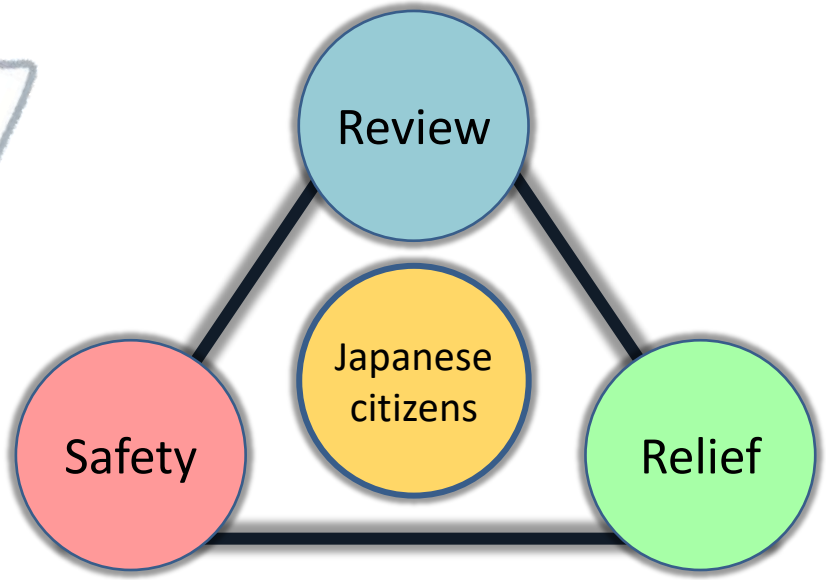
PMDA's Support to Venture Companies

Pharmaceuticals and Medical Devices Agency



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

February, 2024

Key points for your development strategy in Japan

The 3rd Largest Market &
Key for World-Wide Development of
Medical Products!

<PMDA's performance>

1. World Fastest Review
2. Gateway to regulatory approval in Asia
3. Internationally harmonized regulations

<Others>

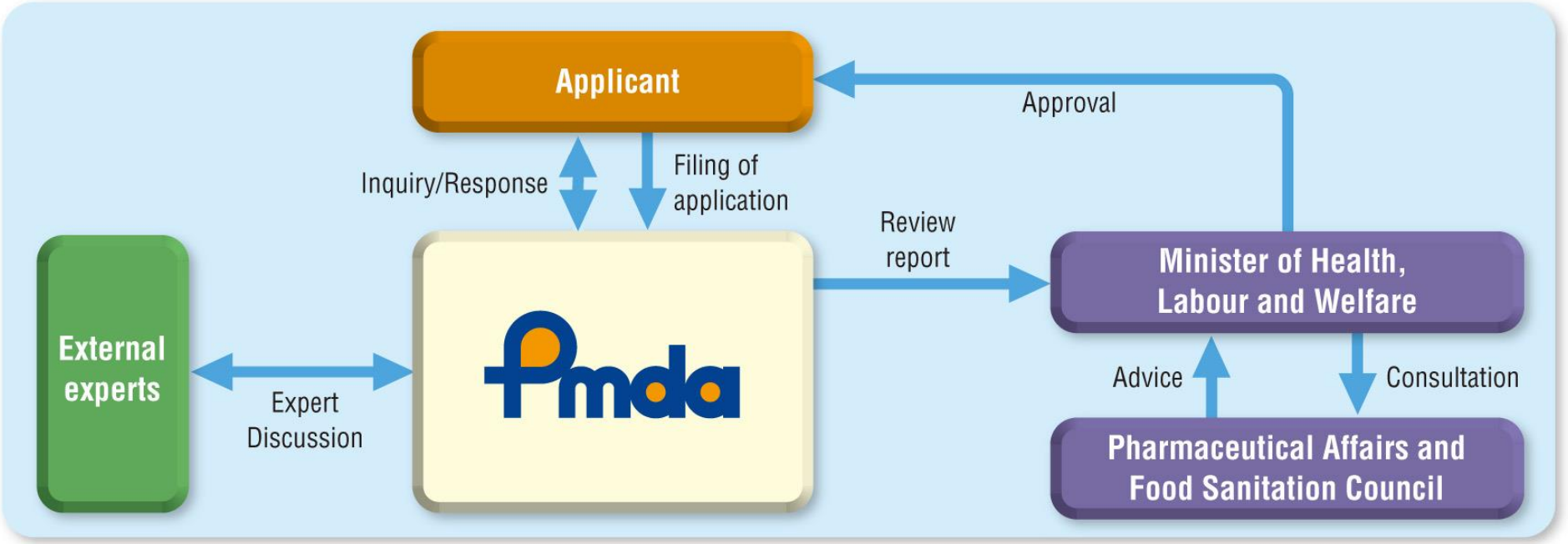
Universal health coverage system in Japan

- ✓ no HTA before inclusion in the NHI Drug Price Standard,
- ✓ 60-90 days from approval to the inclusion,

etc.

Introduction of PMDA

- Pharmaceuticals and Medical Devices Agency (PMDA) is a **Government Affiliated Organization** in Japan.
- PMDA is responsible for **scientific review and consultation** of medical products, which are approved in Japan.

