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# Regulatory approach to promote orphan drug development in Japan

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# Legal basis of orphan drug designation

| Legislation etc. | Corresponding part | Description |
|---|---|---|
| PMD Act[1)] | Article 77-2 | Overview of orphan drug designation system |
| Regulation for Enforcement of PMD Act[2)] | Article 251 | Upper Limit on the Number of Patients |
| PED/MDED Notification No.831-7[3)] | All | Details of designation criteria |

1) Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (https://www.japaneselawtranslation.go.jp/ja/laws/view/3213/en)
2) Regulation of Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (https://www.japaneselawtranslation.go.jp/ja/laws/view/3215/en)
3) https://www.mhlw.go.jp/web/t_doc?dataId=00tc5284&dataType=1&pageNo=1 (Japanese only)

Please see the following paper.

Orphan drug designation and development in Japan: 25 years of experience and assessment. Nat Rev Drug Discov. 2021

# Orphan drugs – Designation system

**Aim**

✓ To promote R&D on products for rare diseases, aiming to provide the people with the safe and effective medicines/medical devices as early as possible

**Designation Criteria**

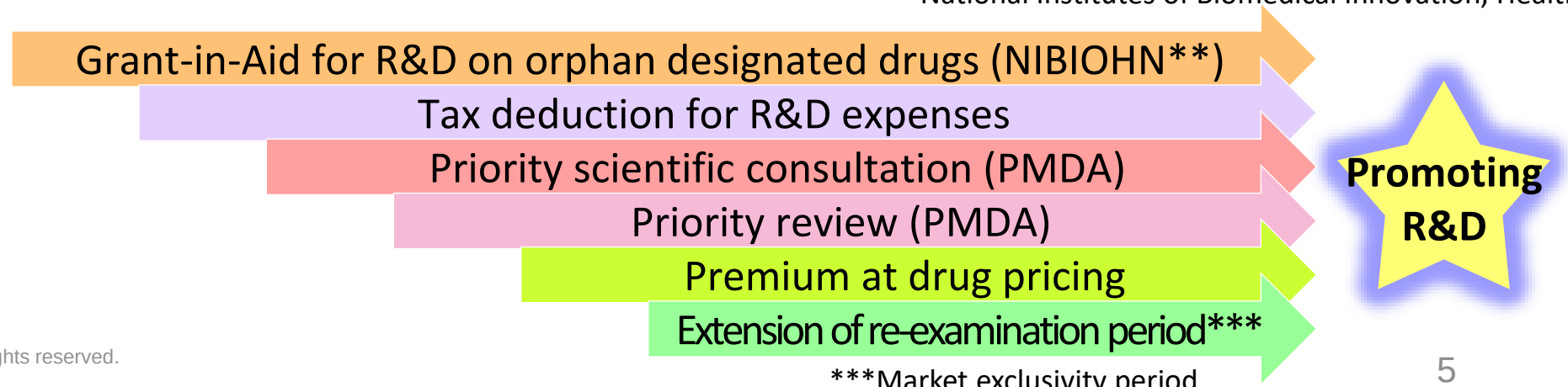
1. Number of patients (that any of the followings is satisfied)
   - Less than 50,000* in Japan
   - The target disease is one of the designated intractable disease

*Equivalent to 0.04% of the Japanese population

2. Medical needs
   - For serious diseases with high medical needs
3. Possibility of development

**Incentives**

**National Institutes of Biomedical Innovation, Health and Nutrition




***Market exclusivity period

# Designated information

**Name of pharmaceutical drug** with a designation

**Name of applicant** receiving the designation

**Anticipated indications or diseases** the orphan drug is intended to treat on the designation

Designated information is posted on the MHLW website.
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html
List of designated drug: https://www.mhlw.go.jp/content/11120000/001099525.pdf

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# PMDA offices responsible for orphan drugs

