DEVELOPMENT of PEDIATRIC DRUGS in JAPAN: REGULATORY VIEWPOINTS

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Agenda

► Present Status of Pediatric Drug Development
► Current Situation in Japan
► Future Challenges
Agenda

► Present Status of Pediatric Drug Development

► Current Situation in Japan

► Future Challenges
Present status of Pediatric Drugs

- Therapeutic orphan?
- Off-Label use
- ICH E 11...Formulations, Age classification, Ethics, Extrapolation...
Status in EU & US

**EU**

- EMA (PDCO)
  - Paediatric regulation (No.1901/2006)
  - PIP (Paediatric Investigation Plan)

**US**

- FDA (PeRC)
- PSP (Pediatric Study Plan) / Written Request

**EU**

- Waiver
- Deferral

**US**

- NDA Submission
- Post marketing
- Written Request

**Legislation**

- FDASIA (FDA Safety & Innovation Act 2012)
- Best Pharmaceuticals for Children Act (BPCA)
- Pediatric Research Equity Act (PREA)
Global Pediatric Clinical Trials

Source: http://ClinicalTrials.gov
As of 18 Oct, 2015
Search Term: pediatrics, Funder type: industry
Include only open studies, exclude studies with unknown status
*Not all of pediatric clinical trials in Japan are registered in ClinicalTrials.gov database.
Is this true?

- Feasibility is much more important in Japan.
- It is difficult to perform pediatric domestic studies verifying the high level of evidences.

Number of children (age 0-14) in 2014

- World: 7125 x 26.3% = 1868 millions
- Japan: 127.1 x 13.0% = 16.5 millions
- US: 320.0 x 19.1% = 61.1 millions
- EU: 508.3 x 15.6% = 79.2 millions
Agenda

► Present Status of Pediatric Drug Development

► Current Situation in Japan

► Future Challenges
Medicine approval in Japan including pediatric indications or dosages

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Paediatric</th>
<th>Ratio(%)</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>2014</td>
<td>119</td>
<td>39</td>
<td>32.8</td>
</tr>
</tbody>
</table>
Approval of pediatric drugs by therapeutic area

- Oncology Products: 9%
- Reproductive & Urologic Products: 7%
- Antimicrobial Products: 15%
- Antimicrobial Products: 15%
- Antimicrobial Products: 15%
- Vaccines: 15%
- Pulmonary, Allergy & Rheumatology Products: 15%
- Gastroenterology Products: 11%
- Metabolism & Endocrinology Products: 9%
- Cardiovascular & Renal Products: 9%
- Neurology & Psychiatry Products: 3%
- Others: 4%

N=162 FY2009 -2013
No special regulation for obligatory development of medicines in children
Incentive?

- Extension of re-examination period
- Public knowledge-based application
- Council on Unapproved Drugs /Off-label Use
Extension of re-examination period

Re-examination period of New Drug 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>

※Re-examination period is similar to marketing exclusivity period.
Extension of re-examination period

Re-examination period can be extended to utmost 10 years, if a clinical trial is planned to study pediatric dosage during or after marketing authorization application of a drug, taking into consideration the necessary time to conduct special drug use survey or post authorization clinical trials.

15 products granted so far.
Extension of re-examination period

4 products approved of pediatric dosage.

<table>
<thead>
<tr>
<th>Pediatric Dosage Approved</th>
<th>Study Completed</th>
<th>Study Ongoing</th>
<th>Study Status?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targocid®</td>
<td>Myslee®</td>
<td>Luvox®</td>
<td>SEIBULE®</td>
</tr>
<tr>
<td>Claritin®</td>
<td>IMIGRAN®</td>
<td>ABILIFY®</td>
<td></td>
</tr>
<tr>
<td>Allegra®</td>
<td>Adoair®</td>
<td>LONASEN®</td>
<td></td>
</tr>
<tr>
<td>Amaryl®</td>
<td>Paxil®</td>
<td>Adcirca®</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ONOACT®</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZILVA®</td>
<td></td>
</tr>
</tbody>
</table>