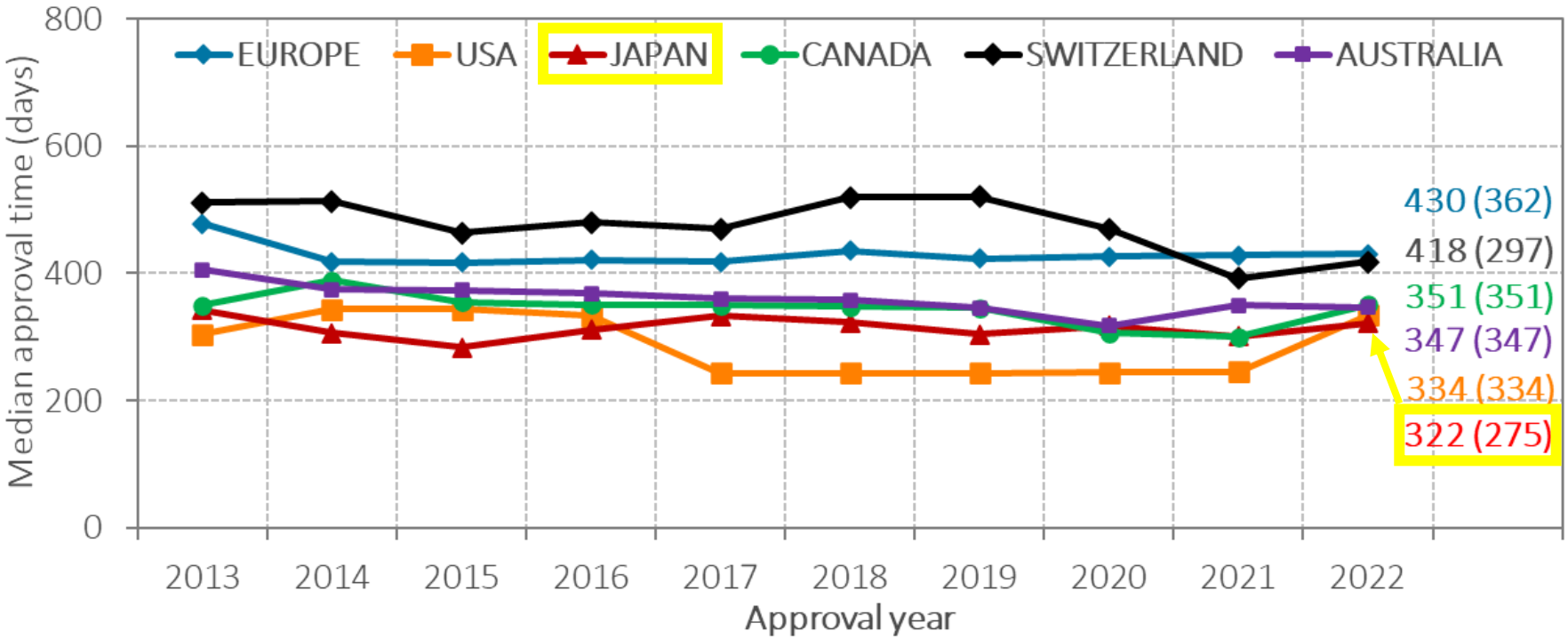


PMDA's performance

1. World fastest review
   - various fast track systems -

Median approval time for New Active Substance

PMDA is one of the fastest review organizations in the world!



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2022; (N2) = median time from submission to the end of scientific assessment for products approved in 2022.

Accelerated review systems in Japan

Japan Offers Various Supporting Schemes for R&D Companies and Researchers.

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 for severe diseases
SAKIGAKE (Forerunner designation)		• Innovative medical products • For serious diseases • Development & NDA in Japan: The NDA submission being the world's first or simultaneous with other countries • Prominent effectiveness expected based on non-clinical and early phase clinical study data
Conditional Early Approval	Drugs	Early application through confirmation of a certain degree of efficacy and safety in clinical trials other than confirmatory clinical trials
	Medical Devices	• High clinical needs • Balancing the pre- and post-market requirements
Conditional and Time-limited Approval	Regenerative Medical Products	• Based on the clinical data from the limited number of patients, efficacy is predicted in a shorter time compared with the conventional process. • Early-phase adverse reactions, etc. can be evaluated for safety in a short period of time.

SAKIGAKE (Forerunner) drugs - Designation System

<Objective>

To put innovative products into medical practice in Japan

<Criteria for designation>

1. Innovativeness - new mode of action (in principle)
2. Severity of the target disease - life-threatening or no curative therapies
3. Prominent efficacy - no existing therapies or probable significant improvement in efficacy or safety compared to existing therapies
4. Plan/System - to submit the NDA in Japan first or at the same timing* as the first NDA submission to other national regulatory authority

<Incentive>

*within 3 months

- Concierge service offered by senior review partner (PMDA)
- Priority scientific advice (PMDA)
- Pre-review in consultation (PMDA)
- Priority review (6 months)(PMDA)
- Premium drug pricing
- Extension of re-examination period

Fastest Practical Use in the world

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Orphan drug – Designation System

