Published the **specific description** of the environmental risk assessment for AAV vectors. • Published the **specific description** of the Type-1 Use Regulation for residual retro/lentiviral vectors in genetically modified cell products. • Eliminated the voluntary PMDA review of draft applications. • Published the Notification related to the acceptance of the application of Clinical Trial Notification and the Type-1 Use Regulation in parallel. • Updated the Notification related to FAQ.

Example of Process Up to the Clinical Trial Notification



Related Guidelines for Early stage of development

Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from early stage of development.

- Cellular and tissue-based products

  Quality: https://www.pmda.go.jp/files/000273777.pdf

  Non-clinical: https://www.pmda.go.jp/files/000273775.pdf

- Gene therapy products

  Quality: https://www.pmda.go.jp/files/000273778.pdf

  Non-clinical: https://www.pmda.go.jp/files/000273779.pdf

Outline

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Approved CGT Products in Japan

Brand name	Category	Orphan	SAKIGAKE	Conditional & Time-limited Approval
Abecma	CAR-T	✓		
Breyanzi	CAR-T	✓		
CARVYKTI	CAR-T	✓		
Delytact	Oncolytic virus	✓	✓	✓
Kymriah	CAR-T	✓		
YESCARTA	CAR-T	✓		
LUXTRNA	AAV	✓		
Nepic	Somatic stem cell	✓		
Ocural	Somatic stem cell	✓		
Sakracy	Somatic stem cell	✓		
Vyznova	Somatic cell	✓		
Akuugo	Somatic stem cell	✓	✓	✓
2025 ELEVIDYS	AAV	✓		✓
STEMIRAC	Somatic stem cell		✓	✓
ZOLGENSMA	AAV	✓	✓	
Collategene	Plasmid vector			✓(expired (27 June 2024))
HeartSheet	Somatic stem cell			✓(withdrawn (25 July 2024))
JACE	Somatic cell	✓GCMN*, EB**		
JACEMIN	Somatic cell			
2025 Vyjuvek	HSV	✓		
Aloficel	Somatic stem cell	✓		
JACC	Somatic cell			
TEMCELL	Somatic stem cell	✓		

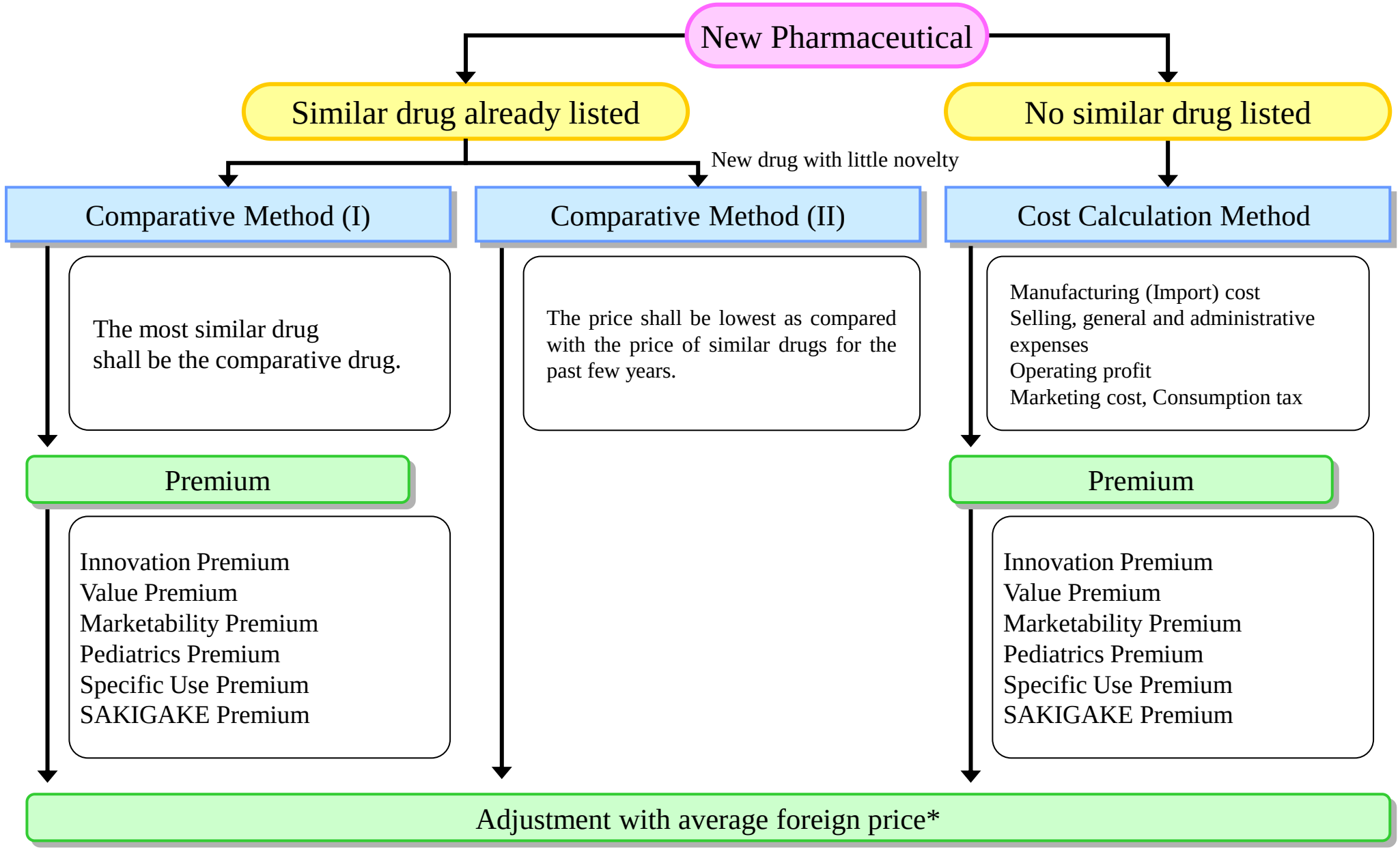
(As of 1 September 2025)

