PMDA perspective and experience with long-term safety study data collection in children

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Pediatric Drugs Working Group
April 13, 2016
Outline

• **Introduction**
  - PMDA Pediatric Drugs WG

• **Post-marketing data collection of long-term safety in children in Japan**
  - Post-marketing surveillance
  - Examples on long-term safety in children
  - Limitations

• **Future challenges**
  - Disease registries
  - Electronic healthcare data
  - Pediatric medical information gathering system
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- Future challenge
  - Disease registries
  - Electronic healthcare data
  - Pediatric medical information gathering system
Pharmaceuticals and Medical Devices Agency

Date of Establishment: April 2004

Major Responsibilities

- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials
- Safety Measures
- Relief Services

Work in close relationship with Ministry of Health, Labor and Welfare (MHLW)
New Drug Approval

<table>
<thead>
<tr>
<th>J-FY*</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>103</td>
<td>114</td>
<td>131</td>
<td>133</td>
<td>128</td>
<td>119</td>
</tr>
<tr>
<td>Paediatric</td>
<td>19</td>
<td>26</td>
<td>35</td>
<td>44</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Ratio(%)</td>
<td>18.4</td>
<td>22.8</td>
<td>26.7</td>
<td>33.1</td>
<td>29.7</td>
<td>32.8</td>
</tr>
</tbody>
</table>

* J-FY is from April to March next year.

Pharmaceuticals and Medical Devices Agency (PMDA)
PMDA Pediatric Drugs WG

- One of the projects across multi-offices in PMDA
- Established in November 2011

**International Collaborations**

Collaboration at Pediatric Cluster

**External Communications**

Discuss pediatric issues with domestic stakeholders

**Analyses**

Analyze and identify pediatric issues raised in past reviews and consultations

**Internal Communications**

Members from Offices of New Drug, Office of Safety, Office of Regulatory Science, etc.
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## Framework of post-marketing safety measures in Japan

<table>
<thead>
<tr>
<th>REVIEW</th>
<th>APPROVAL</th>
<th>POST APPROVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR AND INFECTION REPORTING</td>
<td>RMP</td>
<td>ADR AND INFECTION REPORTING</td>
</tr>
<tr>
<td>APPROVAL CONDITION</td>
<td>EPPV (Early Post-marketing Phase Vigilance) (6MONTH)</td>
<td>Periodic safety reports PSUR/PBRER</td>
</tr>
<tr>
<td>PLAN OF POST APPROVAL SURVEYS AND STUDIES</td>
<td>Post-marketing Surveillance (If necessary) Post-marketing Clinical Trials</td>
<td>RE-EXAMINATION 4-10 Y AFTER</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RE-EVALUATION If necessary</td>
</tr>
</tbody>
</table>

Limited data pre-market

⇒ Continued data collection post-market is important
Post-marketing surveillance

• Conducted in almost all drugs to collect efficacy and safety information under the real clinical use

• May include investigation on long-term treatment, use in children, elderly and patients with renal or hepatic impairment, etc.

• Confirm Adverse Reactions (ARs) of interest, unknown ARs, and factors considered influential to efficacy and safety of the drug

• All-case surveillance are required when limited data available at the time of review, orphan products
Example of surveillance on long-term safety in children

**LIVALO (Pitavastatin Calcium)**

- **Pediatric indication**
  - Familial Hypercholesterolaemia (FH)

- **Date of approval (for pediatric indication)**
  - June 9, 2015

- **Evaluation of efficacy and safety at the time of approval (for pediatric indication)**

<table>
<thead>
<tr>
<th>Location</th>
<th>Age</th>
<th>Number of Patients</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan Phase III</td>
<td>10-15yrs</td>
<td>Male FH, 14 patients</td>
<td>52 week</td>
</tr>
<tr>
<td>Foreign Phase III</td>
<td>6-16yrs</td>
<td>Dyslipidemia, 106 patients</td>
<td>12 week</td>
</tr>
<tr>
<td>Foreign Phase III</td>
<td>6-16yrs</td>
<td>Dyslipidemia, 113 patients</td>
<td>52 week</td>
</tr>
</tbody>
</table>

ARs in long-term treatment
Example of surveillance on long-term safety in children

- Concerns on long-term safety in children at the time of approval

**Growth retardation**
- Pharmacologically, statins are expected to influence cholesterol-derived hormonal system
- In children of growth age, reduction of sex hormones due to drug treatment may cause retardation in pubertal growth
- In the clinical studies, no apparent effect of Pitavastatin was observed on sex hormones (testosterone, estrogen), height or weight

However,
- Patients enrolled in clinical studies are limited
- The drug is expected to be administered over long period

The applicant was requested to set the greatest possible surveillance period in post-marketing surveillance
Example of surveillance on long-term safety in children

