Current research situation and challenges of pediatric clinical studies in Japan

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The views and opinions expressed in this presentation are those of the speaker and are not necessarily those of the PMDA.
Outline of the presentation

A. Current Situation of Pediatric Medicine in Japan

B. Promoting the Development of medicinal products for pediatric use in Japan

C. Efforts for Early Approval of Pediatric Medicine in the PMDA

D. Conclusion
The Current Situation of Pediatric Medicine in Japan
Ongoing pediatric studies worldwide

As of 16th April 2013

Total: 438 trials

Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Search Terms: pediatrics
- Industry funded
- Includes only open studies and excludes studies with unknown status
- Studies with multiple locations are included in each region containing locations
Ongoing pediatric studies in East Asia excluding Japan

As of 16th April 2013

East Asia: 57 trials

Source: www.clinicaltrials.gov
Search Terms: pediatrics
- Industry funded
- Includes only open studies and excludes studies with unknown status
- Studies with multiple locations are included in each region containing locations
ICH E11 Guideline
Clinical Investigation of Medicinal Products in the Pediatric Population

◆ General principles
  • Pediatric patients should be given medicines that have been properly evaluated for use in the intended population
  • Product development programs should include pediatric studies when pediatric use is anticipated
  • Development of product information in pediatric patients should be timely and, often requiring the development of pediatric formulations
  • The rights of pediatric participants should be protected and they should be shielded from undue risk
  • Shared responsibility among companies, regulatory authorities, health professionals and society as a whole
The development of medicinal products for pediatric use has not been progressing easily.

- So-called “Therapeutic Orphans”

Pediatric dosages are not approved for most medicines.

Despite not specifying the appropriate effect-efficacy or dosage and administration, many medicines are administered to children.
Therapeutic Orphans

A term coined in 1968 by Dr Shirkey for the lack of studies about the safety, dosing and efficacy for medicines used in children which have been approved for adults.


Why are medicines for children still therapeutic orphans?

• Targets are various and broad, from newborns to adolescents.
• Finely tuned responses are required for each age group regarding the formulation and pharmacokinetics, etc...
• Sufficient considerations are also required for consent acquisition for clinical trials. etc....
Medical Practices in Japan

As a result.....

◆ Usage other than the approved effect
◆ Usage of medicines for which "The safety in children has not been established" or the dosage and administration are not specified.

At pediatrician’s discretion
According to
- Information from medical articles
- Foreign drug use
- Foreign treatment guidelines
- Dosage and administration for adults etc.

Investigator initiated clinical trials

◆ Modified formulation
  grinding, fractional amounts, injection products changed into inhalation, etc.

Aside from those matters above..

◆ Chemical compounds used as medicine
◆ Medicines imported by individuals (so-called unapproved medicine)
-B-

Promoting Development of medicinal products for pediatric use in Japan
Drug Regulation in Japan

- The Ministry of Health, Labor and Welfare (MHLW)
  Ultimate Responsibilities in policies and administrative measures
  e.g. • Final judgment on approval
  • Product withdrawal from market

- The Pharmaceuticals and Medical Devices Agency (PMDA)
  Scientific review, examination, data analysis, etc.
  to assist the MHLW’s measures
  e.g. • Approval review of drugs and medical devices
  • GMP/GLP/GCP inspection
  • Collection, analysis and provision of information about adverse reactions
Promoting Development of medicinal products for Pediatric Use in Japan

◆ The MHLW has taken some measures to resolve those problems.
  – Extension of the re-evaluation period (the exclusive period)
    • Normally 8 years for a new molecular entity
    • An additional 2 years may be granted, if a pediatric drug development plan is submitted and approved
  – The medicinal products can obtain new dosages/indications without clinical trials, in cases where the dosages/indications are well-known.
    as we say in Japanese “Kouchi-shinsei” 「公知申請」
  – Development Promotion Scheme for Unapproved & Off-label Drugs in High Medical Needs.
In 2009 and 2011, the MHLW widely solicited the demands for approval of unapproved & off-label drugs* in high medical needs situations from the public.