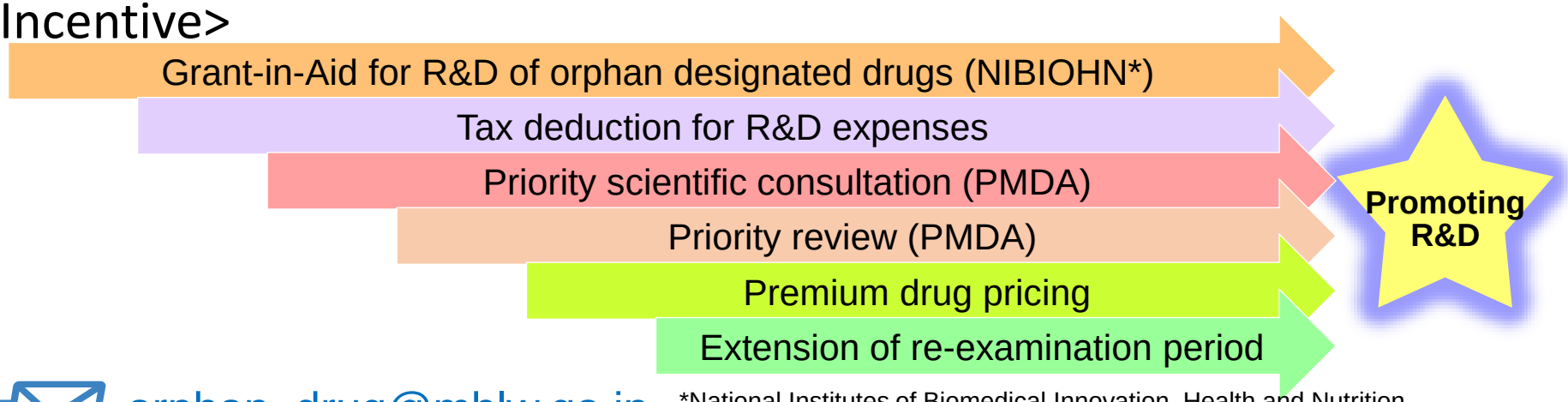
<Objective>

To promote the R&D of the products for rare diseases to provide the patients with safe and effective medicines/medical devices as early as possible

<Criteria for designation>

1. Number of patients (any of the following has to be met)
   - Less than 50,000 in Japan
   - The target disease is one of the designated intractable diseases
2. Medical needs
   - Serious diseases with high medical needs
3. Feasibility of development

<Incentive>



orphan_drug@mhlw.go.jp

*National Institutes of Biomedical Innovation, Health and Nutrition

Examples of the world-first approval granted in Japan

These were designated as SAKIGAKE and/or Orphan Drugs.

The Oncologist

Regulatory Issues: PMDA

Designation Products: Boron Neutron Capture Therapy for Head and Neck Carcinoma

The Oncologist, 2023, XX, 1–7
https://doi.org/10.1093/oncolo/oyad041
Advance access publication 14 March 2023
Review Article

OXFORD

Regulatory Issues: PMDA – Review of Sakigake Designation Products: Oncolytic Virus Therapy with Delytact Injection (Teserpaturev) for Malignant Glioma

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Abstract

In June 2021, the Ministry of Health, Labor and Welfare approved Delytact Injection as a regenerative medical product for oncolytic virus therapy. The active substance of Delytact Injection is teserpaturev, a genetically engineered herpes simplex virus type 1 (strain F) in which the α47 gene and both copies of the γ34.5 gene have been deleted and the infected cell protein 6 (ICP6) gene has been inactivated by the insertion of the lacZ gene from *Escherichia coli*. Delytact Injection, when intratumorally administered to patients with malignant glioma, is expected to exert the following effects: (1) the mutant virus selectively replicates in tumor cells and destroys the infected cells through the replication process, exerting a cytocidal effect, and (2) the administration leads to induction of tumor-responsive T cells, which activates antitumor immunity and thus prolongs the survival of patients with malignant glioma. A Japanese phase II study (Study GD01) was conducted in patients with glioblastoma who had residual or recurrent tumors after radiotherapy with concomitant temozolomide. In Study GD01, however, stable disease continued for an extended period in some patients with glioblastoma. Hence, Delytact Injection is expected to be effective to a certain level. In line with this, Delytact Injection has been approved as an option for the treatment of malignant glioma, with one of the 3 approval conditions including conducting a use-results comparison survey and resubmission of the marketing authorization application within the granted time period of 7 years, under the conditional and time-limited approval scheme described in Article 23–26 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Key words: oncolytic virus therapy; Delytact Injection; teserpaturev; glioma; Sakigake Designation System; conditional and time-limited approval scheme; Pharmaceuticals and Medical Devices Agency (PMDA).

Implications for Practice

Delytact Injection, a regenerative medical product for oncolytic virus therapy, has demonstrated likely predicted efficacy for glioblastoma based on the results of an open-label, uncontrolled Japanese phase II study (Study GD01). Although the information on the efficacy and safety of Delytact Injection is limited at present, the Delytact Injection will become an effective treatment option for malignant glioma under an early approval scheme. The applicant is then required to conduct a post-marketing approval condition assessment to evaluate the predicted efficacy, including survival benefits and safety, and resubmit the marketing authorization application within 7 years.

Introduction

Glioma

Glioma is primary brain tumor originating from glial cells that support neurons. Glioma is highly invasive and intractable with a very limited possibility of complete remission. Based on histopathological findings and clinical malignancy data, it can be classified into Grades I–IV. Glioma classified as highly malignant Grade III (anaplastic astrocytoma and anaplastic oligodendroglioma) and Grade IV (glioblastoma) lesions are referred to as malignant glioma. Estim

that approximately 20 000 individuals develop primary brain tumors annually in Japan.[1] When percentages of patients with brain tumors of each grade reported in the Brain Tumor Registry of The Japan Neurosurgical Society (2005-2008) are applied to the above number, approximately 1260 and 2400 individuals are presumed to develop Grade III malignant glioma and Grade IV glioblastoma annually, respectively. The standard of care for primary malignant glioma in Japan is multidisciplinary treatment including surgical resec-

Received: 8 November 2022; Accepted: 17 January 2023.

