Attractive Market

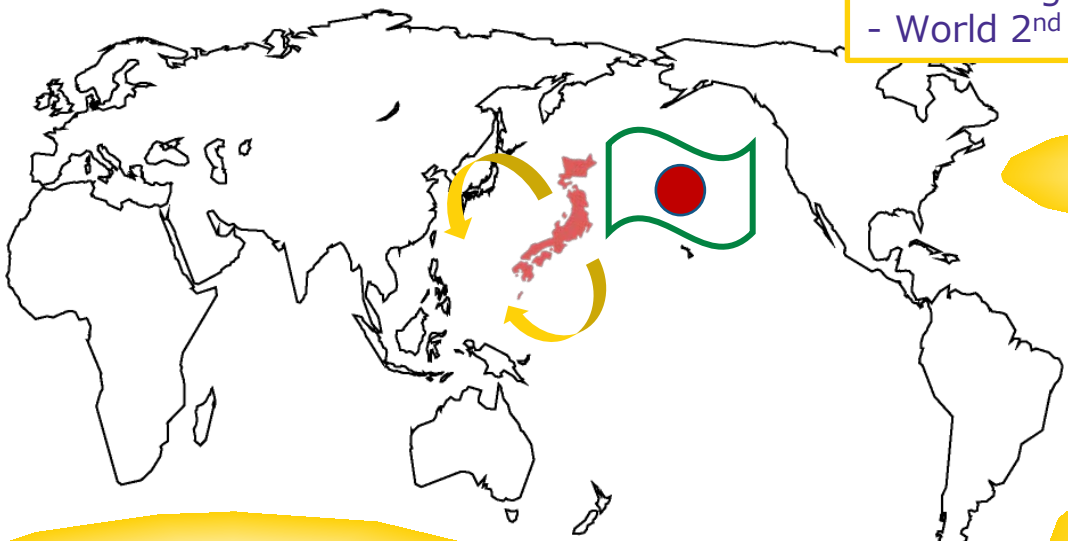
Flexibility/ Predictability

Doing business in Japan: What is attracting?

Advantages

Further merit

1. Attractive Market



- World 3rd largest pharma market.
  New drugs market: expanding.
- World 2nd largest medical device market.

Large Market

Universal Public Health Insurance

- Patients: accessible to new drugs.

Gateway to Asian Countries

2. Flexibility/Predictability

- High predictability
  (Sales timing after NDA)
  :Transparent review timeline

- The world-class faster NDA review
- Prompt NHI Drug Price
  :Within 60 days (without HTA)

- Fine Support
  :Scientific consultations from early stage

- Full International Harmonization
  : Regulation based on ICH standard

Accelerating Approval Pathways for CGT Products in Japan

Brand name	Category	Orphans	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	✓	✓	✓
STEMIRAC	Somatic stem cell		✓	✓
ZOLGENSMA	AAV	✓	✓	
Collategene	Plasmid vector			✓(Expired (27/06//2024))
HeartSheet	Somatic stem cell			✓(Withdrawn (25/07/2024))
JACE	Somatic cell	✓GCMN*, EB**		
JACEMIN	Somatic cell			
Aloficel	Somatic stem cell	✓		
JACC	Somatic cell			
TEMCELL	Somatic stem cell	✓		