- **Post-marketing surveillance (on going)**

<table>
<thead>
<tr>
<th>Planned number of patients</th>
<th>All-case surveillance (100 patients expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance period</td>
<td>From the start of administration <strong>to the end of administration or three years after approval</strong>, whichever is earlier</td>
</tr>
<tr>
<td>Survey items</td>
<td>Lipid parameters, laboratory values related to Rhabdomyolysis, renal and hepatic function test values, <strong>information related to growth</strong>*, etc.</td>
</tr>
</tbody>
</table>

*Information related growth: height, weight, Tanner stages, testicular volume, menarche
Example of surveillance on long-term safety in children

**Ciproxan - I.V. (Ciprofloxacin)**

▶ **Pediatric indication**
- <applicable microorganisms>B. anthracis, E.coli, P. aeruginosa</applicable microorganisms>
  <indication>Complicated cystitis, Pyelonephritis, Anthrax,
  Respiratory infection from Pseudomonas aeruginosa in cystic fibrosis

▶ **Date of approval (for pediatric indication)**
- June 9, 2015

▶ **Evaluation of efficacy and safety at the time of approval (for pediatric indication)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Patients</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign Phase III 1-17 yrs</td>
<td>Complicated cystitis or Pyelonephritis, 684 patients</td>
<td>10-21 days</td>
</tr>
<tr>
<td>Foreign Phase III 5-18 yrs</td>
<td>Cystic fibrosis patients with acute pulmonary exacerbation, 129 patients</td>
<td>12 week</td>
</tr>
<tr>
<td>Japan pediatric utilization study</td>
<td>187 patients</td>
<td></td>
</tr>
</tbody>
</table>

AR follow-up after treatment
Example of surveillance on long-term safety in children

- Concerns on long-term safety in children at the time of approval
  - **Arthropathic disorder**
    - ✓ Risk of arthrotoxicity is suggested in children in use of quinolone antimicrobial agents including ciprofloxacin
    - ✓ In foreign clinical studies, incidence of arthropathy until one month after treatment and until one year after treatment were greater compared to placebo
    - ✓ There were cases occurring more than one year after treatment

Long-term follow-up was considered necessary since arthropathic disorder had been observed after certain period from the end of treatment
Example of surveillance on long-term safety in children

- **Post-marketing surveillance (on going)**

<table>
<thead>
<tr>
<th>Planned number of patients</th>
<th>45 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance period</td>
<td>Until one month after the end of administration. Whenever possible, arthropathic disorder should be surveyed up to one year after the end of administration</td>
</tr>
<tr>
<td>Survey items</td>
<td>Patient characteristics, information on administration, concomitant drugs, susceptibility of the clinical isolates, arthrotoxicity and related AEs, other AEs, efficacy (clinical and bacteriological efficacy), etc</td>
</tr>
</tbody>
</table>
From the examples of surveillance on long-term safety in children

✓ Long-term surveillance is required when the drug is for long-term use or when there is any specific safety concern (e.g. growth retardation, ARs expected after treatment)

✓ When there is any specific safety concern, it is included in the survey items to allow follow-up

✓ Duration of surveillance is determined product by product depending on expected duration of treatment, experience in clinical studies, and safety information of interest
Limitations of post-marketing surveillance on long-term safety in children

Post-marketing surveillances is beneficial

— Allow follow-up of specific safety information in real clinical use
— Useful especially when pre-market data is limited; NMEs, orphan products

However,
• Non-interventional, mostly uncontrolled
• Several survey items; resource limitations in long-term follow-up

Other options for collecting data on long-term safety?
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Disease registries

Building clinical development infrastructure utilizing disease registries
- Clinical Innovation Network -

| National Centers (Development of Disease Registries) |
|---------------------|---------------------|---------------------|---------------------|
| Cancer (NCC)        | Psychiatry (NCNP)   | Children (NCCHD)    | Others              |

Integrate disease information incl. lab results

Share disease information (while protecting personal information)

Medical Institutions in cooperation

Access

(Expectations)
- Smooth and efficient conduct of clinical trials
- Stimulation of drug development in Japan
- Accelerated development of new drugs

- What are expected number of enrollment?
- Where can patients eligible for trials be found?

The registry provides information on rough number of patients and where they are

Long-term follow up is possible including diseases where accumulation of cases is difficult
Electronic healthcare data

**MID-NET Initiative**

MID-NET (Medical Information Database NETwork) is initiated by MHLW / PMDA to establish the EMR DB network for post-marketing drug safety measures using electronic healthcare data.

- Use of healthcare data from various data sources (incl. lab results)
- Data can be used almost real-time
Pediatric medical information gathering system

Development of database for collecting, evaluating and analyzing the following information in children:
- Dosage of drug
- Administration of drug
- Adverse reactions

- Development of new drugs
- Safety measures

Better medicine for children

JACHRI: Japanese Association of Children’s Hospitals and Related Institutions
Conclusions

- In Japan, long-term safety in post-market is mainly evaluated by post-marketing surveillance.
- Post-marketing surveillance allows follow-up of safety information in real clinical use, however, non-interventional and resources are limited.
- Recent effort on building/utilizing patient registries, electronic healthcare data and pediatric medical information gathering system are expected to expand the measure of long-term safety evaluation.