*unapproved drugs: already authorized in US or EU, but not yet approved in Japan
off-label drugs: whose indications (effect-efficacy and/or dosage and administration) have been already authorized in US or EU, but not yet approved in Japan

The Expert conference (EC) assessed the 374 demands (unapproved: 86, off-label: 288) on the first solicitation and 290 demands (unapproved: 47, off-label: 243) on the second in terms of medical needs and necessary studies (clinical trials etc.) in Japan for approval.
Development Promotion Scheme for Unapproved & Off-label Drugs in High Medical Needs -2-

Criteria of the Demands

Meet both (1) and (2), and high medical needs

(1) Severity of the disease meets any one of the following
   • Life-threatening diseases
   • Disease progression is irreversible and interfere with patient’s daily life seriously.
   • Other diseases which interfere with patient’s daily life seriously

(2) Medical benefits meet any one of the following
   • There is no existing therapy for the disease in Japan.
   • The clinical trials conducted in the US or EU etc. revealed that the efficacy and safety of the drug is superior compared to the already existing therapy.
   • The therapy has been established as standard in the US or EU.
As for the demands that the EC regarded as in high medical needs,

(i) The MHLW requested relevant sponsors (e.g., multinational affiliates located in Japan) for unapproved drugs or marketing authorization holders for off-label drugs to develop the drugs / indications.

or

(ii) The MHLW recruited sponsors to develop the drugs when there is no relevant sponsor to develop them in Japan.
Development Promotion Scheme for Unapproved & Off-label Drugs

**Sponsor**
- Examination of the Possibility of Development
  - R&D Timetable
  - Views on the necessary studies for approval
- Conduct Clinical Trials or File an Application w/o Clinical Trials
  - Clinical Trials
- Application

**Expert Conference**
- Hearing
- Evaluation of Medical Needs
  - If criteria are met

**Request to Sponsors for development**
- Opinion
  - Evaluation of Necessity of Clinical Trials and Other Studies
  - If Application w/o Clinical Trials are regarded appropriate
- Advice
- PAFSC Evaluation before Application
- Evaluation of Development Progress

**Academia patients**
- Demand
- Available in US, UK, DE, FR

**Recruit Sponsors for development**
(if no relevant sponsors exist in Japan)

**CSIMC**
- Central Social Insurance Medical Council

**PAFSC**
- Pharmaceutical Affairs and Food Sanitation Council

**Report**
- Reflection on Drug Pricing
### Results of Evaluation on Medical Need

#### < Details of Evaluation >

<table>
<thead>
<tr>
<th>Application w/o clinical trials appropriate, “Kouchi-shinsei”</th>
<th>Already started development</th>
<th>additional clinical trials necessary</th>
<th>Under deliberation on the necessity of clinical trials</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>59(25)</td>
<td>53(10)</td>
<td>52(20)</td>
<td>2(0)</td>
<td>166(55)</td>
</tr>
</tbody>
</table>

111 medicines including 35 medicines for pediatric use were already approved.

#### The first solicitation

<table>
<thead>
<tr>
<th>Approved before EC’s deliberation</th>
<th>Evaluated as in high medical need</th>
<th>Not evaluated as in high medical need</th>
<th>Not approved in the US etc.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>166(55)</td>
<td>20 (7)</td>
<td>81</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>186(62)</td>
<td></td>
<td></td>
<td>374</td>
</tr>
</tbody>
</table>

Sponsor candidates were found for all drugs as of 25 March 2013.
Japanese Children Trials Network (JCTN)

- Established in November 2010
- Mainly consisted of the member of the Japanese Association of Children’s Hospitals and Related Institutions