Maruyama Y, et al. *The Oncologist. 2023; https://doi.org/10.1093/oncolo/oyad041*

Kanno H, et al. *The Oncologist.* 2021; 26(7):e1250-55.

First approval in Japan!

PMDA would like to increase the number of such innovative products!

PMDA's performance

2. Gateway to regulatory approval in Asia
- utilization of the abbreviated review system -

Japan as reference country in Asia [As of May 2023]

Country/ region	System	Population* (million) (2018)	Market scale* (billion USD) (2018)
India	• Waiver of conducting Phase III trials in India	1350	20.9
Indonesia	• Abridged assessment	270	7.3
Malaysia	• Verification process of additional indications	31.5	2.3
Philippines	• Abridged and verification review pathways	106	3.2
Taiwan	• Acceptance of non-clinical study review results • Abbreviated review	23.3 (2013)	6.4 (estimate)
Thailand	• Abridged review • Japanese Pharmacopoeia (JP) as a reference pharmacopoeia	69.4	5.5
Vietnam	• JP as a reference pharmacopoeia	95.5	5.9

*Source: https://healthcare-international.meti.go.jp
(Taiwan only: https://www.meti.go.jp/policy/mono_info_service/healthcare/iryou/downloadfiles/pdf/macrohealthdate_Taiwan.pdf)

Not only providing review reports

PMDA supports these RAs by responding to their queries!

PMDA's performance

3. Internationally harmonized Japanese regulations
- Considerate consultation on R&D –

- ✓ clinical data of Japanese population,
- ✓ fast track application,
- ✓ utilization of Real World Data/Evidence, etc.

Please contact:
rs-contact@pmda.go.jp

PMDA leads international cooperation in regulation

Recent international activities	
ICH (***International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use***)	**Vice-Chair of MC, EWG rapporteurs**
ICMRA (***International Coalition of Medicines Regulatory Authorities***)	Leads various discussions as **Vice-Chair**
MDSAP (***Medical Device Single Audit Program***)	**Chair**

ICH harmonisation for better health

PMDA proposed new topics such as E17 & S12, and led the discussion as rapporteur/regulatory chair.

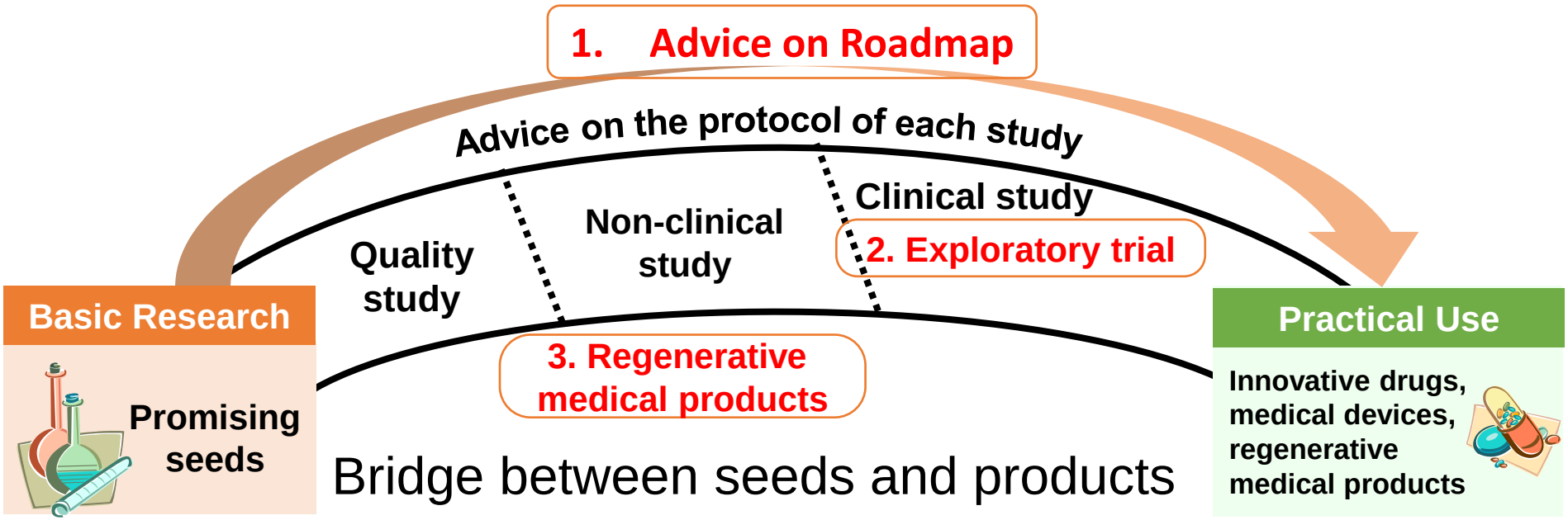
ICMRA

PMDA chaired workshops to accelerate COVID-19-related product development and published the results on the website.

E17: General principles for planning & design of MRCT
S12: Nonclinical biodistribution considerations for gene therapy products

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.



* In collaboration with the Japan Agency for Medical Research and Development (AMED), PMDA is proactively supporting the establishment of an exit strategy via Regulatory Science (RS) Consultation on R&D Strategy.