## New Drug I

**Category 1**
Gastrointestinal drugs, immunosuppressive drugs etc

**Category 6-2**
Drugs for Diabetes mellitus, Osteoporosis, Gout etc

## New Drug II

**Category 2**
Cardiovascular drugs, anti-Parkinsonian drugs, anti-Alzheimer's drugs

**Category 5**
Reproductive system drugs, drugs for urogenital system etc

## New Drug III

**Category 3-1**
Central/peripheral nervous system drugs

**Category 3-2**
Anesthetic drugs, sensory organ drugs, narcotics

## New Drug IV

**Category 4**
Antibacterial drugs, antiviral drugs

**Category 6-1**
Respiratory tract drugs, anti-allergy drugs

## New Drug V

**Oncology drugs**
Antineoplastic drugs

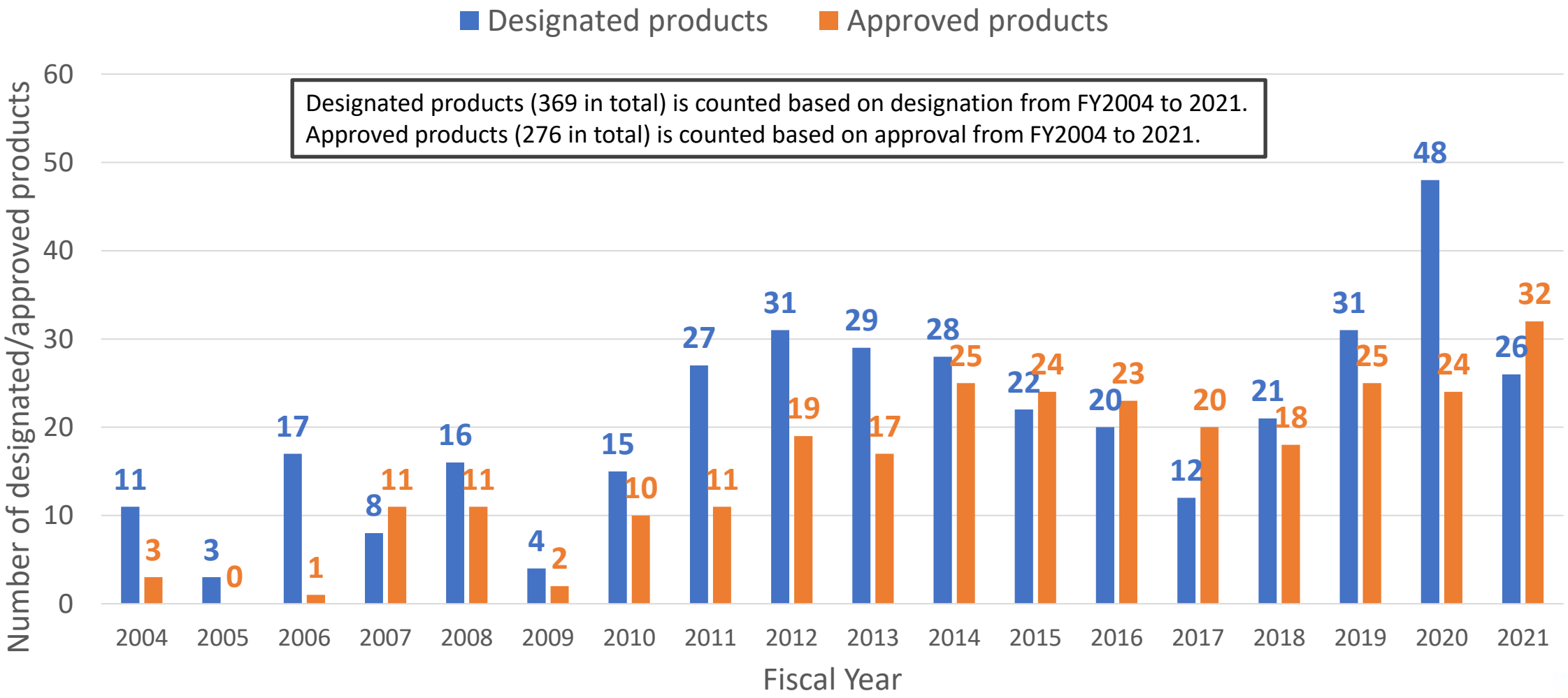
[Others] Office of Cellular and Tissue-based Products, Office of Vaccines and Blood Products

