PMDA's Experiences and Challenges in Pediatric Drug Development

Motoko Ishikawa
Reviewer, Office of New Drug III
Pharmaceuticals and Medical Devices Agency (PMDA), Japan
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• Current situation of development of pediatric drugs in Japan
• Effort to promote development of pediatric drugs in Japan
• Future Challenges
• Current situation of development of pediatric drugs in Japan
• Effort to promote development of pediatric drugs in Japan
• Future Challenges
Current situation of pediatric drug development in Japan

- There is no special regulation for development of medicines for pediatric use. The development lies in the hands of industries.
- Many medicines whose appropriate dosage or targets in pediatric population are not specified are administered to children.
Objects: To evaluate the recent situation of pediatric drug development in Japan quantitatively.

Subjects: (S)NDA approved in recent 10 years - from April 2004 to March 2013.

Material:
① Review reports and application data released on PMDA website
   http://www.info.pmda.go.jp/info/syounin_index.html
② Labeling for HCP/ Interview form

“Number of medicines” is counted based on number of review reports.
Analysis of NDA data

Number and ratio of medicines including pediatric indications or dosages

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Pediatric</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>40</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>2005</td>
<td>55</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>2006</td>
<td>78</td>
<td>19</td>
<td>24.4</td>
</tr>
<tr>
<td>2007</td>
<td>83</td>
<td>20</td>
<td>24.1</td>
</tr>
<tr>
<td>2008</td>
<td>78</td>
<td>17</td>
<td>21.8</td>
</tr>
<tr>
<td>2009</td>
<td>103</td>
<td>19</td>
<td>18.4</td>
</tr>
<tr>
<td>2010</td>
<td>114</td>
<td>26</td>
<td>22.8</td>
</tr>
<tr>
<td>2011</td>
<td>131</td>
<td>35</td>
<td>26.7</td>
</tr>
<tr>
<td>2012</td>
<td>133</td>
<td>44</td>
<td>33.1</td>
</tr>
<tr>
<td>2013</td>
<td>128</td>
<td>38</td>
<td>29.7</td>
</tr>
</tbody>
</table>
Time lag between adult approval and pediatric approval based on indications

- Only pediatric indication/dosage or pediatric dosage change
- More than 10 years
- Between 5 and 10 years
- Less than 5 years
- Same time
Agenda

• Current situation of development of pediatric drugs in Japan
• Effort to promote development of pediatric drugs in Japan
• Future Challenges
Re-examination period of New Drugs in Japan
-under Article 14-4 of the Pharmaceutical Affairs Act.

<table>
<thead>
<tr>
<th>Term</th>
<th>Drug type</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>Orphan Drugs, Drugs need to survey 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>

2000/12/27
“Re-examination period of a drug that already approved can be extended to utmost 10 years, if results of special drug use-results survey or post-marketing clinical study show necessity to conduct a new clinical trial for setting of pediatric dosage.”

※Re-examination period is similar to exclusive sales period.
<table>
<thead>
<tr>
<th>Notification Date</th>
<th>Brand name</th>
<th>Active Ingredient</th>
<th>Therapeutic Category</th>
<th>First Approved In</th>
<th>Pediatric Dosage Approved in</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003/4, 2003/5</td>
<td>Targocid® for Injection, intracutaneous test preparation</td>
<td>Teicoplanin</td>
<td>Antibiotic drug</td>
<td>1998/04</td>
<td>2003/1</td>
</tr>
<tr>
<td>2003/4</td>
<td>Claritin® Tablets</td>
<td>Loratadine</td>
<td>Antiallergic drug</td>
<td>2002/7</td>
<td>2007/10</td>
</tr>
<tr>
<td>2005/1</td>
<td>Luvox® Tablets/Depromel® Tablets</td>
<td>Fluvoxamine maleate</td>
<td>SSRI</td>
<td>1999/4</td>
<td>Study Ongoing (Obsessive-compulsive disorder)</td>
</tr>
<tr>
<td>2005/1</td>
<td>Allegra® Tablets</td>
<td>Fexofenadine Hydrochloride</td>
<td>Antiallergic drug</td>
<td>2000/9</td>
<td>7 years and over: 2006/10 6 months to 7 years: 2014/1</td>
</tr>
<tr>
<td>2005/9</td>
<td>Amaryl® Tablets</td>
<td>Glimepiride</td>
<td>Antidiabetic Drug</td>
<td>1999/9</td>
<td>2010/6</td>
</tr>
<tr>
<td>2006/8</td>
<td>Myslee® Tablets</td>
<td>Zolpidem Tartrate</td>
<td>Drug for insomnia</td>
<td>2000/9</td>
<td>N/A</td>
</tr>
<tr>
<td>2006/9</td>
<td>Paxil® Tablets</td>
<td>Paroxetine Hydrochloride Hydrate</td>
<td>SSRI</td>
<td>2000/9</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Extension of re-examination period