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

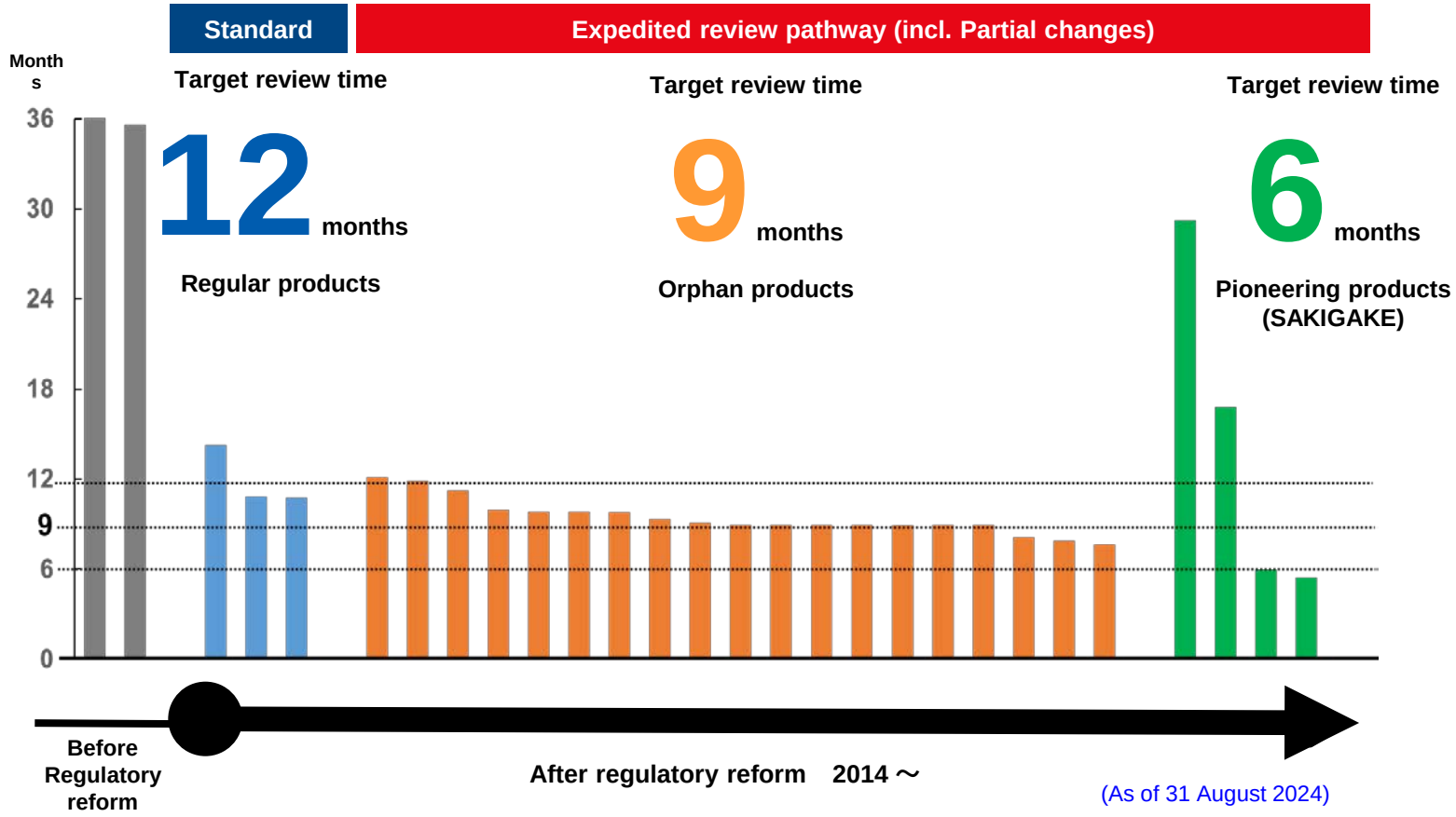
19

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

(As of 31 August 2024)

Total Review Time for CGT Products

High predictability



(As of 31 August 2024)