# PMDA offices responsible for orphan drugs


**Each review office responsible for review, scientific consultation and designation of orphan drugs**

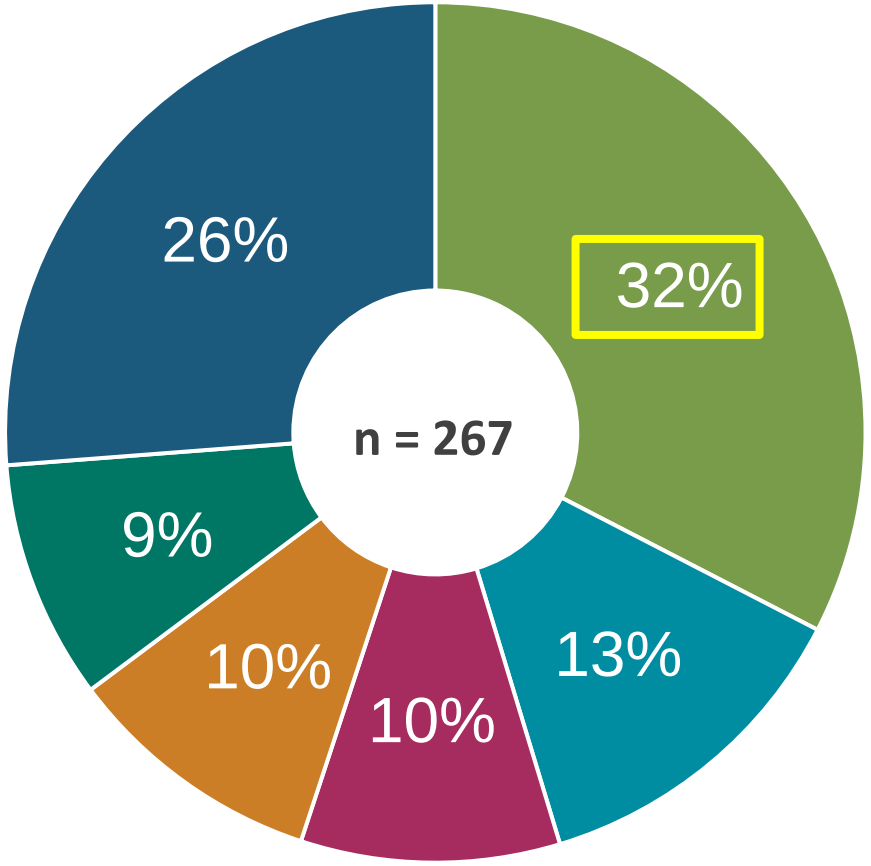
[Others] Office of Cellular and Tissue-based Products, Office of Vaccines and Blood Products

