

Pediatric Drug Development in Japan

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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

- Pediatric Drug Development in Japan
- International Regulatory Collaboration

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PMDA

Pharmaceuticals and Medical Devices Agency

Date of Establishment : April 2004



Hokuriku Branch

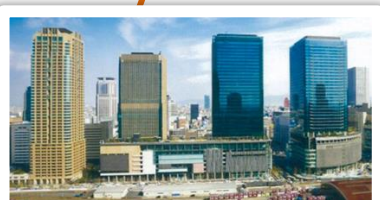


Toyama



Tokyo

Osaka



Kansai Branch

Major Responsibilities

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

MHLW



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

PMDA Pediatric Drugs WG

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

International Collaborations

Collaboration at Pediatric Cluster

US FDA, EMA,
Health Canada, TGA

External Communications

Discuss pediatric issues
with domestic stakeholders

**PMDA
Pediatric
Drugs WG**

Members from Offices of
New Drug, Office of Safety,
Office of Regulatory
Science, etc.

Analysis

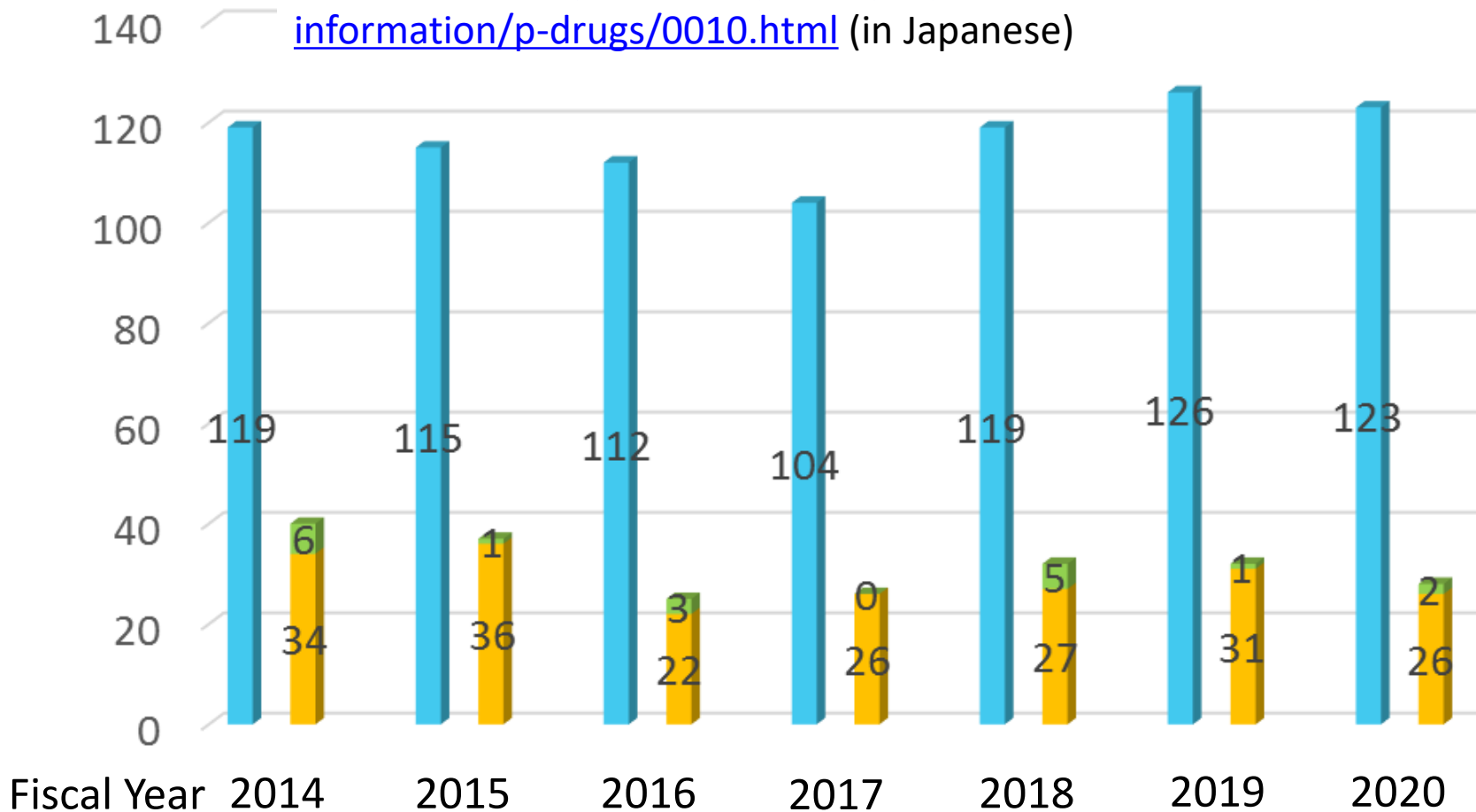
Analyze and identify pediatric
issues raised in past reviews and
consultations