**Efforts of the JCTN**

- Centralization of administrative functions
- Establishment of central IRB
- Education and training of member institutions
- Promotion of efficiency of clinical trials and infrastructure development
- Feasibility survey of clinical trials
- Making requests to pharmaceutical companies for cooperation in clinical trials conducted by physicians
Efforts for Early Approval of Pediatric Medicines in the PMDA
Efforts for Early Approval of Pediatric Medicines in the PMDA

- Scientific advice for development of pediatric medicines (including advice for investigator initiated trials)
- Cooperation to the Development Promotion Scheme for Unapproved & Off-label Drugs in High Medical Needs
- Establishment of a Pediatric Working Group in the PMDA
- Pharmaceutical affairs consultations on R&D strategy
Efforts for Early Approval of Pediatric Medicines in the PMDA

• Pediatric Working Group
• Analysis of NDA data of approved medicinal products
• International Collaboration
• Pharmaceutical Affairs Consultation on R&D Strategy
Major Projects Across Multi-Offices in the PMDA

- Microdose Trials Project
- Post-approval Manufacturing Changes Project
- In Vitro Companion Diagnostics Project
- Pediatric and Orphan Drugs Project
  - Pediatric WG
  - Orphan drug WG
- QbD Assessment Project
- Innovative Statistical Strategies for New Drug Development
- Nanomedicine Initiative Project
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Omics Project
Outline of the Pediatric WG

- Established in November 2011

- 16 members (currently)
  Including 5 pediatricians from the Office of New Drugs and the Office of Safety

- We can invite appropriate reviewers outside of the WG on a case by case basis.
Tasks of the Pediatric WG

- Encourage industries and investigators to develop medicinal products for children

- Standardize development of medicinal products for pediatric use
  - Necessary data for approval
  - Labeling description
  - Timing of development

- Strengthen collaboration with other regulatory agencies for development of pediatric medicines
Steps taken so far

- **Analysis of the NDA data of approved medicinal products for children**
  - Study design
  - Number of subjects
  - Labeling description etc..

- **Collaboration and exchanging of opinions with other domestic stakeholders**

- **Collaboration with other regulatory agencies**
  - Joint teleconferences with the FDA, EMA and Health Canada
  - Visit other regulatory agencies
Efforts for Early Approval of Pediatric Medicines in PMDA

• Pediatric Working Group
• Analysis of NDA data of approved medicinal products
  • International Collaboration
• Pharmaceutical Affairs Consultation on R&D Strategy
Methods

We investigated the marketing authorization of the medicines whose pediatric dosages and administration had been approved, based on the product evaluation reports on the PMDA HP. 
http://www.pmda.go.jp/

Subjects

781 medicines approved between April 2004 and December 2012

H. Sugai, et.al. 133th Annual meeting of the Pharmaceutical Society of Japan, March 2013
Analysis of NDA data of approved medicinal products -2-

Number and proportion of medicines whose pediatric dosages and administration were approved

- Total number of approved medicine
- Medicine approved for pediatrics
- Proportion of medicine approved for pediatrics to total

<table>
<thead>
<tr>
<th>Year</th>
<th>Medicine approved for pediatrics</th>
<th>Total number of approved medicine</th>
<th>Proportion of medicine approved for pediatrics to total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>10</td>
<td>50</td>
<td>20%</td>
</tr>
<tr>
<td>2005</td>
<td>15</td>
<td>80</td>
<td>19%</td>
</tr>
<tr>
<td>2006</td>
<td>20</td>
<td>100</td>
<td>20%</td>
</tr>
<tr>
<td>2007</td>
<td>25</td>
<td>120</td>
<td>21%</td>
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<tr>
<td>2008</td>
<td>30</td>
<td>140</td>
<td>21%</td>
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<td>2009</td>
<td>35</td>
<td>160</td>
<td>22%</td>
</tr>
<tr>
<td>2010</td>
<td>40</td>
<td>180</td>
<td>22%</td>
</tr>
<tr>
<td>2011</td>
<td>45</td>
<td>200</td>
<td>22%</td>
</tr>
<tr>
<td>2012</td>
<td>50</td>
<td>220</td>
<td>23%</td>
</tr>
</tbody>
</table>
Analysis of NDA data of approved medicinal products -3-