# Trend in designation and approval of orphan drugs in Japan



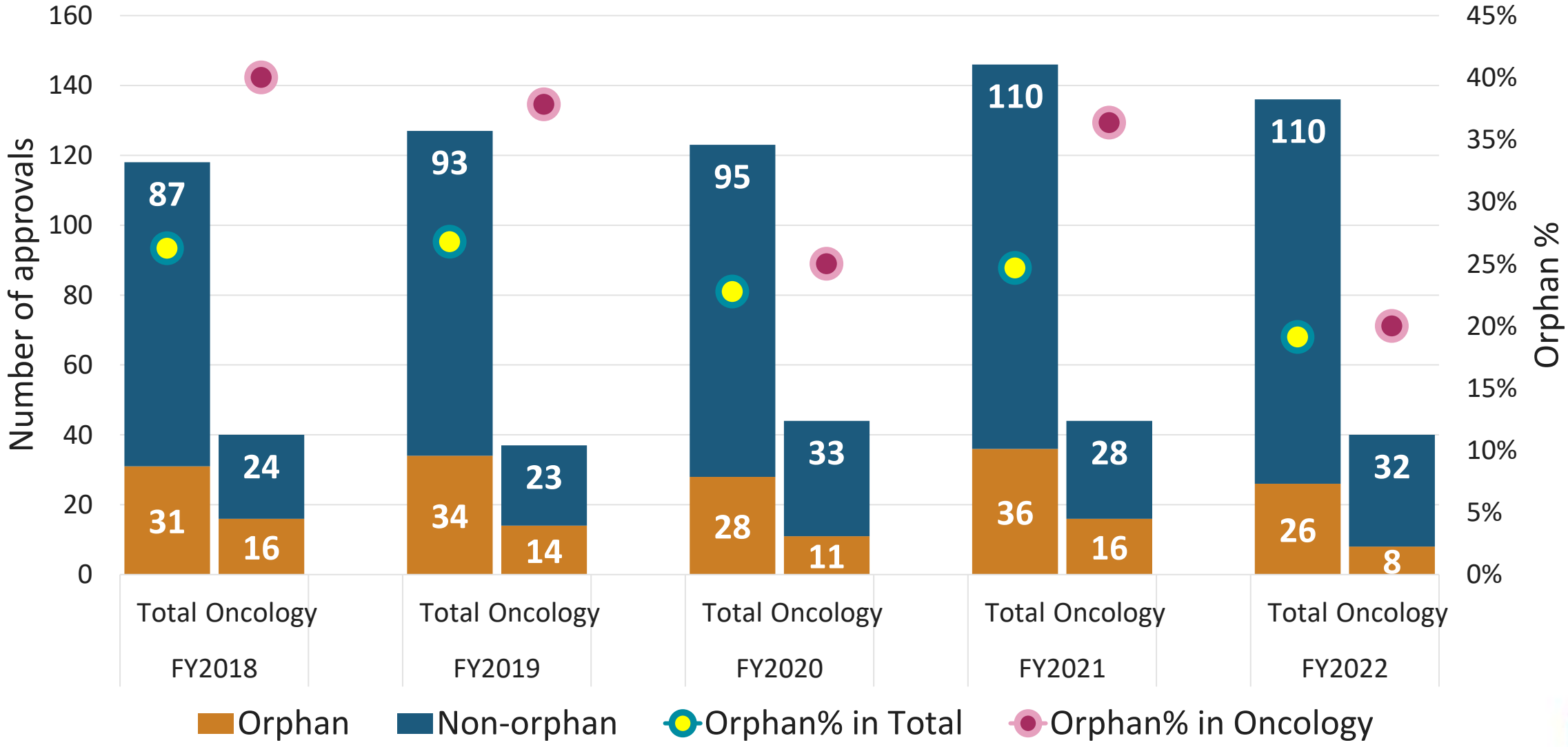
# Distribution of orphan drug designations by disease categories

Data from FY 2004 to FY 2018




- Oncology drugs
- Central/peripheral nervous system drugs (Category 3-1)
- Respiratory tract drugs, anti-allergy drugs, sensory organ drugs for inflammatory diseases (Category 6-1)
- Cardiovascular drugs, anti-parkinsonian drugs, anti-Alzheimer's drugs (Category 2)
- Hormone drugs, drugs for metabolic disorders (Category 6-2)
- Other