<table>
<thead>
<tr>
<th>Notification Date</th>
<th>Brand name</th>
<th>Active Ingredient</th>
<th>Therapeutic Category</th>
<th>First Approved In</th>
<th>Pediatric Dosage Approved in</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007/6</td>
<td>IMIGRAN® Tablets</td>
<td>Sumatriptan</td>
<td>Drugs for migraine</td>
<td>2001/6</td>
<td>Study Completed (migraine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010/3</td>
<td>ABILIFY® Tablets, Powder, Oral solution</td>
<td>Aripiprazole</td>
<td>Antipsychotic drugs</td>
<td>2006/1</td>
<td>Study Ongoing (schizophrenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011/3</td>
<td>SEIBULE® Tablets</td>
<td>Miglitol</td>
<td>Antidiabetic Drug</td>
<td>2005/10</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011/11</td>
<td>LONASEN® Tablets, Powder</td>
<td>Blonanserin</td>
<td>Antipsychotic Drug</td>
<td>2008/1</td>
<td>Study Ongoing (schizophrenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013/3*</td>
<td>Adoair® Diskus®/Aerosol</td>
<td>Salmeterol Xinafoate/Fluticasone Propionate</td>
<td>Drug for asthma</td>
<td>2007/4</td>
<td>Study Ongoing (asthma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014/2</td>
<td>Adcirca® Tablets</td>
<td>Tadalafil</td>
<td>Drug for Pulmonary arterial hypertension</td>
<td>2009/10</td>
<td>Study Ongoing (PAH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*for 6 month to 4 year-old children

**Information from:**
- Notification by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW
- Interview Form of each drug
- JAPIC Clinical Trials Information [http://www.clinicaltrials.jp/user/cteSearch.jsp](http://www.clinicaltrials.jp/user/cteSearch.jsp)
However, this system can not always provide incentive…
PFSB/ELD and HPB/ RDD Notification dated 1999/2/1

-When an off-label indication or dosage is regarded as having public knowledge, MAH can file an application for partial change of the indication or dosage without conducting new clinical trials.
2005/1～

Committee for Unapproved drugs or Off-label Drugs

- Evaluating evidence for the efficacy and safety of unapproved drugs or off-label drugs including drugs for pediatric use.

- Promoting development of those drugs.

<table>
<thead>
<tr>
<th>Subjects for Evaluation</th>
<th>Judged to have high medical need</th>
<th>Request for development</th>
<th>Sponsor recruited</th>
<th>Approved by 2014/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicitation from 2010 to 2011</td>
<td>374 (39)</td>
<td>185 (29)</td>
<td>165</td>
<td>20</td>
</tr>
<tr>
<td>Solicitation in 2011 summer</td>
<td>290 (43)</td>
<td>100 (15) (not finished)</td>
<td>83</td>
<td>17</td>
</tr>
</tbody>
</table>

*parenthesis: number of drugs discussed in the pediatric group*
So far, the subject for evaluation are limited to drugs already authorized in the US or EU.
Orphan Drug Designation

1993.10.1~

• Criteria:
  ① Number of patients (less than 50,000 in Japan)
  ② Medical needs
  ③ Possibility of development

• Incentives:
  ① Grant-in-Aid for R&D Expenses
  ② Administrative and Scientific Advices
  ③ Authorization of R&D Expenses for Tax Deduction
  ④ Priority review
  ⑤ Extension of re-examination period
From April 2004 to March 2013, 943 (s)NDA were approved
- including 129 orphan drugs
- including 238 pediatric drugs
→18%(43/238) of approved pediatric drugs designated as orphan drugs.