Rate of approved pediatric medicine according to the medicinal effect

- Biologics: 12%
- Genitourinary agents, etc.: 3%
- Cardiovascular agents, etc.: 20%
- Antimicrobial agents
- Antiepileptic agents, etc.: 9%
- Antibody products: 1%
- Gastroenterological agents, etc.: 9%
- Blood products: 8%
- Medicines for anemia of prematurity, hemophilia, etc.: 8%
- Medicines for AIDS: 1%
- Vaccines
- Anticancer agents: 4%
- Radioactive agents: 1%
- Intracorporeal diagnostic agents: 0%
- Medicines for allergy, etc.

Total 177 products
Proportion of approved pediatric medicine (according to the medicinal effect)

<table>
<thead>
<tr>
<th>Medicinal Effect</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterological agents, etc.</td>
<td>80</td>
</tr>
<tr>
<td>Cardiovascular agents, etc.</td>
<td>97</td>
</tr>
<tr>
<td>Antiepileptic agents, etc.</td>
<td>101</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>94</td>
</tr>
<tr>
<td>Genitourinary agents, etc.</td>
<td>49</td>
</tr>
<tr>
<td>Medicines for allergy, etc.</td>
<td>155</td>
</tr>
<tr>
<td>Intracorporeal diagnostic agents</td>
<td>16</td>
</tr>
<tr>
<td>Radioactive agents</td>
<td>7</td>
</tr>
<tr>
<td>Anticancer agents</td>
<td>123</td>
</tr>
<tr>
<td>Medicines for AIDS</td>
<td>16</td>
</tr>
<tr>
<td>Biologics</td>
<td>24</td>
</tr>
<tr>
<td>Blood products</td>
<td>17</td>
</tr>
</tbody>
</table>

Excluding Pediatric Medicine

Pediatric Medicine
**Development strategy**

- We investigated 66 pediatric medicines that were approved between April 2009 and December 2012 (excluding 40 medicines approved by the “Kouchi-shinsei” scheme).
- No medicine was approved based on data from global clinical studies.

![Development strategy chart]

- **Unclassifiable**
- **Mainly based on data from Japanese adult studies**
- **Mainly based on data from foreign pediatric studies**
- **Mainly based on data from Japanese pediatric studies**

<table>
<thead>
<tr>
<th>Year</th>
<th>Unclassifiable</th>
<th>Mainly based on adult studies</th>
<th>Mainly based on foreign pediatric studies</th>
<th>Mainly based on Japanese pediatric studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2010</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>7</td>
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<tr>
<td>2011</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>
Number of medicines according to randomized controlled studies including pediatric participants

- Randomized controlled study was conducted in both Japan and Foreign countries respectively
- Randomized controlled study was conducted in Japan
- Placebo controlled study was conducted in Japan

Year

Number

- 2009
- 2010
- 2011
- 2012
Efforts for Early Approval of Pediatric Medicines in the PMDA

- Pediatric Working Group
- Analysis of NDA data of approved medicinal products
- International Collaboration
- Pharmaceutical Affairs Consultation on R&D Strategy
International Collaboration

◆ FDA/EMA Joint teleconferences, once a month
  (PMDA and Health Canada are regular observers.)
  • To discuss product specific pediatric development and general
    scientific/regulatory/safety issues related to product classes
  • In 2012: 10 times
    26 medicines and 13 general topics were discussed.

◆ Cooperation on development of guidelines and specific
  issues in pediatrics
  • Inflammatory Bowel Diseases
Efforts for Early Approval of Pediatric Medicines in the PMDA

• Pediatric Working Group
• Analysis of NDA data of approved medicinal products
• International Collaboration
• Pharmaceutical Affairs Consultation on R&D Strategy
To create innovative pharmaceuticals and medical devices originating from Japan, PMDA started a new scientific consultation service, ‘Pharmaceutical Affairs Consultation on R&D Strategy’ for university laboratories, venture businesses, etc. on July 1st, 2011.