# Recent trend in approvals in Japan



# Oncology orphan drugs recently designated and approved

## Approved orphan drugs

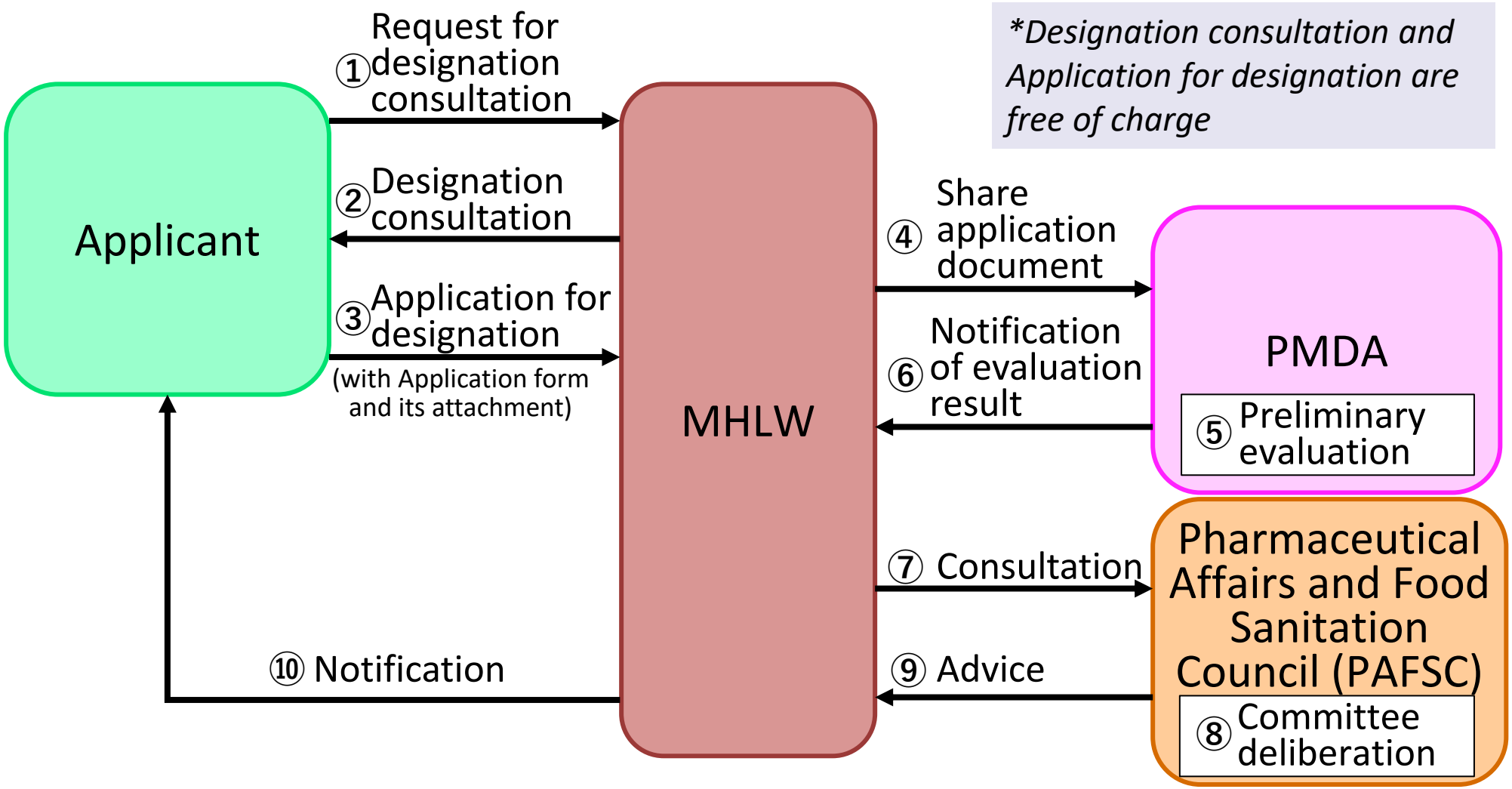
- **Scemblix (asciminib hydrochloride)** - CML
- **Unituxin (dinutuximab)** - Neuroblastoma
- **Hiyasta (tucidinostat)** - ATLL
- **Retevmo (selpercatinib)** - RET fusion gene-positive NSCLC
- **Raiatt (3-Iodobenzylguanidine ($^{131}$I))** - MIBG-positive pheochromocytoma/paraganglioma
- **Megludase (glucarpidase)** - Methotrexate detoxication
- **Lumakras (sotorasib)** - KRAS G12C mutation-positive NSCLC
- **Ezharmia (valemetostat tosilate)** – ATLL