Area of disease	#
Oncology	6
Ophthalmology	5
Brain, Nerve	4
Circulation	(2)
Dermatology	3
Others	3

21(2)

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

NHI Pricing Method for New Pharmaceuticals



Orphan Designation

(1) Number of patients

The number of patients who may use the drugs, medical device or regenerative medicine should be less than 50,000 in Japan (125.7 million people in 2021).

(2) Medical needs

- The drugs, medical devices or regenerative medicine should be indicated for the treatment of serious diseases, including difficult-to-treat diseases. In addition, they must be drugs, medical devices or regenerative medicine for which there are high medical needs satisfying one of the following criteria.
- There is no appropriate alternative drug/medical device/regenerative medicine or treatment
- High efficacy or safety is expected compared with existing products

(3) Possibility of development

- There should be a theoretical rationale for the use of the product for the target disease, and the development plan should be appropriate.

Orphan Products Development Support Program

(1) Subsidy Granting

- NIBN (National Institutes of Biomedical Innovation, Health and Nutrition) grants financial assistance to the developers.

(2) Guidance and Advice

- Consultation by NIBN and PMDA.

(3) R&D Expenses Applicable to Corporate Tax Credits

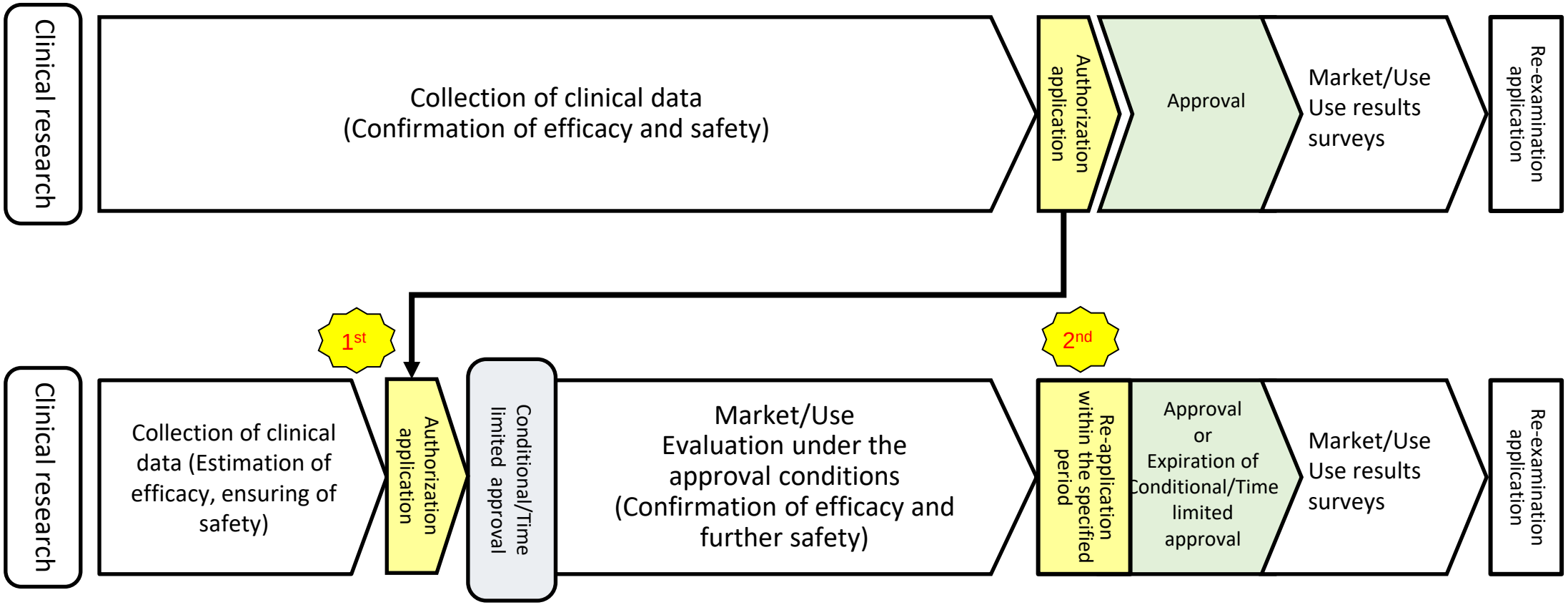
- The developers can receive a tax credit for the subsidy period based on the outcome of these assessments (20% × [R&D cost − subsidy amount]).

(4) Extend re-evaluation period

- 10 years.

Conditional and Time-limited Approval

[Regular approval scheme]



[Conditional Time-limited approval scheme]

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Regulatory Pitfalls: Conditional and Time-limited Approval

- Acceptable level of clinical effectiveness vs patient access to the new therapy.
- Acceptable risk vs expected benefit.

- Guidance for conditional and time-limited approval for regenerative medical products and the development of subsequent efficacy evaluation plan, PSB/MDED Notification No.0329-3, 2024.
  Japanese: https://www.pmda.go.jp/files/000267914.pdf