Outline of the RS Consultation

Category	Objective	Consultant	Style	Period from application to consultation	Duration	Fee	Minutes
General Consultation	Introduction of general information on: -Consultation system -Pharmaceutical regulatory system -Related guidelines	Technical Experts	F2F / Online	1 to 3 weeks	20min	Free	Not shared
Pre-consultation meeting	Clarification of discussion points, consultation dossiers	Technical Experts and Reviewers	F2F / Online	2 to 5 weeks	30min	Free	Not shared
Consultation	Scientific discussion	Technical Experts and Reviewers	F2F / Online	2 to 3 months	Max. 2hr	Charged	Shared

PMDA offers 90% reduction to venture companies.

Please contact:

rs-contact@pmda.go.jp

Prerequisites for fee reduction in RS Consultation

In principle, all of the following prerequisites have to be fulfilled.

(Venture companies)

- An SME (i.e., the number of employees is 300 or less or the company's capital is JPY 300MM or less)
- Another corporate body does not hold shares or capital contributions equivalent to 1/2 or more of the total number of shares or the total amount of contributions.
- Two or more corporate bodies do not hold shares or capital contributions equivalent to 2/3 or more of the total number of shares or the total amount of contributions.
- Net profit is not recorded or is recorded without business revenue in the previous fiscal year.

Other support programs in Japan

1. MEDISO (MEDical Innovation Support Office)
2. Clinical Research Core Hospitals
3. Registry search system

MEDISO (MEDical Innovation Support Office)

What We Do

- **MEDISO provides support for venture companies, academia**, and individuals intending to put into practical use pharmaceuticals, medical devices, and regenerative medicinal products.

Typical Questions from Overseas

- What procedures are required to manufacture and supply pharmaceutical product in Japan?

Content of consultation	• I would like to know the laws and regulations in case of manufacturing and selling pharmaceuticals in Japan. • I would like to introduce our pharmaceuticals into Japan.
Content of advice	• Explained the definition of pharmaceuticals under the Pharmaceuticals and Medical Devices Act and the business license required for manufacturing and marketing • Explained the procedures for applying for approval of pharmaceuticals. • As additional information, we also explained regulations on advertising of pharmaceuticals.

MEDISO consultation is available free of charge !!!

mediso@ml.mri.co.jp

Clinical Research Core Hospitals

Abundant experience in:
- Planning, implementation, and analysis of clinical research and trials
- Commercialisation of innovative seeds

Diverse human resources:
- Experts in clinical research and commercialisation
- Cooperation from various departments in the hospitals
- Biostatisticians and data managers
- CRC and other operational units
- Review committee bodies such as CRBs
- Staff experienced in PMDA

Support by making the most of features, etc.

Clinical Research Core Hospitals have similar difficulties and experiences with venture companies.

"Clinical Research Core Hospitals" can provide **a range of support tailored to your needs**!

- National Cancer Centre Central Hospital
- Tohoku University Hospital
- Osaka University Hospital
- National Cancer Centre East Hospital
- Nagoya University Hospital
- Kyushu University Hospital
- University of Tokyo Hospital
- Keio University Hospital
- Chiba University Hospital
- Kyoto University Hospital
- Okayama University Hospital
- Hokkaido University Hospital
- Juntendo University Hospital
- Kobe University Hospital
- Nagasaki University Hospital

Registry search system

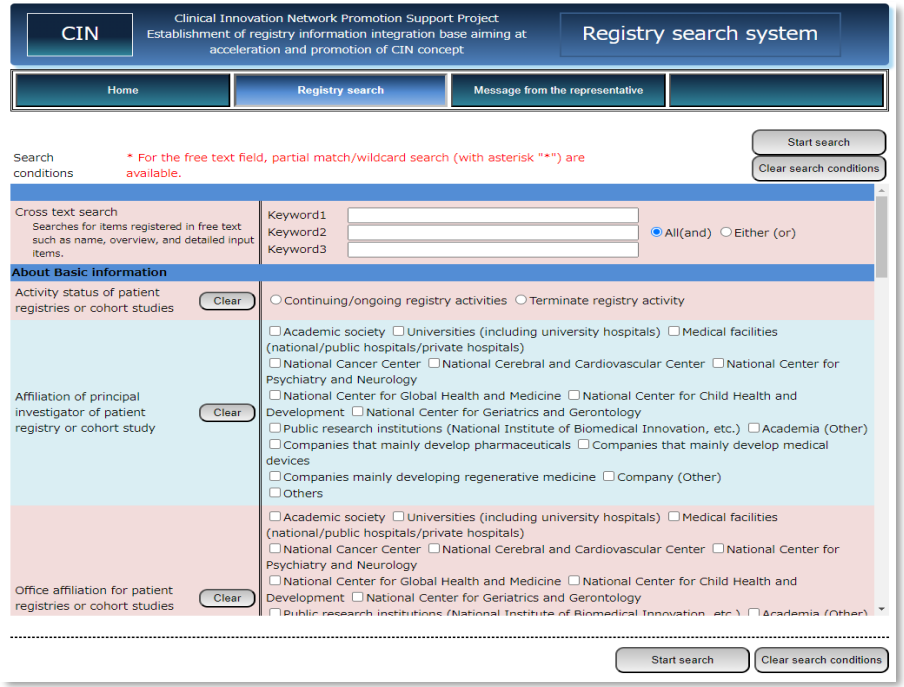
- NCGM; Registry Search System (patient registries in Japan)
- Total 585 (in Japanese) / 536 (in English) registries (as of October 2023)