## Designated orphan drugs

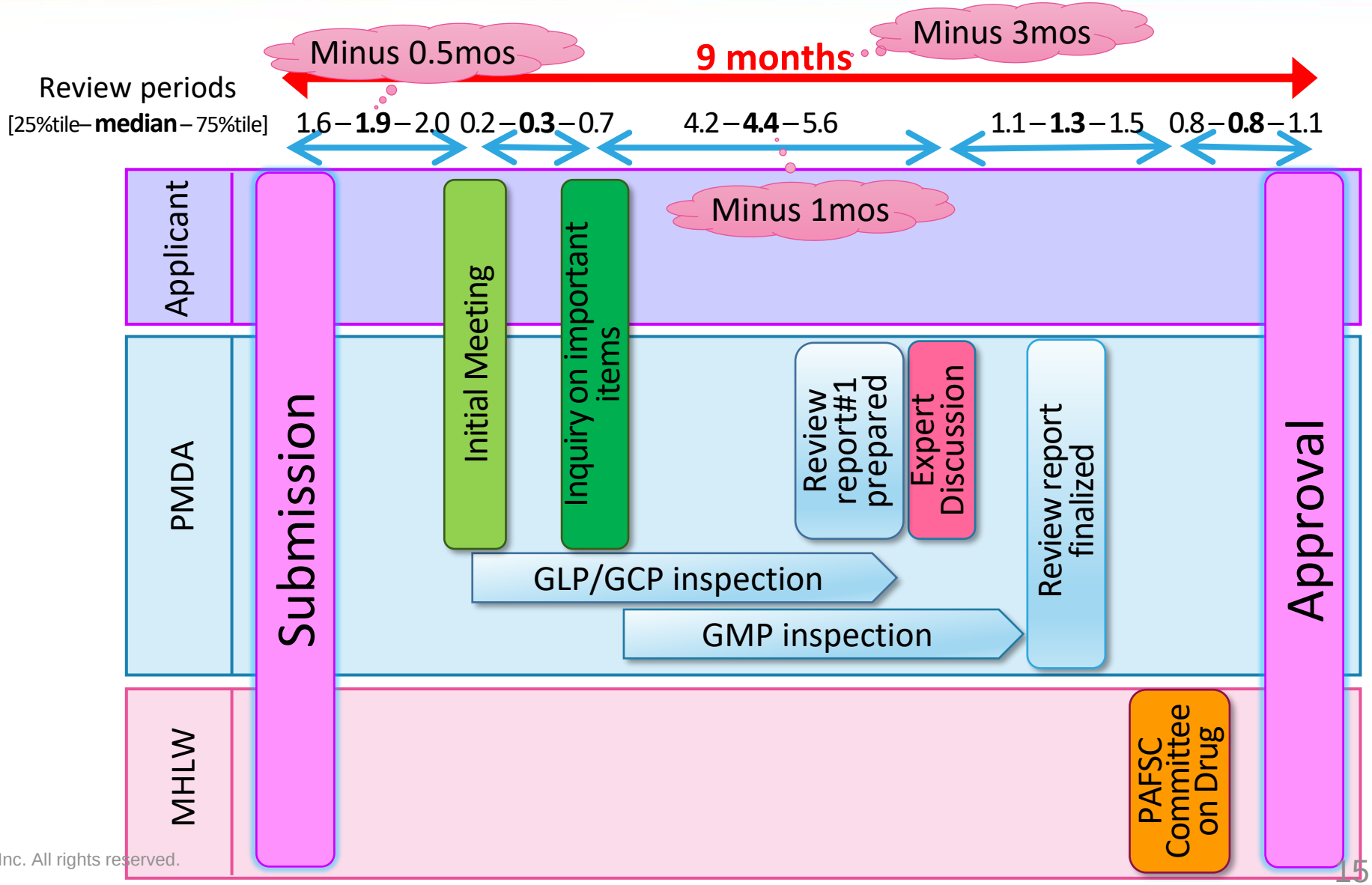
- **Daunorubicin and Cytarabine Liposome** - AML
- **Pemigatinib** - FGFR1 fusion gene-positive MLN
- **Azacitidine** – Maintenance therapy for AML
- **Luspatercept** - Anemia associated with myelodysplastic syndrome
- **Trastuzumab deruxtecan** – HER2 mutation-positive NSCLC
- **Pembrolizumab** – PMBCL
- **Nivolumab** - Malignant mesothelioma
- **Elranatamab** - MM
- **Nivolumab** – Epithelial skin malignancy

AML: acute myeloid leukemia
ATLL: adult T-cell leukemia-lymphoma
CML: chronic myelogenous leukemia
MLN: myeloid/lymphoid neoplasms
MM: multiple myeloma
NSCLC: non-small cell lung cancer
PMBCL: primary mediastinal large B-cell lymphoma