  English: https://www.pmda.go.jp/files/000274350.pdf
- Guidance on conditional and time-limited approval for human cell-processed products derived from mesenchymal stem cells or mesenchymal stromal cells of human origin and evaluation for subsequent efficacy evaluation plan, PSB/MDED Notification No. 0329-4, 2024.
  Japanese: https://www.pmda.go.jp/files/000267915.pdf
  English: https://www.pmda.go.jp/files/000274351.pdf
- Draft Notification: Handling of Conditional and Time-limited Approval Scheme
  Japanese: https://public-comment.e-gov.go.jp/pcm/download?seqNo=0000296199
  (Published for public consultation on 25 July 2025)
  https://public-comment.e-gov.go.jp/pcm/detail?CLASSNAME=PCMMSTDETAIL&id=495250120&Mode=0

Where to Find Information? (For CGT Products)

Regenerative Medical Products

2. Approved Regenerative Medical Prodcuts

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

3. Support to Venture Companies

- PMDA's Support to Venture Companies [2.1MB]
- Doing business in Japan: What is attracting? [1.4 MB]
- Supports from Japanese government (MHLW)

4. Related Guidelines and Notifications for Regenerative Medical Products

Marketing authorization application (MAA)

- Questions and answers (Q&A) on release testing of the imported regenerative medical products, PSB/MDED, PSB/CLD Administrative Notice, 2024. [Japanese [144KB]] [English [143KB]]
- Guideline for comparability of human cell-processed products subject to changes in their manufacturing process, PSB/MDED Notification No. 0329-1, 2024. [Japanese [431KB]] [English [245KB]]

Good tissue practice (GTP)

- Standards for biological raw materials, MHLW Notification No. 210, 2003. [Japanese [315KB]] [English [73KB]]

Review Reports: Regenerative Medical Products

A

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Abecma Initial Approval	Idecabtagene vicleucel	January 2022		
Abecma Partial Change Approval	Idecabtagene vicleucel	December 2023	English [607.25 KB]	Japanese [847.24 KB]
Alofisel	Darvadstrocel	September 2021		

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

Thank you!

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