14th DIA Japan Annual Meeting 2017
November 12-14, 2017 | Tokyo Big Sight | Ariake

PEDiatric Drug Development in Japan and International Regulatory Collaboration

Masakazu Hirata, MD, PhD
Review Director
Office of Cellular and Tissue-based Products
Member of Pediatric Drug Working Group
PMDA
Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. DIA and the DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Pharmaceuticals and Medical Devices Agency
Established 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

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

Hokuriku Branch
Toyama

Kansai Branch
Osaka

Tokyo
PMDA Pediatric Drugs WG

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

**International Collaborations**
- FDA
- European Medicines Agency
- Health Canada
- TGA

**Collaboration at Pediatric Cluster**
- Analyze and identify pediatric issues raised in past reviews and consultations

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

**External Communications**
- Discuss pediatric issues with domestic stakeholders

**Internal Communications**
Today’s topics

- Pediatric Drug Development in Japan
- Pediatric Drug Regulation in US
- Pediatric Drug Regulation in EU
- International Regulatory Collaboration in Pediatric Drug Development
“Off-label drug use remains an important public health issue, especially for infants, young children, and children with rare diseases. Evidence, not label indication, remains the gold standard from which practitioners should draw when making therapeutic decisions for their patients. The PREA and BPCA have been extremely successful and represent an essential first step in expanding this evidence as a means of achieving the ultimate goal that any and all drugs used to treat children will have age-appropriate evidence sufficient to provide information for labeling. However, labeling with pediatric information still exists in less than 50% of products, such that much work remains to be done to ensure the best possible practice for therapeutic decision-making in pediatrics.”

From the American Academy of Pediatrics Policy Statement
Today’s topics

- Pediatric Drug Development in Japan
- Pediatric Drug Regulation in US
- Pediatric Drug Regulation in EU
- International Regulatory Collaboration in Pediatric Drug Development
Pediatric Drug Development in Japan

Number of Pediatric Approvals in Japan (FY2009-FY2016)

- Total Approvals and Alterations
- Pediatric New Approvals
- Pediatric Alterations
- Public Knowledge

<table>
<thead>
<tr>
<th>Year</th>
<th>Products</th>
<th>Total Approvals and Alterations</th>
<th>Pediatric New Approvals</th>
<th>Pediatric Alterations</th>
<th>Public Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>106</td>
<td>106</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>114</td>
<td>114</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>130</td>
<td>130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>132</td>
<td>132</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>135</td>
<td>135</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>119</td>
<td>119</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>115</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>112</td>
<td>112</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pediatric Drug Development in Japan

Promoting Pediatric Drug Development

- Extension of re-examination period
- Public knowledge-based application
- Council on Unapproved Drugs /Off-label Use
## Pediatric Drug Development in Japan

Re-examination Period (market exclusivity and data protection) of New Drugs in Japan

<table>
<thead>
<tr>
<th>Re-examination period</th>
<th>Drug type</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>Orphan Drugs, Drugs need to be surveyed by pharmacoepidemiological method</td>
</tr>
<tr>
<td>8 years</td>
<td>Drugs with new active ingredients</td>
</tr>
<tr>
<td>4 years</td>
<td>New combination drugs, Drugs with a new route of administration</td>
</tr>
<tr>
<td>4~6 years</td>
<td>Drugs with new indications, Drugs with a new dosage</td>
</tr>
</tbody>
</table>

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.

18 products granted extension for pediatric study as of Oct 2017.
Pediatric Drug Development in Japan

Number of Pediatric Approvals in Japan (FY2009-FY2016)

- Total Approvals and Alterations
- Pediatric New Approvals
- Pediatric Alterations
- Public Knowledge-based Alterations

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Approvals</th>
<th>Pediatric New Approvals</th>
<th>Pediatric Alterations</th>
<th>Public Knowledge-based Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>106</td>
<td>18</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>114</td>
<td>23</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>130</td>
<td>34</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>132</td>
<td>35</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2013</td>
<td>135</td>
<td>36</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>119</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2015</td>
<td>115</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>112</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Council for Unapproved Drugs/Indications

- Established in 2010 as advisory council of MHLW
- Identifies highly-needed unapproved drugs/indications, including pediatrics, which are widely used in at least one of the 6 countries (Australia, Canada, France, Germany, UK, US) *
- MHLW requests pharmaceutical industries to develop or submit the NDA of designated drugs/indications
- 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 regulatory authority in one of the 6 countries
  - Usage described in major medical textbooks or guidance documents
- 157 products/indications have been approved as of Dec 2015 including 29 pediatric dosage or indications

*From 2015, unapproved/off label drugs in these countries can also be considered
Today’s topics

- Pediatric Drug Development in Japan
- Pediatric Drug Regulation in US
- Pediatric Drug Regulation in EU
- International Regulatory Collaboration in Pediatric Drug Development
## Pediatric Drug Regulation in US