**Internal Communications
with Review Teams**

Recent New Drug Approvals in Japan

Number

Data Source: <https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0010.html> (in Japanese)



- Total number of drug approvals
- Number of public knowledge based approvals in pediatrics
- Number of pediatric approvals other than public knowledge based approvals

Pediatric Regulations In Japan

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

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

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

(*Drugs/indications those are authorized in these counties, but are not approved in Japan. From 2015, unapproved/off label drugs in these countries can also be considered.)

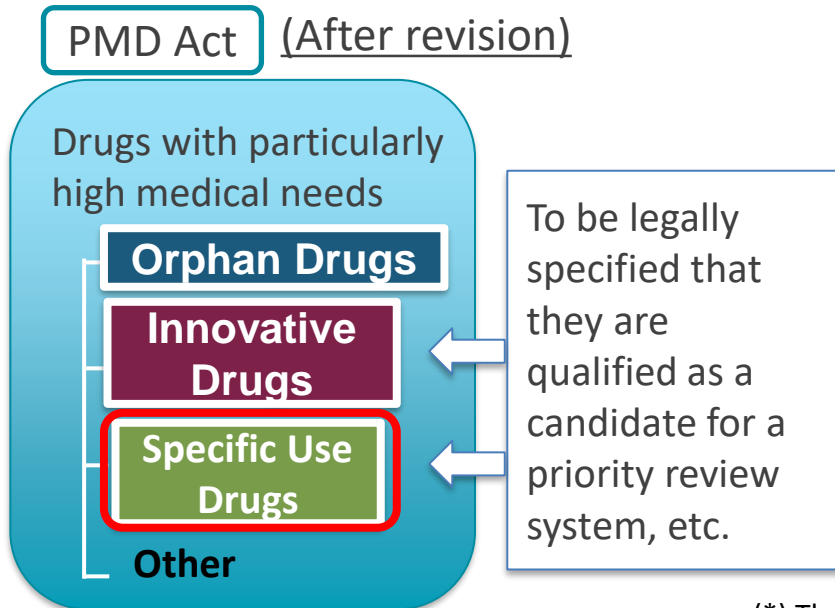
- The MHLW requests pharmaceutical industries to develop or submit the NDA of designated drugs/indications
- The PMDA reviews NDAs on fast track and can accept public knowledge as the basis for approval such as:
 - Large experience of (off-label) clinical use in Japan plus clinical data submitted to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

Legislation of “Specific Use Drug Designation System”

From 1st Sep. 2020

- A system to designate drugs addressing significant unmet medical needs such as drugs with no indication for pediatric 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

Specific use drugs	<ol style="list-style-type: none">1. Being used for the treatment of specific diseases (*).<ul style="list-style-type: none">• Being used to treat pediatric 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
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(*) The number of patients who may use the drug should be less than 50,000 in Japan or the drugs should be indicated for difficult-to-treat diseases

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

Extension of Re-examination Period

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



Revised

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

Today's Agenda

- Pediatric Drug Development in Japan
- International Regulatory Collaboration

International Regulatory Collaboration

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

Pediatric 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.

Pediatric Cluster

- Although a lot of products discussed in cluster TC have not been developed for children in Japan, the content of the meetings are very useful in helping us develop various approaches to:
 - finding appropriate endpoints
 - choosing comparators
 - extrapolating efficacy data from studies in adults to pediatrics, 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 pediatric drug development
- ✓ More aggressive PMDA contribution to the projects such as writing articles, development of guidelines, and so on.

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

Once a year since 2018

- To promote pediatric drug development globally
 - To assist capacity building related to pediatric drug development in Asia and other countries/regions
- This seminar is intended for regulatory authority officials who are engaged in the review of pediatric drug development programs.
 - This seminar covers current pediatric guidelines and practices in the United States and Japan, and provides the opportunity for the participants to share current pediatric guidelines and practices in their respective countries and regions.
 - Case study sessions on pediatric 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 last 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 pediatric drug development like the EU and the US.
- However, the environment for pediatric drug development in Japan is improving through various efforts.
- It is expected that pediatric 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 is trying to promote regulatory convergence and active involvement of Japan for pediatric drug development.

Better Medicine for Children!