Paediatric Drug Development in Japan and International Regulatory Collaboration

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Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency.

Today's Agenda

- Paediatric Drug Development in Japan
- International Regulatory Collaboration

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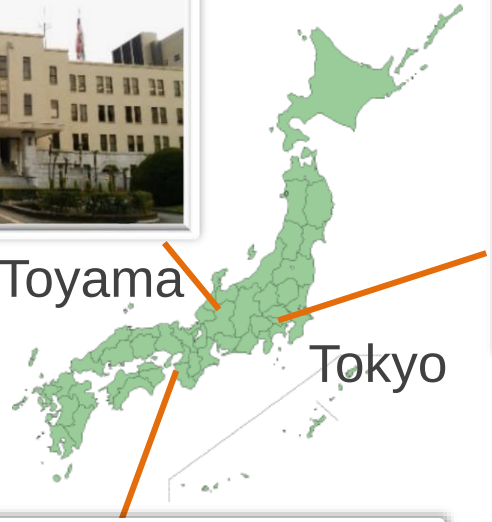
PMDA
Pharmaceuticals and Medical Devices Agency

Date of Establishment : April 2004

Major Responsibilities

- **Scientific Review for Drugs, Medical Devices and Regenerative Medical Products**
- **GCP, GMP Inspection**
- **Consultation on Clinical Trials**
- **Safety Measures**
- **Relief Services**

Hokuriku Branch



Kansai Branch

MHLW

厚生労働省
Ministry of Health, Labour and Welfare

Working in close relationship with Ministry of Health, Labor and Welfare (MHLW)

PMDA Paediatric Drugs WG

- An across-office project team in the PMDA
- Started in November 2011

International Collaborations

Collaboration at Paediatric Cluster

FDA, EMA, Health Canada and TGA

External Communications

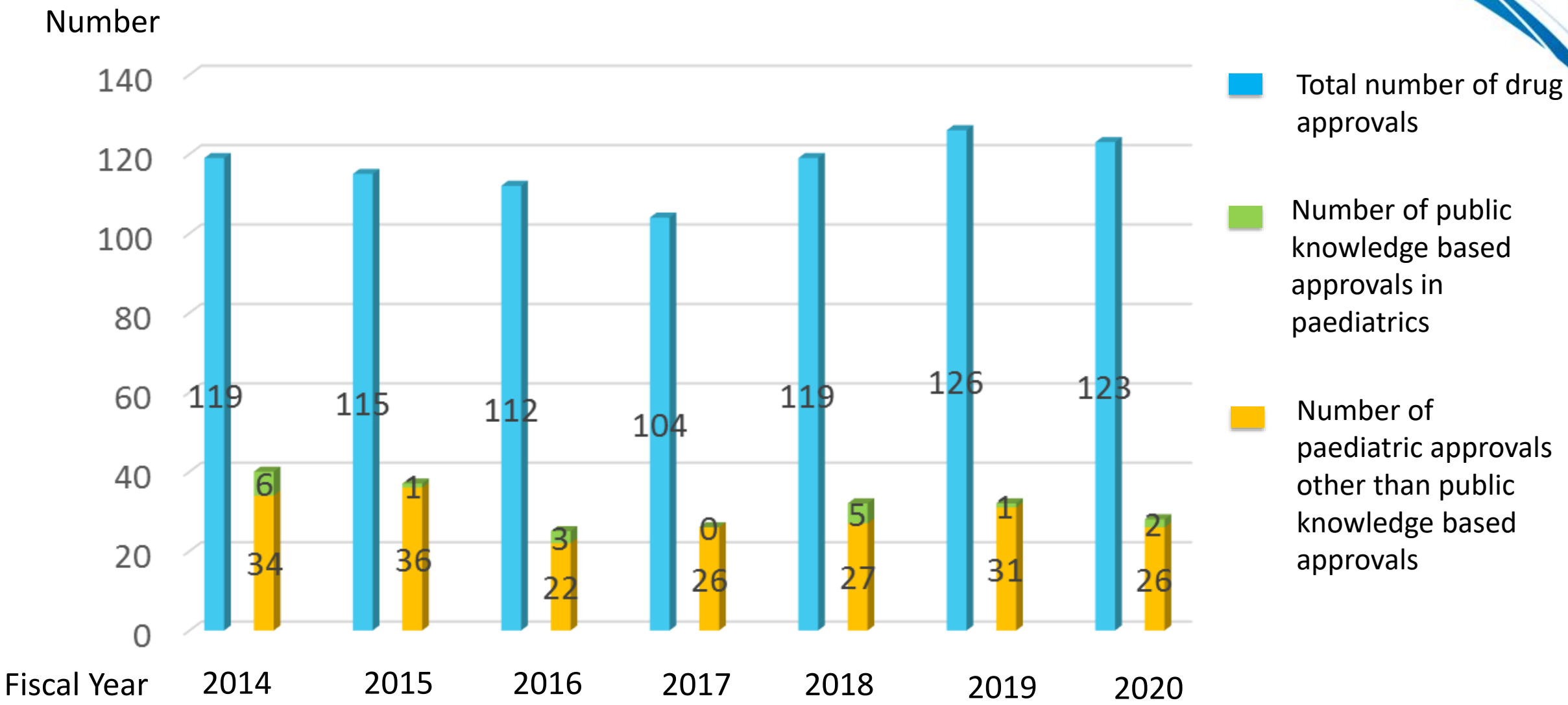
Discuss paediatric issues with domestic stakeholders