NCGM: National Center for Global Health and Medicine

Registry Search System
https://cinc.ncgm.go.jp/cin/en/G001.php

Enter search conditions (example)

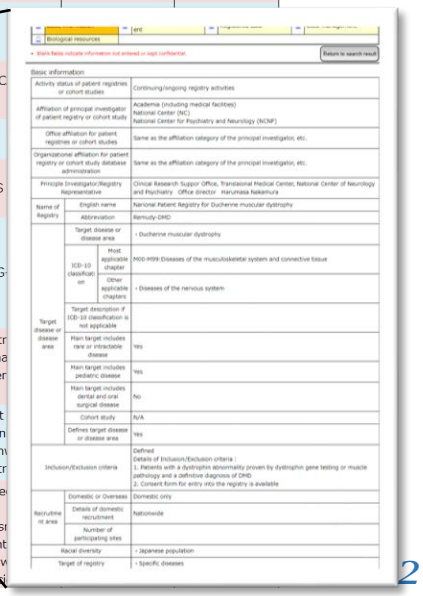
Search by
- Target disease
- ICD-10 classification
- Racial diversity (Japanese and/or non-Japanese)



Search result (example)

- Objectives
- Inclusion / exclusion criteria, Recruitment area
- Number of registration, Type of collected data
- Contact information, etc.

No.	Record No.	ICD-10 classification	Name of Registry	Abbreviation	Target disease (area) information	Information updated on:
1	1	M00-M99	Former Miyagawa village Cohort	Miyagawa Cohort Study	knee osteoarthritis	2022/04/11
2	2	M00-M99	Surveillance Study of Unplanned Surgery in Primary Malignant Bone Tumor Patients			
3	3	M00-M99	Yamagata prefectural committee of atypical femoral fractures study	YamaC study		
4	4	I00-I99	Japan Association of Rehabilitation Database	JARD		
5	5	9999999	Japan Gerontological Evaluation Study	JAGES		
6	6	C00-D48	Study on the prognosis of cases confirmed of histopathological complete response (breast) after combination therapy of preoperative Trastuzumab + Cytotoxic Anticancer Drug	JBCRG		
7	8	C00-D48	Comprehensive Registry of Esophageal Cancer in Japan	Registr Esopha Cancer Japan		
8	10	C00-D48	Nationwide Registry	Breast Screen Nation Registr		
9	14	J00-J99	Single-institutional Prospective QOL assessment in patients underwent thoracic surgery	Prospe QOL assessr patient underv thorac		



Others

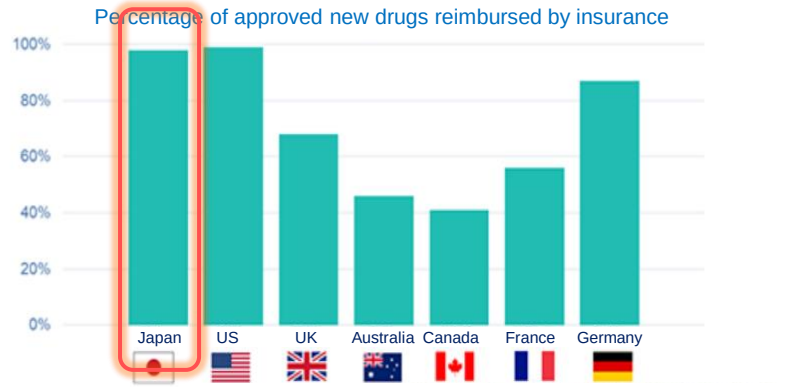
- Universal health coverage system in Japan
- Medicine Spending and Usage Trends in Japan
- Tax credits and incentives for research and development (R&D) cost

Universal Health Coverage system in Japan

- **All citizens (125 million people) are publicly insured**.
- **The world's third largest** pharmaceutical market.
- **60-90 days** from approval to inclusion in the NHI Drug Price Standard and **no HTA** before the inclusion.

❖ Status of cost-effectiveness in other countries

In countries where HTA is used to determine reimbursement, patient access to medicines is limited.

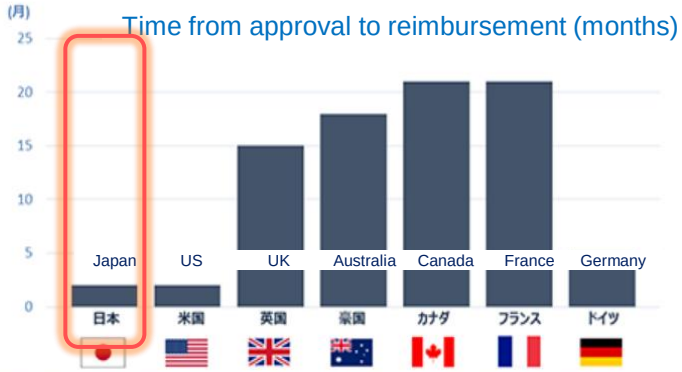


*The reason the figure is not 100% for JP and US is not all approved drugs are on the market.

Source: PhRMA analysis of IQVIA Analytics Link, U.S. Food and Drug Administration, European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, Health Canada, Australia Therapeutic Goods Administration, and government insurance coverage data on new active substances approved from 2011 to Q3 2019.

❖ Status of cost-effectiveness in other countries

In countries where HTA is used to determine reimbursement, patient access to new drugs is delayed.