High predictability

Regulation of GMO/LMO in the Cartagena Act

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

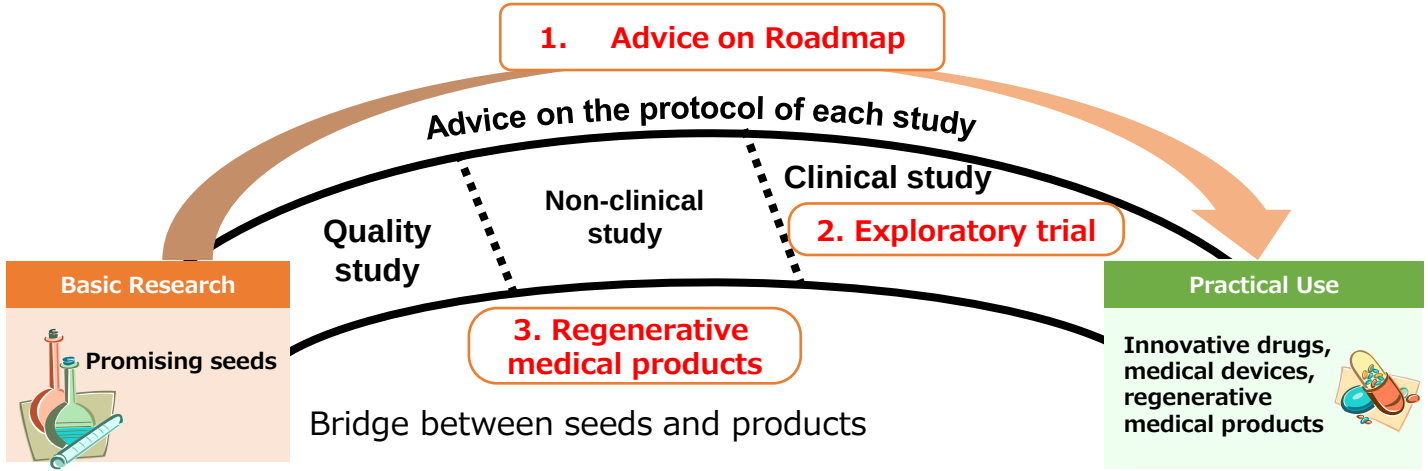
Review Time Median (months) (Min-Max)	2019 (8 cases)	2020 (6 cases)	2021 (8 cases)	2022 (15 cases)	2023 (5 cases)
Regulatory	4.7 (2.6-6.6)	4.2 (3.6-6.3)	3.2 (0.9-4.3)	3.3 (1.3-5.3)	2.8 (1.1-4.0)
Applicant	0.9 (0.1-4.2)	2.5 (0.6-4.3)	0.2 (0-1.0)	1.2 (0-4.9)	0.2 (0-3.1)
Total	5.9 (3.2-9.9)	6.6 (5.1-10.5)	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-1Use Regulation. • Established the **official consultation** related to the Cartagena Act.
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.

- Fine Support
  :Scientific consultations from early stage

Regulatory Science Consultation on R&D Strategy

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.



Bridge between seeds and products

FY	2018	2019	2020	2021	2022
Quality Non-clinical	25 [54]	29 [53]	25 [55]	25 [46]	20 [39]
Clinical	5	11	13	16	7
Total	59	64	68	62	46

The figures in brackets indicate the total number of these sessions.

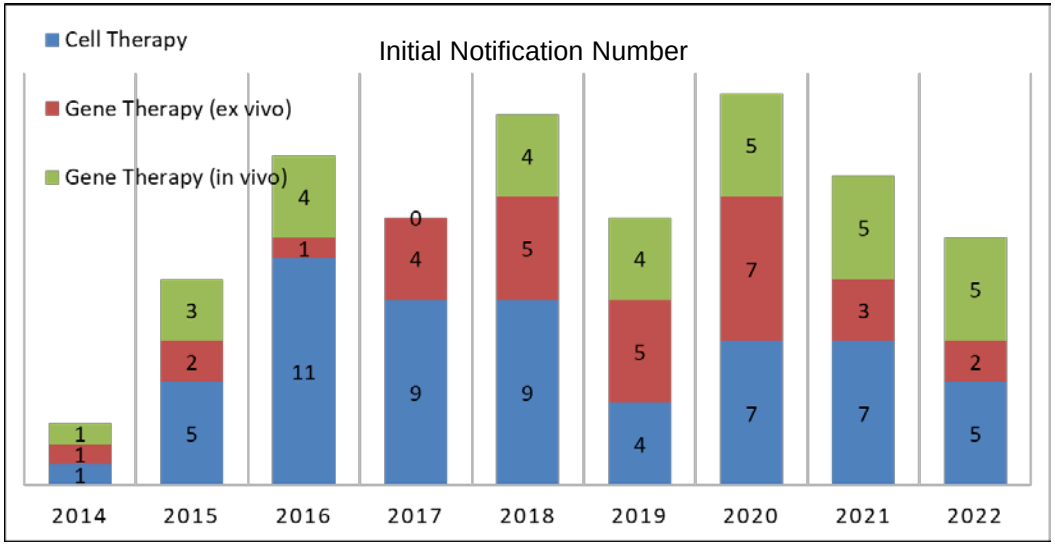
PMDA offers 90% reduction to venture companies.