Analyze and identify paediatric issues raised in past reviews and consultations

Analyses

Internal Communications with Review Teams

Recent New Drug Approvals in Japan



Paediatric Regulations In Japan

- There is no regulation mandating paediatric drug development.
- ICH-E11 and ICH E11(R1)
- Several frameworks to enhance paediatric drug development have been implemented so far.
  - Extension of re-examination period (revised in 2020) New
  - Drug reimbursement premium
  - Council for unapproved and off-labelled drugs with high medical needs
  - Paediatric clinical trial network
  - Considerations for clinical evaluation of drugs in paediatric patients (10 or 12 years of age and older) who can be evaluated together with adults
  - Specific Use Drug Designation System New

Council for Unapprved and Off-label Drugs with High Medical Needs

- Established in 2010 as an advisory council of the MHLW
- Identifies highly-needed unapproved drugs/indications, including paediatrics, which are widely used in at least one of the 6 countries (Australia, Canada, France, Germany, UK, US)

  (From 2015, unapproved/off label drugs in these countries can also be considered)
- The MHLW requests pharmaceutical industries to develop or submit the NDA of designated drugs/indications
- The PMDA reviews NDA on fast track and can accept public knowledge as the basis for approval such as:
  - Large experience of (off-label) clinical use in Japan plus clinical data submitted to the regulatory authority in one of the 6 countries
  - Usage described in major medical textbooks or guidelines