However, “Orphan Drug” can not be designed for ‘age groups’ (e.g. neonate, pediatric, elderly…) but only for ‘indication’.
• Started in November 2011
• Consists of 18 members (as of 2014/9)
  - including pediatricians, physicians and pharmacists from the Office of New Drugs and Office of Safety etc.
• Routine internal meeting
• Cluster TC with FDA, EMA, HC, and TGA
Our Task

• Promote industries and investigators to develop medicinal products for children
• Collaborate with foreign regulatory agencies for development of pediatric medicines
• Analyze and clarify issues raised in past reviews and cases of consultations
• Exchange views with domestic stakeholders (medical institutions, industry group, etc)
• Current situation of development of pediatric drugs in Japan
• Effort to promote development of pediatric drugs in Japan
• Future Challenges
In Japan, industries tend to show reluctance to take action aggressively on pediatric drug development due to lack of special pediatric regulations such as BPCA/PREA and PIP.

What can we do in order to solve current situation? Regulation and/or stronger incentives?
Pediatric domestic studies of a certain scale leading to high level of evidences is often difficult to perform in Japan.

- Number of children (age 0-14) in the world in 2013
  
<table>
<thead>
<tr>
<th>Region</th>
<th>Population (in millions)</th>
<th>Percentage</th>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>7125</td>
<td>26.3%</td>
<td>7125 × 26.3%</td>
<td>1868</td>
</tr>
<tr>
<td>US</td>
<td>316.1</td>
<td>19.5%</td>
<td>316.1 × 19.5%</td>
<td>61.8</td>
</tr>
<tr>
<td>EU</td>
<td>506.7</td>
<td>15.6%</td>
<td>506.7 × 15.6%</td>
<td>78.9</td>
</tr>
<tr>
<td>Japan</td>
<td>127.3</td>
<td>13.1%</td>
<td>127.3 × 13.1%</td>
<td>16.6</td>
</tr>
</tbody>
</table>


→ Feasibility is much more important in Japan and must be considered before implementation of regulation.
• Some incentive system which can promote pediatric drug development from early stage, similar to orphan drug designation, is predicted to be effective.

• Global Collaboration is even more needed.
  - Multi-Regional Clinical Trial (MRCT) etc.
Phase 3 Randomized, Double Blind, Placebo/Sham-controlled Study including Pediatric Patients

- For **Duchenne Muscular Dystrophy**
  - GSK2402968 in EU, JP, Canada, etc.
  - Tadalafil in US, EU, JP, Canada, etc.

- For **Spinal Muscular Atrophy**
  - ISIS-SMN Rx in US, EU, JP, Canada, Australia, etc.

- For **Epilepsy**
  - Perampanel in US, EU, JP, Australia, etc.

- Others (For Asthma, Crohn’s disease, Ulcerative Colitis…)

From ClinicalTrials.gov
- Continue to analyze NDA and consultation data to establish more appropriate strategies.
- Effort to provide guidance of pediatric drug development for industry.

PMDA should think about original way of extrapolation.
Pediatric Working Group’s Attempt

• Promoting global harmonization and active involvement of Japan in the development of pediatric drugs in the world
• Development of new technologies and their utilization
  - New analytical methods (e.g. modeling & simulation)
  - Biomaker
• Efficient Data Collection and Provision
  - Global database?
  - Off-label use?
The better medicine for children!

Motoko Ishikawa
E-mail: ishikawa-motoko@pmda.go.jp
PMDA website:

If you have any question or are interested in collaborating some kind of research, don’t hesitate to contact me!