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Office of Vaccines and Blood Products
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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) → Waiver

Deferral

Phase I → Phase II → Phase III → NDA Submission

US

FDA (PeRC)

PSP (Pediatric Study Plan) / Written Request

FDASIA (FDA Safety & Innovation Act 2012)

Best Pharmaceuticals for Children Act (BPCA)

Pediatric Research Equity Act (PREA)

FDASIA (FDA Safety & Innovation Act 2012)

Post marketing

Written Request
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

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (in billions)</th>
<th>Percentage</th>
<th>Total (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>7125</td>
<td>26.3%</td>
<td>1868</td>
</tr>
<tr>
<td>Japan</td>
<td>127.1</td>
<td>13.0%</td>
<td>16.5</td>
</tr>
<tr>
<td>US</td>
<td>320.0</td>
<td>19.1%</td>
<td>61.1</td>
</tr>
<tr>
<td>EU</td>
<td>508.3</td>
<td>15.6%</td>
<td>79.2</td>
</tr>
</tbody>
</table>
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

N=162 FY2009 -2013

- Antimicrobial Products: 15%
- Vaccines: 15%
- Pulmonary, Allergy & Rheumatology Products: 15%
- Gastroenterology Products: 11%
- Cardiovascular & Renal Products: 9%
- Metabolism & Endocrinology Products: 7%
- Reproductive & Urologic Products: 4%
- Neurology & Psychiatry Products: 3%
- Others: 15%
- Oncology Products: 5%
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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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 2009.7</td>
<td>≥2y pJIA 2008.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adalimumab</td>
<td>≥4y pJIA 2011.7</td>
<td>≥4y pJIA 2008.2</td>
<td>≥2y pJIA 2008.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tocilizumab</td>
<td>≥2y pJIA / sJIA 2008.4</td>
<td>≥2y pJIA / sJIA 2011.4</td>
<td>≥2y pJIA (+MTX) 2008.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥2y sJIA 2011.5</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>canakinumab</td>
<td>CAPS 2011.9</td>
<td>≥4y CAPS 2009.7</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></th>
<th><strong>JAPAN</strong></th>
<th><strong>US</strong></th>
<th><strong>EU</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eftrenanocog Alfa rFIX-Fc</strong></td>
<td>FIX deficiency Approved 2014.7.4</td>
<td>≥12y Hemophilia B Approved 2014.3.28</td>
<td>Haemophilia B MAA 2015.6.26</td>
</tr>
<tr>
<td><strong>Efraloctocog Alfa rFVIII-Fc</strong></td>
<td>FVIII deficiency Approved 2014.12.26</td>
<td>≥12y Hemophilia A Approved 2014.6.6</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**
  - FDA
  - Health Canada
  - EMA
  - TGA

- **External Communications**
  - Exchange views with domestic stakeholders

- **Past reviews and cases consultations of pediatric drug development**

- **Analyses**

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

- **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
Thank you for your attention

The better medicine for children!

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PMDA (Pharmaceuticals and Medical Devices Agency)
Web: http://www.pmda.go.jp/english/index.html
Ask