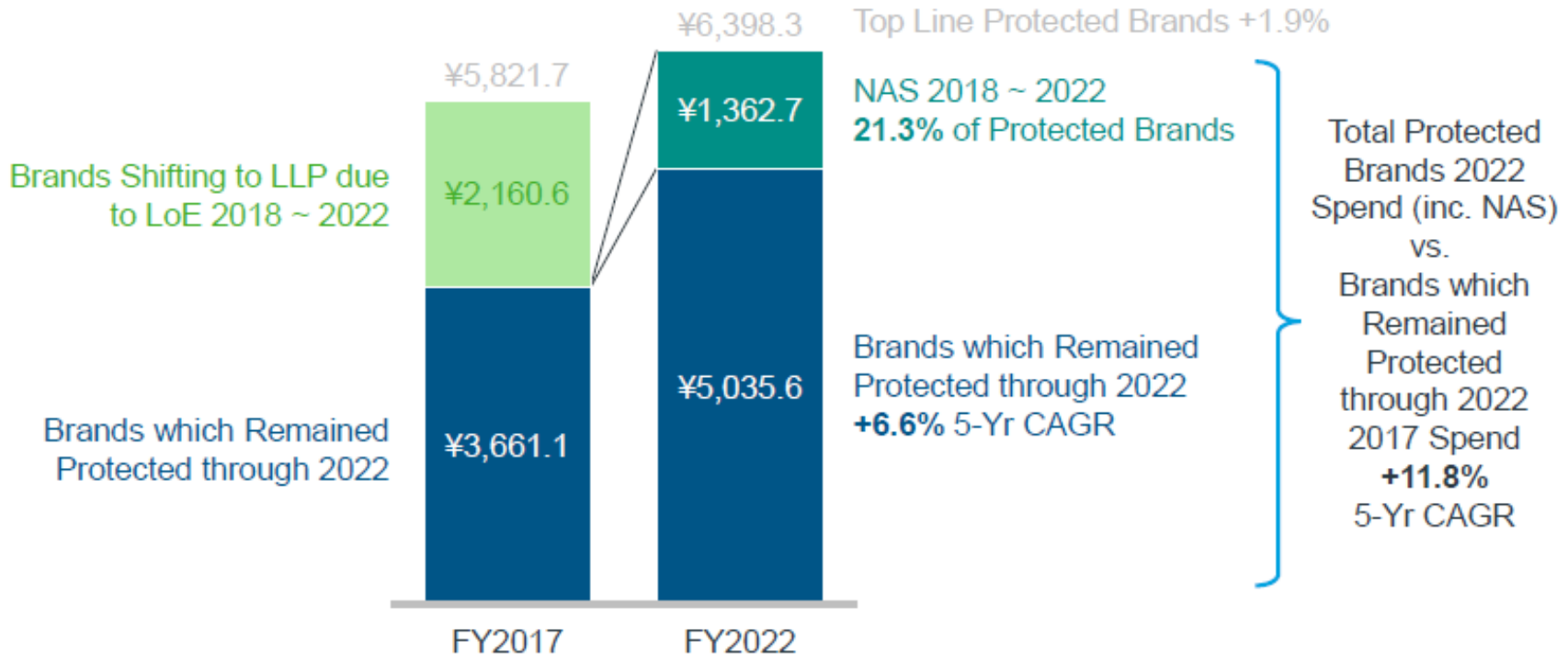
Source: PhRMA analysis of IQVIA Analytics Link, U.S. Food and Drug Administration, European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, Health Canada, Australia Therapeutic Goods Administration, and government insurance coverage data on new active substances approved from 2011 to Q3 2019.

HTA: Health Technology Assessment, Source: https://www.phrma-jp.org/hta/

Spend of Protected Brands, LoE/LLP shift and NAS

Factoring for LLP shift, protected innovation continued to provide improved patient outcomes and treatment options

Protected Brands, LoE/LLP Shift and NAS (¥Billion)