### Historical Outline of US regulation

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulations</th>
<th>Effects</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>FDAMA Pediatric Exclusivity (6 months)</td>
<td>incentive</td>
<td>Jan 2002: Exclusivity Sunsets</td>
</tr>
<tr>
<td>1998</td>
<td>Pediatric Rule Regulation</td>
<td>requirement</td>
<td>enjoined 2002 by court-FDA lacked authority</td>
</tr>
<tr>
<td>Jan 2002</td>
<td><strong>BPCA</strong> - Best Pharmaceuticals for Children Act</td>
<td>incentive</td>
<td>NIH to develop priority list of drugs</td>
</tr>
<tr>
<td>Dec 2003</td>
<td><strong>PREA</strong> - Pediatric Research Equity Act</td>
<td>requirement</td>
<td></td>
</tr>
<tr>
<td>Sep 2007</td>
<td>Food &amp; Drug Administration Amendments Act</td>
<td>reauthorized BPCA &amp; PREA</td>
<td>includes devices, labeling mandates</td>
</tr>
<tr>
<td>2012</td>
<td>Title V of FDA Safety and Innovation Act (FDASIA)</td>
<td>BPCA &amp; PREA permanent</td>
<td></td>
</tr>
</tbody>
</table>
# Pediatric Drug Regulation in US

**BPCA vs PREA**

<table>
<thead>
<tr>
<th>BPCA</th>
<th>PREA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voluntary program driven by public health need</strong></td>
<td><strong>Requirement program triggered by NDA submission for adult indication</strong></td>
</tr>
<tr>
<td>All indications where there is potential benefit from study</td>
<td>Limited to indications proposed for adults</td>
</tr>
<tr>
<td></td>
<td>Orphan drugs exempted</td>
</tr>
<tr>
<td></td>
<td>No incentives</td>
</tr>
<tr>
<td><strong>Written Request (WR)</strong></td>
<td><strong>Pediatric Study Plan (PSP)</strong></td>
</tr>
<tr>
<td>- Outline of study requested by FDA</td>
<td>- Sponsor submit PSP at end of Phase 2</td>
</tr>
<tr>
<td>- Proposed Pediatric Study Request (PPSR) can be submitted by sponsor for WR</td>
<td>- Waiver and Deferral</td>
</tr>
</tbody>
</table>

## Agreed PREA requirements

- Marketing Approval
- Post marketing

## WR issued (BPCA)

- Phase I
- Phase II
- Phase III

## PSP modifications

- Phase II
- PSP
- NDA
- Marketing Approval

---

Voluntary program driven by public health need

All indications where there is potential benefit from study

- 6 months patent extension
- Priority Review

**Written Request (WR)**

- Outline of study requested by FDA
- Proposed Pediatric Study Request (PPSR) can be submitted by sponsor for WR

**Pediatric Study Plan (PSP)**

- Sponsor submit PSP at end of Phase 2
- Waiver and Deferral

**Agreed PREA requirements**

- Marketing Approval
- Post marketing

**WR issued (BPCA)**

- Phase I
- Phase II
- Phase III

---

**Pediatric Drug Regulation in US**

**BPCA vs PREA**

- Voluntary program driven by public health need
- All indications where there is potential benefit from study
  - 6 months patent extension
  - Priority Review
- Written Request (WR)
  - Outline of study requested by FDA
  - Proposed Pediatric Study Request (PPSR) can be submitted by sponsor for WR
- Pediatric Study Plan (PSP)
  - Sponsor submit PSP at end of Phase 2
  - Waiver and Deferral

**Agreed PREA requirements**

- Marketing Approval
- Post marketing

**WR issued (BPCA)**

- Phase I
- Phase II
- Phase III
BPCA

Voluntary program driven by public health

**On-patent** (incentive: 6-month patent extension)

**Off-patent or generic process** (List and contracting process coordinated by NICHD)

- Written Request (WR)
  - Legal document that outlines studies requested by FDA

NIH prepares priority list in consultation with FDA and experts and publishes the list, supports studies by Pediatric Trials Network

Sponsor or NIH can submit Proposed Pediatric Study Request (PPSR) to FDA and FDA issues WR

WRs declined by sponsor can be sent to NIH

WRs sent to NIH may enter priority list and initiate NIH supported studies

Prioritize

NIH drafts PPSR to FDA

FDA issues WR to NDA holder

WR declined, FDA sends WR to NIH

NIH as Sponsor

Submit Data to FDA

Label Change
## Pediatric Drug Regulation in US

**WR of Drugs sent to NIH and listed in Priority List**  
(as of June 30, 2017)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Lithium</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>baclofen</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>lorazepam</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td>griseofulvin</td>
</tr>
<tr>
<td>Pediatric hypertension</td>
<td>sodium nitroprusside</td>
</tr>
<tr>
<td>Anesthesia/sedation</td>
<td>lorazepam</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>13-cis-retinoic acid*</td>
</tr>
<tr>
<td>Oncology</td>
<td>methotrexate</td>
</tr>
<tr>
<td></td>
<td>vincristine</td>
</tr>
<tr>
<td></td>
<td>daunomycin</td>
</tr>
<tr>
<td></td>
<td>actinomycin D</td>
</tr>
<tr>
<td>Infections in neonate</td>
<td>ampicillin</td>
</tr>
<tr>
<td>Neonatal necrotizing enterocolitis</td>
<td>meropenem</td>
</tr>
<tr>
<td>Apnea of Prematurity</td>
<td>caffeine**</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>azithromycin</td>
</tr>
<tr>
<td>Neonatal pain</td>
<td>morphine</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>hydroxyurea</td>
</tr>
</tbody>
</table>