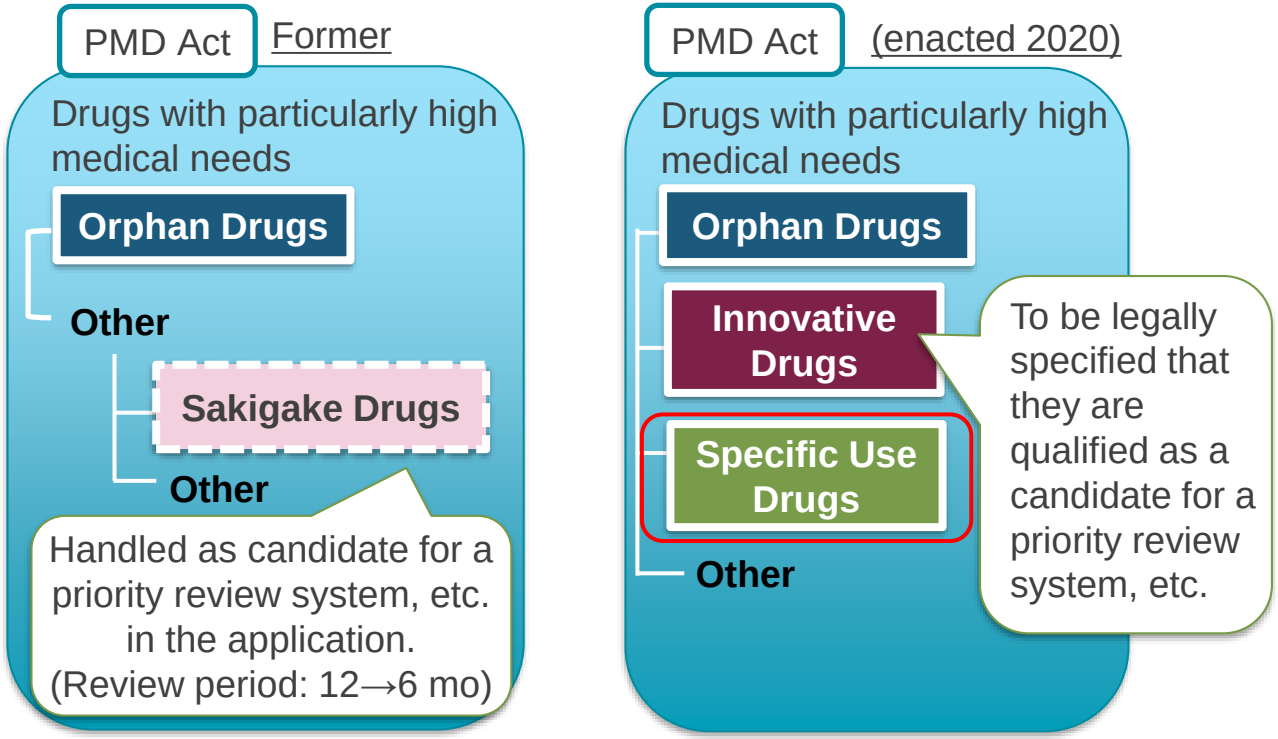
Legislation of "Sakigake Designation System" and "Specific Use Drug Designation System"

○ A system to designate drugs/medical devices/regenerative medical products whose action mechanisms are clearly different from those approved in Japan/other countries as "**innovative drugs**" shall be defined by law, and the designated products shall be clearly qualified by law to be a candidate for a priority review system, etc.

○ A system to designate drugs addressing significant unmet medical needs such as drugs with no indication for paediatric patients as "**specific use drugs**" shall be defined by law, and the designated products shall be clearly qualified by law to be a candidate for a priority review system, etc.

○ It shall be legally stipulated that specific use drugs (limited to those for a small number of patients) are eligible for tax benefits and subsidies to promote development as well as existing orphan drugs.

(*) Tax benefits have already been included in the 2019 tax reform plan.



Designation requirements

Innovative drugs	1. Having clearly different action mechanisms from products approved in Japan/other countries. 2. Markedly useful in that particular use ➢ Assuming the same drugs for the current "Sakigake designation system".
Specific use drugs	1. Being used for the treatment of specific diseases (*). • Being used to treat paediatric diseases but dosage and administration for children not stipulated. • Infectious diseases caused by drug-resistant bacteria, etc. 2. The need for specific use drugs is significantly unmet. 3. Markedly useful in that specific use

Specific Use Drugs

Drugs which are intended for use in the diagnosis, treatment or prevention of disease in children and satisfying all of the following requirements.

A. To develop either (i) Change of dosage and administration or (ii) Additional dosage form.

B. Significantly unmet medical needs ((i) No standard treatment or (ii) More medically useful than existing treatments)

C. Particularly excellent utility value ((i) target disease is serious and (ii)established as standard therapy in guidelines etc. or high evidence based on RCTs).