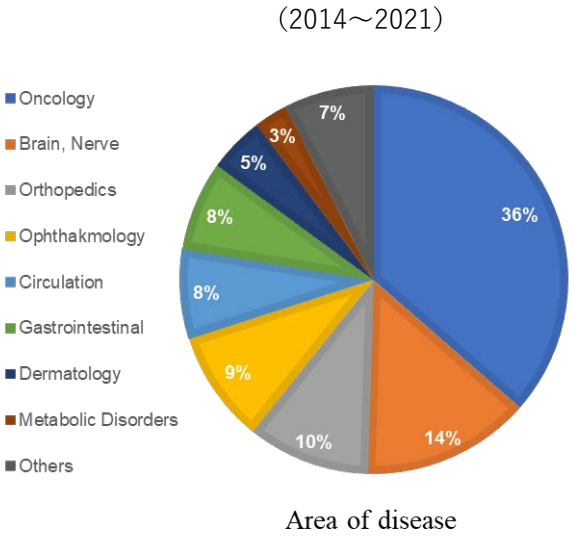
INDs Reviewed by PMDA

- **Fine Support**
  :Scientific consultations from early stage

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 [52]
2nd or later	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	25 [14]	121 [51]

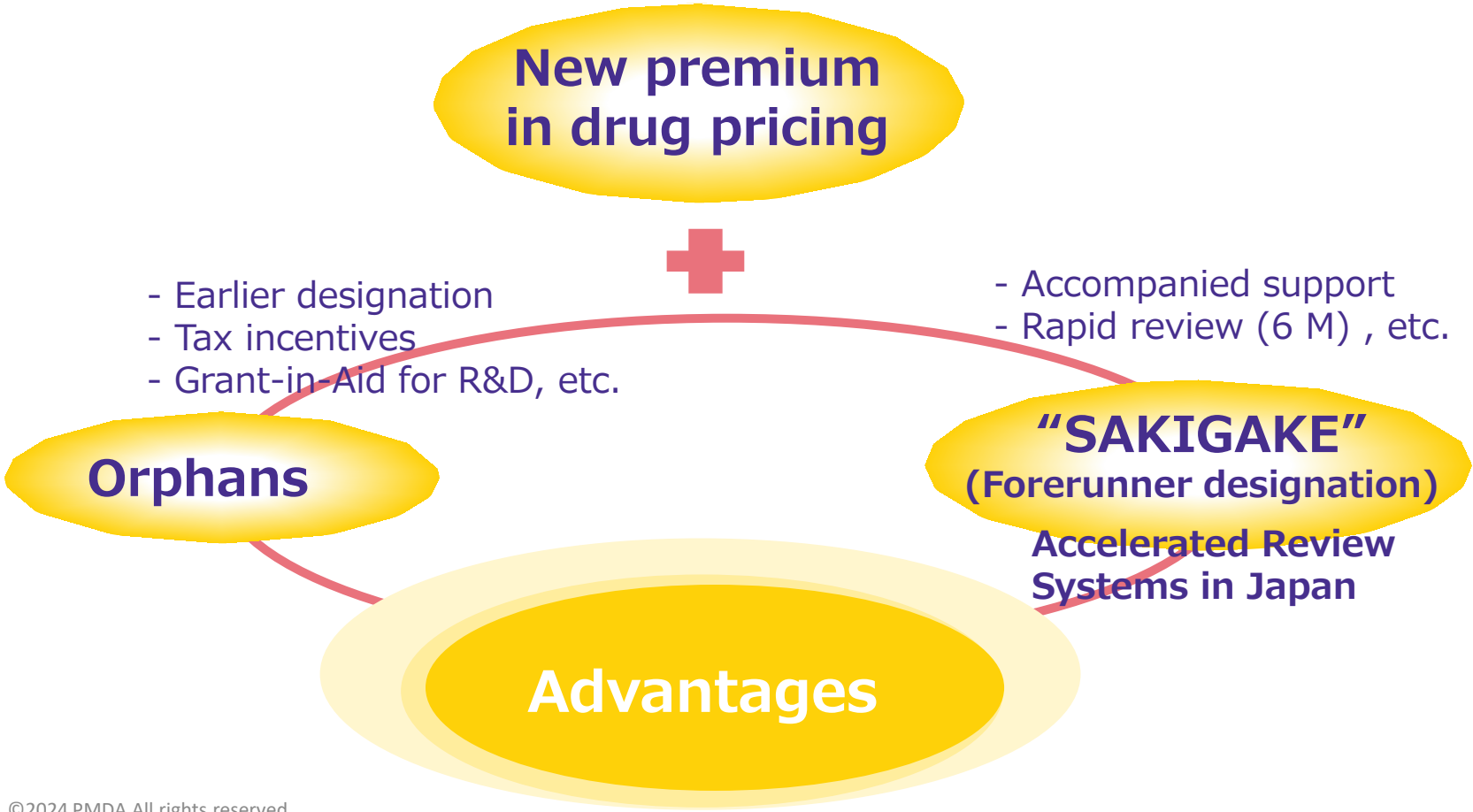
Note: The table in brackets in parentheses indicate the number of notifications of “investigator-initiated clinical trials (IIT).
https://www.pmda.go.jp/files/000265813.pdf





Area of disease

3. Advantages: Designation for each product characters



Orphan Designation

Orphans

(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.