* PPSR from NIH to FDA, WR declined by MAH

** PPSR from NIH to FDA

[https://bpca.nichd.nih.gov/prioritization/priority_lists/Pages/priority_list.aspx](https://bpca.nichd.nih.gov/prioritization/priority_lists/Pages/priority_list.aspx)
Today’s topics

- Pediatric Drug Development in Japan
- Pediatric Drug Regulation in US
- Pediatric Drug Regulation in EU
- International Regulatory Collaboration in Pediatric Drug Development
# Pediatric Drug Regulation in EU

## Paediatric Investigational Plan (PIP)
- Sponsor obtains agreement from EMA for new product, indication, route of administration, or formulation
- Submitted at end of adult Phase 1
- Adult submission **must** be accompanied by execution of PIP
- Waiver and Deferral

### Incentives
- 6 months patent extension or SPC
- 2 yr data protection for orphan drugs
- Off patent: Paediatric Use Marketing Authorization grants 10 yr exclusivity and 8yr data protection

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulation</th>
<th>Note</th>
</tr>
</thead>
</table>
| 2007 | Regulation (EC) No 1901/2006 Paediatric Regulation | • Paediatric Committee (PDCO)  
• Paediatric Investigation Plan (PIP)  
• Incentives |
Today’s topics

- Pediatric Drug Development in Japan
- Pediatric Drug Regulation in US
- Pediatric Drug Regulation in EU
- International Regulatory Collaboration in Pediatric Drug Development
International Regulatory Collaboration in Pediatric Area

Pediatric Cluster Activity

Monthly Teleconferences
In August 2007, EMA and FDA established monthly teleconferences between regulators called the Pediatric Cluster to discuss product-specific pediatric development (PSP and PIP) and topics related to product classes under the terms of confidentiality agreement.

Objectives:
• enhance the science of pediatric trials
• avoid exposing children to unnecessary trials

PMDA joined these teleconferences in November 2009 and Health Canada in September 2010 as observers. They are now active participants in these monthly exchanges.

Australia's Therapeutic Goods Administration (TGA) joined the teleconferences in January 2014.
International Regulatory Collaboration in Pediatric Area

Pediatric Cluster Activity

413 drugs and 132 general topics discussed between Sep 2007 and Jun 2016

- Pediatric Drug Development Plan (incl trial design) and Safety issues are the focus

http://www.fda.gov/scienceresearch/specialtopics/pediatrictherapeuticsresearch/ucm106621.htm
http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM451789.pdf
International Regulatory Collaboration in Pediatric Area

Cluster Activity: Additional Frameworks

Common Commentary
The Common Commentary is a tool to inform sponsors of products discussed at the Pediatric Cluster. The document provides informal, non-binding comments to sponsors on pediatric development plans that have been submitted to both FDA and EMA, which are under review by both agencies and have been discussed at the Pediatric Cluster.

Area Specific Working Groups
Inflammatory Bowel Disease WG for paediatric ulcerative colitis (2012) and Crohn’s disease (2014-15). They published a number of joint articles and editorials.

Workshops
Gaucher Disease WS (2012)
Paediatric Pulmonary Hypertension WS (2017)
International Regulatory Collaboration in Pediatric Area  
Cluster Activity: Additional Frameworks

PMDA collaborated with FDA, EMA, HC in International IBD WG


International Regulatory Collaboration in Pediatric Area

ICH E11 (2000)
Pediatric formulation, Timing and types of studies (including extrapolation), Pediatric age classification, Ethical consideration

ICH E11(R1) - addendum to E11 (Step 4 in 2017)
Ethical consideration, Common scientific approach, Pediatric subgroups, Approaches to optimize pediatric drug development (extrapolation and M&S), Practicality of clinical trials, Pediatric formulation

ICH Pediatric Extrapolation Guidance Topic (2017-)

Regulatory members from FDA, EMA and PMDA

Regulatory members from FDA, EMA, PMDA, HC, Swiss medic and ANVISA
Conclusion

- Regulation is effective in increasing evidence for safe and effective therapeutics for children.
- Pediatric drug development is not mandatory while being encouraged in Japan.
- US and EU have mandatory pediatric drug development regulations.
- PMDA has regular exchange of information with FDA, EMA, HC and TGA in pediatric area.
Ask