The targets of this new consultation, as a general rule, are products that correspond to the following priority areas.

- Regenerative medicine (cell- and tissue-based products)
- Difficult-to-treat diseases and rare diseases
- Other than the above, products utilizing particularly innovative technologies

(Note) Regardless of the order among the areas.

At present, university laboratories, venture companies, etc. that discover promising resources are not always familiar with development strategies that lead to commercialization of products.

- Early regulatory scientific consultation is recommended.
Pharmaceutical Affairs Consultation on R&D Strategy -2-

Introductory consultations
free of charge

pre-consultations
free of charge

Summarize issues

university laboratories, venture businesses, etc.

Face to Face scientific consultations
Need to pay a fee
Between July 2011 and December 2012, 35 products including 8 pediatric products reached the scientific consultation on clinical trials stage.

<table>
<thead>
<tr>
<th>Medicinal effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer agents</td>
<td>5</td>
</tr>
<tr>
<td>Anticoagulant agents</td>
<td>1</td>
</tr>
<tr>
<td>Medicines for inborn errors of metabolism</td>
<td>1</td>
</tr>
<tr>
<td>Medicines for neuromuscular disease</td>
<td>1</td>
</tr>
</tbody>
</table>
Conclusion
Even though pediatric medicines are “therapeutic orphans”, their development is. Furthermore the quality of the clinical trials has improved.

“Kouchi-shinsei” scheme and Development Promotion Scheme for Unapproved & Off-label Drugs in High Medical Needs have attained some progress in development of medicinal products for pediatric use.

These efforts are effective for catching up with the US and EU and resolving drug-lag, but should not be ultimate solutions.
No medicine approved based on data from global clinical studies. However, medicinal product development will be more globalized in pediatric medicines. It will be important to consider the participation in the global studies early in medicinal product development.

Cooperation among all is necessary for the success of the pediatric drug development in Japan. So, international collaboration is also important.

The pediatric WG will continuously cooperate with these stakeholders, and will make efforts to promote development of medicinal products for pediatric use.
Let’s consider Global Drug Development
To increase feasibility of clinical trials in the pediatric field
To establish more appropriate strategies to develop medicines for children

Don’t miss a chance to develop/provide medicine to children of the world!
Thank you for your attention!
Number of medicines whose pediatric dosages and administration were approved

Junko Sato, 薬事 2012; 54: 229-234
Outline of Approval Review Process

PMDA

Conformity Audits
( GLP/GCP/GMP etc. )
+
Scientific Reviews

External Experts

Minister

Consultation
Advice

Advisory body
PAFSC

Approval

Application

Consultation

Review Report

Sponsor
Analysis of NDA data of approved medicinal products -6-

Number of pediatric medicines approved by “Kouchi-shinsei” scheme

- Total number of approved pediatric medicines
- Pediatric medicines approved by “Kouchi-shinsei”

Number

Gastroenterological agents, etc.
Cardiovascular agents, etc.
Antiepileptic agents, etc.
Antimicrobial agents
Genitourinary agents, etc.
Medicines for allergy, etc.
Intracorporeal diagnostic agents
Radioactive agents
Anticancer agents
Medicines for AIDS
Biologics
Blood products
Pediatric regulation in the US and EU

**EU**
- **EMA (PDCO)**
  - Pediatric regulation (No. 1901/2006)
  - PIP (Pediatric Investigation Plan)
  - Waiver
  - Deferral
  - Phase One
  - Phase Two
  - Phase Three
  - Written Request
  - NDA Submission
  - Postmarketing

**US**
- **FDA (PeRC)**
  - FDAAA (FDA Amendments Act of 2007)
  - Best Pharmaceuticals for Children Act (BPCA)
  - Pediatric Research Equity Act (PREA)
  - Written Request
  - NDA Submission
  - Postmarketing