(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 medical products 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.

https://www.nibiohn.go.jp/en/activities/orphan-support.html

Orphan Products Development Support Program

(1) Subsidy Granting

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

(2) Guidance and Advice

- Consultation by NIBOHN 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.

https://www.nibiohn.go.jp/en/activities/orphan-support.html

SAKIGAKE Designation

"SAKIGAKE"
(Forerunner designation)

(1) Innovativeness of the products

(2) Treatment for which the earliest commercialization is required for target diseases

- Serious or life-threatening medical condition
- Medical condition with persistent symptoms for which there is no other curative treatment

(3) Highly effective treatment against the target medical condition

(4) Develop the product rapidly and file an application for approval in Japan, ahead of other countries (filling within 3 months of global submission)

Designation Advantages

"SAKIGAKE"
(Forerunner designation)

To shorten the time to approval

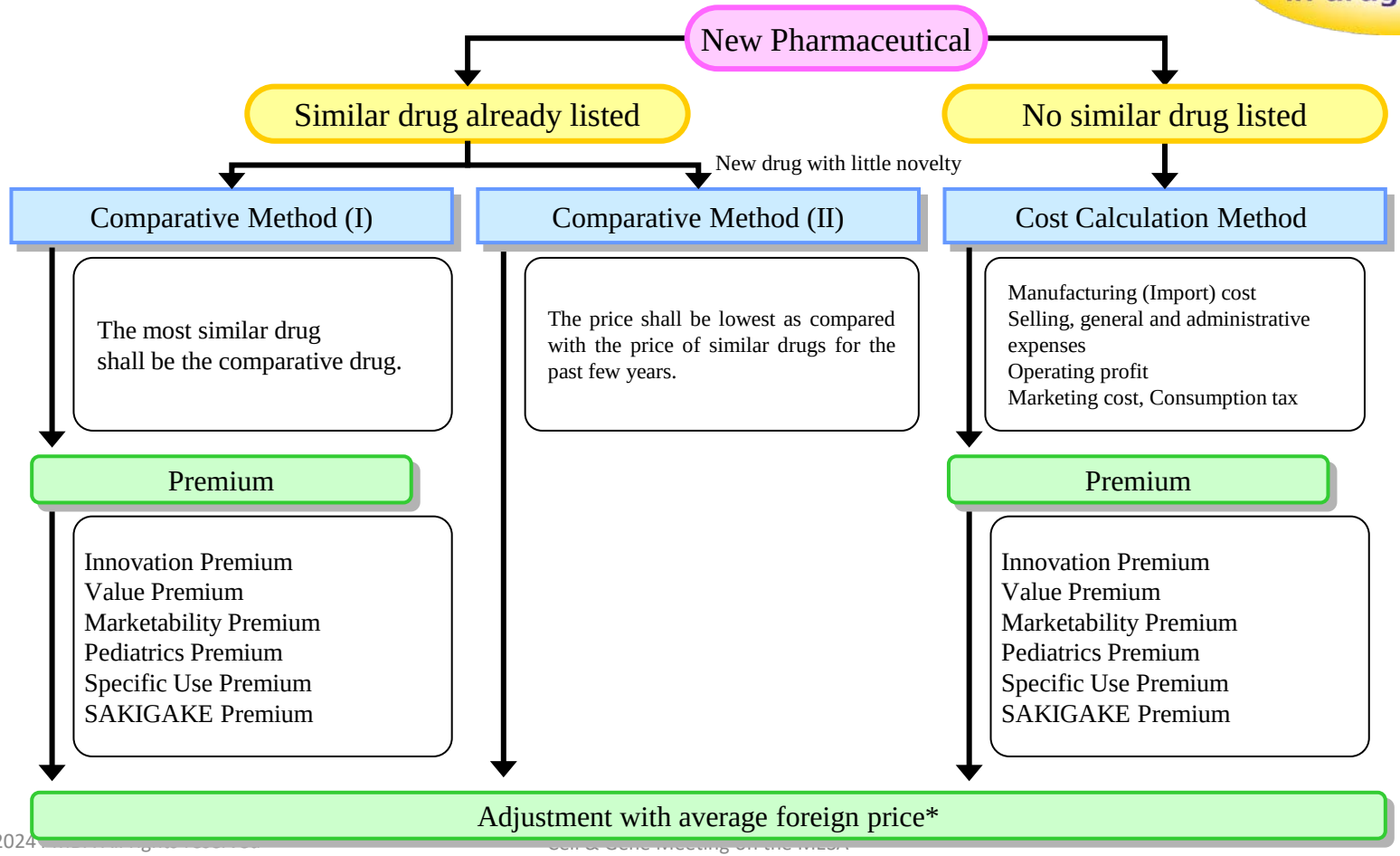
1. Prioritized Consultation [Waiting time: 2 months→1 month]
2. Substantialized Pre-application Consultation
   [de facto review before application]
3. Prioritized Review
   [Target total review time 12 months → 6 months]