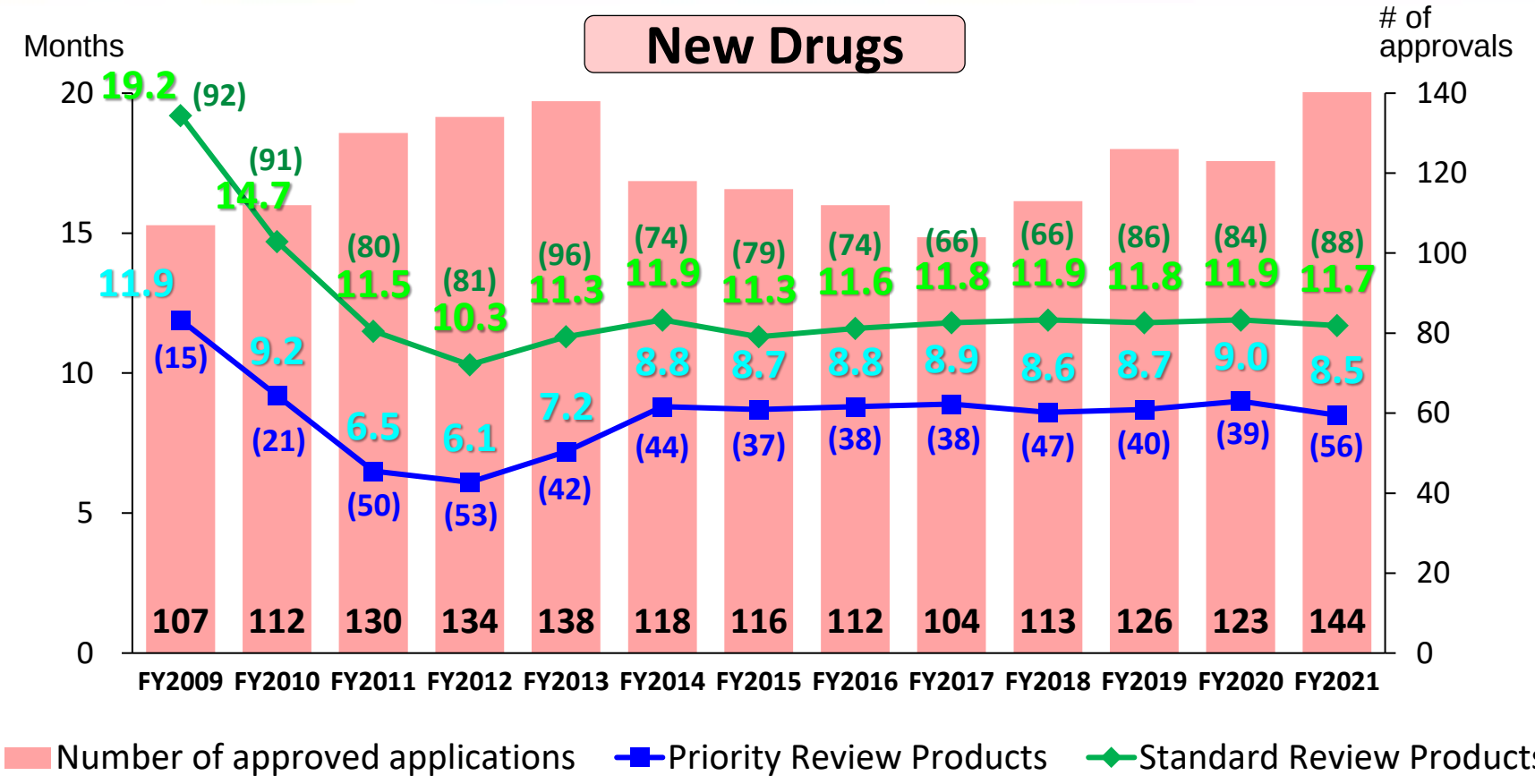
# Flow for granting Orphan drug designation



# Review timeline for new drugs (priority review)



# Number of Approvals and Review Periods




| FY | | | '09 | '10 | '11 | '12 | '13 | '14 | '15 | '16 | '17 | '18 | '19 | '20 | '21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Target median value (Month) | New Drugs | Priority | 11 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | | Standard | 19 | 16 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |

# Projects across Multi-Offices in PMDA

- Cardiovascular Risk Evaluation WG
- Companion Diagnostics WG
- Global Clinical Study WG
- ICH Q12 WG
- Innovative Manufacturing Technology WG
- Medical Device International Affairs WG
- Nanomedicine Initiative WG
- Omix WG
- **Orphan Drugs WG**
- Patient Centricity WG
- Pediatric Drugs WG
- RWD WG

# Who are involved in Projects across Multi-Offices

# Orphan Drugs Working Group in PMDA

## Objectives

To make proposals for supportive measures for facilitating the orphan drug development

## Activities

- **Perceive issues and new movements pertaining to orphan drug development**
  - Analyze previous experience regarding orphan drug development and review
  - Collect information regarding new approaches for orphan drug development driven by advancement of science
- **Strengthen collaboration with other regulatory agencies for orphan drug development**
  - Terms of reference between PMDA and EMA (2012)

# Work together for rapid availability of drugs with better quality to people