Re-examination Period

- Post-marketing safety and efficacy for new drugs are reviewed a certain period after the approval for marketing authorization.
- Generic drugs are not approved for marketing prior to the post-marketing review of new drugs.
  - ➡ Similar to the exclusive sales period for new drugs

Re-examination period	Drug type
10 years	Orphan Drugs, Drugs that need to be surveyed by pharmacoepidemiological method
8 years	Drugs with new active ingredients
4 years	New combination drugs, Drugs with a new route of administration
4 – 6 years	Drugs with new indications, Drugs with a new dosage

Extention of Re-examination Period

- The re-examination period can be extended to 10 years, if a clinical trial is planned to study paediatric dosage **during or after marketing authorization application of a drug**, per the necessary time to conduct appropriate study. (Dec. 2000)

Revised

- For drugs that were recognized to require clinical trials regarding the setting of dosage for paediatric patients at the time of approval, a development plan for paediatric dosage setting was submitted and planned **by the end of the approval review**, and the planned clinical trials were started without delay. In that case, the re-examination period can be extended to a range not exceeding 10 years. (Aug. 2020)

Today's Agenda

- Paediatric Drug Development in Japan
- International Regulatory Collaboration

International Regulatory Collaboration

- Paediatric Cluster
- PMDA Asia Training Center & U.S.FDA Paediatric Seminar
- EnprEMA (European Network of Paediatric Research at the European Medicines Agency) Working Group on International Collaboration
- International Neonatal Consortium

Paediatric Cluster

- Regular teleconference once a month
- Exchange opinions between EMA, US FDA, Health Canada, PMDA and TGA
  - Clinical trial design on developing products
  - Safety concerns on developing/already approved products
  - General issues
    - Development of guidelines etc.

Paediatric Cluster

- Although a lot of products discussed in cluster teleconferences have not been developed for children in Japan, contents of the meeting are very useful in helping us develop various approaches to:
  - finding appropriate endpoints
  - choosing comparators
  - extrapolating efficacy data from studies in adults to paediatrics, if possible etc.
- Also, the TC helps us exchange information about safety.

Future Expectations

- ✓ More involvement of Japanese children at an early stage of the paediatric drug development
- ✓ More aggressive PMDA contribution to the projects such as writing articles, development of guidelines, and so on.

The Impact of the US FDA PSP and EU PIP in Japan

- The PSP and PIP are sometimes the trigger for pharmaceutical companies to consider paediatric drug development in Japan.
- In fact, some pharmaceutical companies include Japanese children in their multi-regional clinical trails that are planned in the PSP and/or PIP.
- The data from clinical trials in the PSP and/or PIP are utilized as much as possible for paediatric drug development in Japan.

PMDA Asia Training Center & U.S. FDA Paediatric Review Seminar

Once a year since 2018

- To promote paediatric drug development globally
- To assist capacity building related to paediatric drug development in Asia and other countries/regions

- This seminar is intended for regulatory authority officials who are engaged in the review of paediatric drug development programs.
- This seminar covers current paediatric guidelines and practices in the United States and Japan, and provides the opportunity for the participants to share current paediatric guidelines and practices in their respective countries and regions.
- Case study sessions on paediatric drug development programs are also planned for small group discussions among the participants.
- Face to face meetings between the US FDA, the PMDA and participants took place if they wanted. (Before SARS-CoV-2 pandemic)
- We invited a lecturer from the EMA this year.

Summary and Future Perspectives

- In Japan, pharmaceutical companies show reluctance to take action aggressively on drug development for children due to a lack of laws or regulations that mandate paediatric drug development like the EU and the US.
- However, the environment for paediatric drug development in Japan is improving through various efforts.
- It is expected that paediatric drug development will gain further momentum with the latest revision of the PMD Act (Specific Use Drugs Designation) and other new initiatives in Japan.
- The PMDA are trying to promote regulatory convergence and active involvement of Japan for paediatric drug development.

Better Medicines for Children!