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Supplementary information

Orphan drug designation and development in Japan: 25 years of experience and assessment

In the format provided by the authors

Supplementary Box 1 | **Key characteristics of orphan drug development in Japan**

Criteria for orphan drug designation

Patient population

- The number of patients who may use the drugs, medical device or regenerative medicine should be less than 50,000 in Japan, or the disease has to be designated as Nan-byo (intractable and rare disease).
- Intractable and rare diseases are designated as Nan-byo by the MHLW based on the Japanese Act on Medical Care for Patients with Intractable/Rare Diseases. As of January 2021, a total of 333 diseases are designated as Nan-byo and a list is available on the MHLW website: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/nanbyou/index.html

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

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.

Incentives for orphan drug development

Financial incentives

- Financial subsidies for up to 50% of expenses for clinical and non-clinical research through the NIBIOHN to reduce the financial burden of product development
- Tax reduction and marketing application fee reduction.

Marketing exclusivity

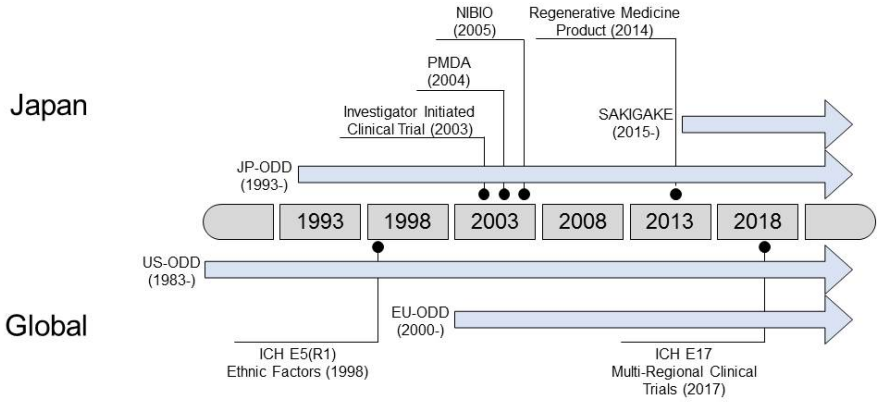
- Extension of the re-examination period up to 10 years at marketing authorization

Consultation

- Consultation fee reduction (scientific advice/protocol assistance)
- Priority consultation

Submission and review

- Priority review



Supplementary Figure 1 | **A timeline of orphan-drug-related events and milestones in Japan and worldwide.** The Orphan Product Development Support Program in Japan was launched in 1993. The investigator-initiated clinical trial was introduced in 2003. The Pharmaceuticals and Medical Devices Agency (PMDA) was established in 2004. NIBIO was established in 2005. The category of regenerative medicine product was introduced in 2014. The SAKIGAKE designation system was launched in 2015. NIBIO: National Institute of Biomedical Innovation (Currently, National Institutes of Biomedical Innovation, Health and Nutrition), JP-ODD: Orphan Drug Designation in Japan, US-ODD: Orphan Drug Designation in US, EU-ODD: Orphan Drug Designation in EU.

Supplementary Box 2 | **Data sources and analysis**

Data sources and handling

Orphan drug designations and designations that received approval for marketing were counted from the list of designated orphan drugs provided by the NIBIOHN and approval data from the Pharmaceuticals and Medical Devices Agency (PMDA). Some orphan drugs have been withdrawn, or re-designated or have multiple approvals; in such cases, the first designation and first approval for the designated indication were counted. Moreover, two orphan drug designations transferred to regenerative medicine products were excluded in Figure 1 and in the approval rate calculation.

The list of orphan drugs designated from 1993 FY is available at the website of the NIBIOHN: https://www.nibiohn.go.jp/nibio/part/promote/orphan_support/

The data on orphan drugs in Japan were obtained from internal PMDA data such as orphan designation reports since the establishment of PMDA in 2004. Although data on designations and approvals before 2004 are also available, data on the distribution of prevalence and disease category for orphan drug designations in Japan is not. An orphan drug designated between January 2004 and March 2004 was included in the analysis presented in Figure 2.

For each designation, this data includes information related to the criteria of orphan designation and approval with review reports (https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html and https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html).

Data on orphan drugs in the United States comes from REF. 1. Data on orphan drugs in the European Union comes from REF. 2.

Orphan disease categorization

Orphan diseases were categorized using the category used in Japan: (https://www.pmda.go.jp/files/000232603.pdf)

- Gastrointestinal drugs, dermatologic drugs, and others (Category 1)
- Cardiovascular drugs, anti-parkinsonian drugs, anti-Alzheimer's drugs (Category 2)
- Central/peripheral nervous system drugs (Category 3-1)
- Anesthetic drugs, sensory organ drugs, narcotics (Category 3-2)
- Antibacterial drugs, antiviral drugs, antifungal drugs, antiprotozoal drugs, anthelmintic drugs (Category 4)
- Reproductive system drugs, drugs for urogenital system, combination drugs (Category 5)
- Respiratory tract drugs, anti-allergy drugs, sensory organ drugs for inflammatory diseases (Category 6-1)
- Hormone drugs, drugs for metabolic disorders (Category 6-2)
- Oncology drugs
- Anti-HIV drugs
- In vivo diagnostics
- Blood products
- Vaccines

References

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2. European Medicines Agency. Annual report on the use of the special contribution for orphan medicinal products: Year 2018: https://www.ema.europa.eu/en/documents/report/annual-report-use-special-contribution-orphan-medicinal-products-2018_en.pdf