PMDA’s support to Venture companies

Pharmaceuticals and Medical Devices Agency


November, 2023
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.
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.
1. World fastest review
   - various fast track systems -
PMDA is one of the fastest review organizations in the world!

Median approval time for New Active Substance

*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. $N_1 =$ median approval time for products approved in 2022; $N_2 =$ 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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Area</th>
<th>Product features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expedited review</td>
<td>Any product categories</td>
<td>In a particular situation requiring expedited review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Designated as:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Orphan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Apparent improvement of medical care for severe diseases</td>
</tr>
<tr>
<td>Priority review</td>
<td></td>
<td>• Innovative medical products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For serious diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Development &amp; NDA in Japan: The NDA submission being the world’s first or simultaneous with other countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prominent effectiveness expected based on non-clinical and early phase clinical study data</td>
</tr>
<tr>
<td>SAKIGAKE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Forerunner designation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional Early Approval</td>
<td>Drugs</td>
<td>Early application through confirmation of a certain degree of efficacy and safety in clinical trials other than confirmatory clinical trials</td>
</tr>
<tr>
<td></td>
<td>Medical Devices</td>
<td>• High clinical needs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Balancing the pre- and post-market requirements</td>
</tr>
<tr>
<td>Conditional and Time-limited Approval</td>
<td>Regenerative Medical Products</td>
<td>• Based on the clinical data from the limited number of patients, efficacy is predicted in a shorter time compared with the conventional process.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Early-phase adverse reactions, etc. can be evaluated for safety in a short period of time.</td>
</tr>
</tbody>
</table>
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>
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

*within 30 days

Fastest Practical Use in the world

senku_iyakuhin@mhlw.go.jp
**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>**

- Grant-in-Aid for R&D of orphan designated drugs (NIBIOHN*)
- Tax deduction for R&D expenses
- Priority scientific consultation (PMDA)
- Priority review (PMDA)
- Premium drug pricing
- Extension of re-examination period

Promoting R&D

*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.

First approval in Japan!

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


2. Gateway to regulatory approval in Asia
   - utilization of the abbreviated review system -
## Japan as reference country in Asia [As of May 2023]

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>• Waiver of conducting Phase III trials in India</td>
<td>1350</td>
<td>20.9</td>
</tr>
<tr>
<td>Indonesia</td>
<td>• Abridged assessment</td>
<td>270</td>
<td>7.3</td>
</tr>
<tr>
<td>Malaysia</td>
<td>• Verification process of additional indications</td>
<td>31.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Philippines</td>
<td>• Abridged and verification review pathways</td>
<td>106</td>
<td>3.2</td>
</tr>
<tr>
<td>Taiwan</td>
<td>• Acceptance of non-clinical study review results</td>
<td>23.3</td>
<td>6.4 <em>(estimate)</em></td>
</tr>
<tr>
<td></td>
<td>• Abbreviated review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>• Abridged review</td>
<td>69.4</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>• Japanese Pharmacopoeia (JP) as a reference pharmacopoeia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>• JP as a reference pharmacopoeia</td>
<td>95.5</td>
<td>5.9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Recent international activities</th>
<th></th>
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<tbody>
<tr>
<td><strong>ICH</strong> <em>(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)</em></td>
<td><strong>Vice-Chair of MC, EWG rapporteurs</strong></td>
</tr>
<tr>
<td><strong>ICMRA</strong> <em>(International Coalition of Medicines Regulatory Authorities)</em></td>
<td><strong>Leads various discussions as Vice-Chair</strong></td>
</tr>
<tr>
<td><strong>MDSAP</strong> <em>(Medical Device Single Audit Program)</em></td>
<td><strong>Chair</strong></td>
</tr>
</tbody>
</table>

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

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
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

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

PMDA offers 90% reduction to venture companies.

**Please contact:**

rs-contact@pmda.go.jp
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
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?

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

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
❖ Kyushu 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

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.