To facilitate R&D

4. Review Partner [PMDA manager as a concierge]
   Overall management for whole process toward approval

NHI Pricing Method for New Pharmaceuticals

New premium in drug pricing



* This is limited to cases where there are no drugs with similar pharmacological effects in comparative method (I) or cost calculation method.

Adjustment Premium at Time of New Drug Listing

New premium in drug pricing

Innovation premium (70 ~ 120%)

Newly listed products that **meet all** the following requirements
(a) Have **clinically useful novel mechanism of action.**
(b) It has been objectively shown to have **high efficacy or safety** compared with similar drugs or existing therapies.
(c) The newly listed product has been objectively shown to **improve the treatment method** for the disease or injury targeted by the newly listed product.

Usefulness premium (I) (35 ~ 60%)

Newly listed products that **meet two of the three requirements** of the innovation premium

Usefulness premium (II) (5 ~ 30%)

Newly listed products * (a) to (c) that **meet any of the requirements** below are the same as the requirements for the innovation premium.
(a) It has a clinically useful novel mechanism of action.
(b) It has been objectively shown to have high efficacy or safety compared with similar drugs or existing therapies.
(c) The newly listed product has been objectively shown to improve the treatment method for the disease or injury targeted by the newly listed product.
(d) it has been objectively demonstrated to exhibit higher medical usefulness **compared to similar drugs or existing therapies due to its innovative formulation.**

Determined by the number of requirements met

*If more than one adjustment premium is applicable, the sum of the proportions of each premium shall be used for calculation. (For cellular and tissue-based products, the premium rate shall be adjusted according to the market size, etc.)

Marketability premium (I) (10 ~ 20%)

Orphan drug for which the efficacy/effectiveness related to the target disease, etc. is the primary efficacy/effectiveness

Marketability premium (II) (5%)

Products for which the primary efficacy/effectiveness corresponds to an efficacy separately specified as **products with a small market size**

Specified use premium (5 ~ 20%)

Products designated as **Specified drug**

Pediatric premium(5 ~ 20%)

Products for which the primary **efficacy/effectiveness** or the **dosage and administration** related to such efficacy **explicitly includes a pediatric efficasy**

Not calculated

Sakigake Premium (10 ~ 20%)

Products designated as **pioneering drugs** (including products designated under the old system)
< Developed in Japan first in the world > 【New】

Rapid introduction premium (5 ~ 10%)

Products that are introduced in Japan in an expedited manner in accordance with the above (products that meet the following requirements)
・Products under international development (e.g., implementation of global clinical trials)
・Priority Review Items
・Products for which application and approval are earlier than those in the US and Europe or within 6 months after the first application and approval in the US and Europe

Not calculated

*Not eligible for premium if comparator drug receives premium (With some exceptions.)

4. Further merit

Acceleration for MRCTs

- Japanese Ph1 trial : not necessarily required prior to the start of later phase MRCTs.

PMDA Washington D.C. office (TBA)

- Promote further international harmonization.
- Provide various Japanese information.

PMDA Asia Office (Bangkok, Thailand)

(1 July 2024)

- “Gateway” to Asia countries

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