Source: Notification by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW
JAPIC Clinical Trial Information
ClinicalTrial.gov

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Medicinal Products of Pediatric Indication & Dosages in JAPAN

New Approval | Partial Change | Public Knowledge Based

<table>
<thead>
<tr>
<th>FY</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<td>3</td>
<td>12</td>
<td>14</td>
<td>15</td>
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<tr>
<td></td>
<td>11</td>
<td>14</td>
<td>19</td>
<td>20</td>
<td>22</td>
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</tbody>
</table>
As of July 10, 2015
## Case 1: Anti-rheumatic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>JAPAN</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>≥4y pJIA 2009.7</td>
<td>≥2y pJIA 1999.5</td>
<td>≥2y pJIA 2008.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2y pJIA 2008.2</td>
<td>≥2y pJIA 2008.7</td>
</tr>
<tr>
<td>adalimumab</td>
<td>≥4y pJIA 2011.7</td>
<td>≥2y pJIA 2011.4</td>
<td>≥2y pJIA (+MTX) 2008.4</td>
</tr>
<tr>
<td></td>
<td>≥2y sJIA 2008.4</td>
<td>≥2y sJIA 2011.5</td>
<td>≥2y sJIA 2011.5</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>≥2y pJIA / sJIA 2008.4</td>
<td>≥2y pJIA / sJIA 2011.4</td>
<td>≥2y pJIA (+MTX) 2009.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abatacept</td>
<td>N/A</td>
<td>≥6y pJIA 2008.4</td>
<td>≥6y pJIA (+MTX) 2009.12</td>
</tr>
<tr>
<td>canakinumab</td>
<td>CAPS 2011.9</td>
<td>≥4y CAPS 2009</td>
<td>≥2y CAPS 2009.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2y sJIA 2013.5</td>
<td>≥2y sJIA 2013.7</td>
</tr>
</tbody>
</table>

pJIA: Polyarticular juvenile idiopathic arthritis, sJIA: Systemic JIA
CAPS: Cryopyrin-associated periodic syndrome
## Case 2: Anti-hemophilic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Approval Date</th>
<th>Country</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eftrenanocog Alfa rFIX-Fc</td>
<td>FIX deficiency</td>
<td>2014.7.4</td>
<td>JAPAN</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>US</td>
<td>≥12y Hemophilia B Approved 2014.3.28</td>
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<td></td>
<td></td>
<td></td>
<td>EU</td>
<td>Haemophilia B MAA 2015.6.26</td>
</tr>
<tr>
<td>Efraloctocog Alfa rFVIII-Fc</td>
<td>FVIII deficiency</td>
<td>2014.12.26</td>
<td>JAPAN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US</td>
<td>≥12y Hemophilia A Approved 2014.6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EU</td>
<td>Haemophilia A MAA 2014.10.31</td>
</tr>
</tbody>
</table>
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Efforts on early approval of pediatric drugs in PMDA

- Pediatric working group in PMDA
- International collaboration
- Pharmaceutical affairs consultation on R & D strategy
Established in November 2011, Consists of 19 members (as of 2015/10)

International Collaborations

External Communications

Past reviews and cases consultations of pediatric drug development

Cross-Sectional Membership in PMDA
(From Review Section, Safety Section, etc.)

Analyses

Exchange views with domestic stakeholders

Internal Communications
5 Priority Areas

- Regenerative medicine
  (Cell- and tissue-based products)
- Cancer
- Difficult-to-treat diseases and rare diseases
- Pediatrics
- Other than the above, products utilizing particularly innovative technologies
To develop the better medicine for children

- Accelerating multi-regional pediatric studies
- Organization and utilization of collected knowledge through review/consultation
- Contribution to development of new technologies e.g. Modeling & simulation
  Biomarker
The better medicine for children!

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Ask