<table>
<thead>
<tr>
<th>No.</th>
<th>Record No.</th>
<th>ICD-10 classification</th>
<th>Name of Registry</th>
<th>Abbreviation</th>
<th>Target disease area information</th>
<th>Information updated on</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>M00-M99</td>
<td>Survivors Study of Unrelated Sibling Registry Bone Tumor Patients</td>
<td>YAMAC study</td>
<td>YAMAC study</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>M00-M99</td>
<td>Survivors Study of Unrelated Sibling Registry Bone Tumor Patients</td>
<td>YAMAC study</td>
<td>YAMAC study</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>M00-M99</td>
<td>Survivors Study of Unrelated Sibling Registry Bone Tumor Patients</td>
<td>YAMAC study</td>
<td>YAMAC study</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>I00-I09</td>
<td>Japan Association of Rehabilitation Database</td>
<td>JARD</td>
<td>JARD</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>O00-O99</td>
<td>Japan Gerontological Evaluation Study</td>
<td>JAGES</td>
<td>JAGES</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>C00-C48</td>
<td>Study on the prognosis of cases confirmed of histopathological complete response (breast) after combination therapy of preoperative Taxotere + Nabokin Drug</td>
<td>IBORC</td>
<td>IBORC</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>C00-C48</td>
<td>Comprehensive Registry of Esophageal Cancer in Japan</td>
<td>Regist Cancer Registry</td>
<td>Regist Cancer Registry</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
<td>Screen Nation Regist</td>
<td>2020/04/12</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
<td>Screen Nation Regist</td>
<td>2020/04/12</td>
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<td>11</td>
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<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
<td>Screen Nation Regist</td>
<td>2020/04/12</td>
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<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
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<td>2020/04/12</td>
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<td>13</td>
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<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
<td>Screen Nation Regist</td>
<td>2020/04/12</td>
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<tr>
<td>14</td>
<td>14</td>
<td>C00-C48</td>
<td>Nationwide Registry</td>
<td>Screen Nation Regist</td>
<td>Screen Nation Regist</td>
<td>2020/04/12</td>
</tr>
</tbody>
</table>
• Universal health coverage system in Japan
• Medicine Spending and Usage Trends in Japan
• Tax credits and incentives for research and development (R&D) cost
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.

Percentage of approved new drugs reimbursed by insurance

Status of cost-effectiveness in other countries

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

Time from approval to reimbursement (months)

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

HTA: Health Technology Assessment, Source: https://www.phrma-jp.org/hta/
Factoring for LLP shift, protected innovation continued to provide improved patient outcomes and treatment options

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

**Brands Shifting to LLP due to LoE 2018 ~ 2022**
- ¥2,160.6

**Brands which Remained Protected through 2022**
- ¥5,035.6
  - +6.6% 5-Yr CAGR

**Top Line Protected Brands +1.9%**
- ¥1,362.7
- NAS 2018 ~ 2022
- 21.3% of Protected Brands

**Total Protected Brands 2022 Spend (inc. NAS) vs. Brands which Remained Protected through 2022**
- 2017 Spend
- +11.8% 5-Yr CAGR

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

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

Segment Spend and Growth (¥Billion)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Protected Brands</td>
<td>¥10,515.5</td>
<td>+¥1,374.5</td>
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<tr>
<td>LLP</td>
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<td>¥1,220.3</td>
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<tr>
<td>NAS FY2018 ~ 2022</td>
<td></td>
<td></td>
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<td>-¥1,441.7</td>
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<td>NYL</td>
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<td>+¥192.1</td>
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<td>Unprotected</td>
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<td>-¥276.4</td>
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<td>FY2022 Spend</td>
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<td>¥10,968.8</td>
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</tbody>
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LLP: Long Listed Products, NAS: New Active Substances
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:

<table>
<thead>
<tr>
<th>Movement in R&amp;D ratio (increase or decrease in ratio)</th>
<th>Tax credit ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>8% &lt;</td>
<td>9.9% + (movement in R&amp;D ratio - 8%) × 0.3 (upper limit of 10% but increased to 14% through 31 March 2021)</td>
</tr>
<tr>
<td>8% ≥</td>
<td>9.9% - (8% - movement in R&amp;D ratio) × 0.175 (lower limit is 6%)</td>
</tr>
</tbody>
</table>

### 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:

<table>
<thead>
<tr>
<th>R&amp;D expenditure ratio (R&amp;D expenditure of average gross sales in the past three years)</th>
<th>Tax credit ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% &lt;</td>
<td>9.9% + (movement in R&amp;D ratio - 8%) × 0.3 × α (upper limit is 10%)</td>
</tr>
<tr>
<td></td>
<td>α = (R&amp;D expenditure ratio - 10%) × 0.5</td>
</tr>
</tbody>
</table>

Source: [https://taxsummaries.pwc.com/japan/corporate/tax-credits-and-incentives](https://taxsummaries.pwc.com/japan/corporate/tax-credits-and-incentives)
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