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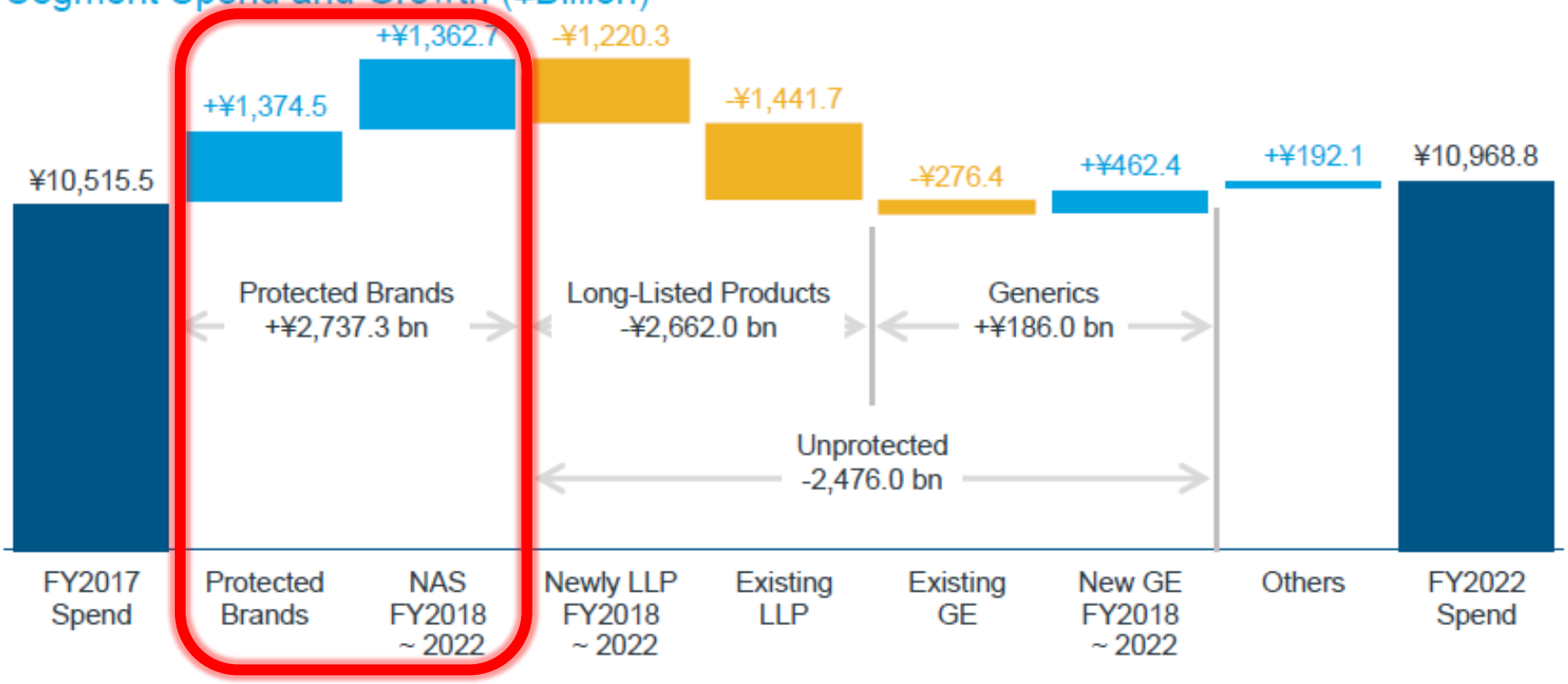
IQVIA

LoE: Lose of Exclusivity, LLP: Long Listed Products,
NAS: New Active Substances, CAGR: Compound Average Growth Rate

Spend and Growth by Segment

Innovation driving improved patient outcomes while healthcare savings continue to be made within the unprotected market

Segment Spend and Growth (¥Billion)



IQVIA

LLP: Long Listed Products, NAS: New Active Substances

Tax credits and incentives for research and development (R&D) cost

Under the 2019 Tax Reform, R&D tax incentives (the R&D tax credit system) were revised to promote innovation by (i) increasing the tax credit ratio, (ii) increasing the limitation of tax credits for qualified venture companies (i.e., from 25% to 40% of the corporate tax amount), and (iii) expanding the scope of open innovation R&D activities to include the cost of B2B outsourced R&D activities. These new rules apply to the tax years beginning on or after 1 April 2019.
To claim the R&D tax credit, a taxpayer is required to meet an investment amount threshold (i.e., the annual investment amount exceeding 10% of taxpayer's aggregated annual depreciation expenses). Under the 2020 Tax Reform Act, the investment threshold was increased from 10% to 30%.

R&D tax credits (permanent measures)

The tax credit ratio formula was modified as shown in the following table:

Movement in R&D ratio (increase or decrease in ratio)	**Tax credit ratio**
8% <	9.9%＋(movement in R&D ratio - 8%) × 0.3 (upper limit of 10% but increased to 14% through 31 March 2021)
8% ≧	9.9% - (8% - movement in R&D ratio) × 0.175 (lower limit is 6%)

R&D tax credits for corporations with higher R&D expenditure ratios

A preferential tax credit ratio and tax credit limitation is temporarily provided to taxpayers with higher R&D expenditure ratios (more than 10% of average gross sales). Under the 2019 Tax Reform Act, these preferential measures were incorporated into the R&D tax credit system above, and the applicable period was extended through 31 March 2021.
The formula of the preferential tax credit ratio for corporations with higher R&D expenditure ratios was modified as shown in the following table:

R&D expenditure ratio (R&D expenditure of average gross sales in the past three years)	**Tax credit ratio**
10% <	9.9% ＋ (movement in R&D ratio - 8%) × 0.3 × α (upper limit is 10%)
	α = (R&D expenditure ratio - 10%) x 0.5

Source: https://taxsummaries.pwc.com/japan/corporate/tax-credits-and-incentives

Tax credits and incentives for research and development (R&D) cost

Open innovation R&D tax credits

The scope of R&D expenditure that is qualified as 'open innovation' includes B2B outsourced R&D activities (i.e., R&D conducted jointly with certain R&D focused venture companies, or R&D expenditure arising from contracts with certain R&D focused venture companies). Depending on the nature of the R&D expenditure, 20%, 25%, or 30% of the R&D expenditure is allowed for credit.

The tax credit limitation for open innovation R&D expenditure is 10%.

R&D incentives for SMEs

The special measures providing a preferential tax credit limitation (an upper limit of 35% of corporate tax liabilities) where the ratio of increased R&D expenditure exceeds a certain threshold was modified (the threshold was increased from 5% to 8% by the 2019 Tax Reform Act), and the applicable period was extended through 31 March 2021.

The previous special measures provide a preferential tax credit ratio for an increased R&D expenditure ratio (more than 10% of average gross sales) .

Source: https://taxsummaries.pwc.com/japan/corporate/tax-credits-and-incentives