Effort will be continued to develop framework and utilize surveillance/study for an enhanced safety data collection and evaluation.
Thank you for your attention!
Back up
Responsibilities of MHLW and PMDA

[MHLW]  (厚生労働省)

Planning basic policy, enforcement of administrative measures, such as approval, administrative order, etc, which are based on the PAL (薬事法)

- Final judgment on approval
- Directions of withdrawal and issuance of emergency safety information
- Safety measures for emergent and significant cases

[PMDA]  (医薬品医療機器総合機構)

Implementation of work, such as review, examination, data analysis, etc before administrative measures

- Scientific review of Pharmaceuticals and Medical Devices
- GLP/GCP/GMP/QMS inspection, Clinical trial consultation
- Collection, examination, analysis, assessment and provision of ADR information
Preparation of the protocol of EPPV

Delivery of new drugs to medical institutions

every 2 wks

once a month

giving information by visiting, letters, FAX, E-mail etc.

Reports of Adverse Reaction
Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV

- EPPV was introduced in October 2001.
Legislation of the GPMSP

- Good Post-marketing Study Practice (GPMSP) was legislated in 1997
- It was revised in 2001, Early Post-Marketing Phase Vigilance (EPPV) was introduced

Subsequently...

- GPMSP divided into Good Post-marketing Study Practice (GPSP) and Good Vigilance Practice (GVP) by the revised Pharmaceutical Affairs Act in 2005
Periodic Safety Reports & Reexamination

- Approval
  - EPPV
  - Periodic Safety Reports
  - ADR and infection report
- Reexamination
  - 4-10 years (8 years in principle for Drugs with New Active Ingredients)
  - If necessary
- Reevaluation
  - 6 months
Contents of Periodic Safety Reports

• Survey period and Number of cases surveyed
• Shipped quantity
• Surveillance results summary and results of analysis
• Occurrence of different types of adverse reactions
• Listing of cases of adverse reactions
• Regulatory measures adopted
• Package inserts
• Future safety measures in light of surveillance results

PBRER /PSUR (If a drug markets in a foreign country)
ADR Reporting by Companies

- Reporting by FD
- Reporting by paper documents
- Electronic reporting transmitted by internet

Note: Direct Investigation by PMDA according to the electronic/Fax/Postal mail reporting from medical institutions has also started since July 2010 (limited in the case of death or severe ADR)
Post-marketing review of New Drugs in Japan

- Post-marketing safety and efficacy of new drugs are reviewed a certain period after the approval for marketing authorization.
- Generic drugs are not approved for the marketing prior to the post-marketing review of corresponding new drugs. Equal to the exclusive sales period for new drugs.

<table>
<thead>
<tr>
<th>Terms for post-marketing review</th>
<th>Type of Drugs</th>
</tr>
</thead>
</table>
| 10 years                       | • Orphan Drugs  
                              | • Drugs required long-term pharmacoepidemiological study |
| 8 years                        | • Drugs with new active ingredients |
| 4 years                        | • New combination drugs  
                              | • Drugs with a new route of administration |
| 4-6 years                      | • Drugs with a new indications  
                              | • Drugs with a new dosage |

The term can be extended up to 10 years if IND for pediatric study is applied.
Evaluation of surveillance result

Post-marketing Surveillance

(If necessary) Post-marketing Clinical Trials

Periodic Safety Report (Submitted with PSUR)

Re-examination

- Reconfirmation of the clinical usefulness of drugs after approval
- Timing for re-ex is designated at the time of their approval as new drugs.
- NDAs: 8 years (maximum 10 years)

Evaluation of long-term safety
- Evaluate result of long-term surveillance
- Comparison of ARs with short-term use and pre-market data from clinical studies (incidence, profile, severity, outcome), evaluation of specific safety concern
- Overall assessment including related information (ADR, literature, safety measures taken abroad)
Re-examination

• Aim: reconfirmation of the clinical usefulness of drugs after approval
• Timing of re-examination: designated by MHLW at the time of their approval as new drugs.
  – new drug substance: 8 years (maximum 10 years)
• Rationale for necessity of Re-examination
  – Unknown adverse events/effects must be identified by being used for many people after approval since the number of patients is limited in clinical trials.
  – While patient’s conditions, such as age, complications, dose, concomitant medications and so on, are well controlled in clinical trials, practical use of a drug is different from the use in clinical trials.
Re-examination (cont.)

- Surveys and studies required for re-examination applications: in compliance with the GPSP, GCP or GLP depending on their objective
- Result of Re-examination is following;
  1. Withdrawal
  2. Restriction or modification of indications
  3. No action
The revised Pharmaceutical Affairs Act in 1979 (enacted in 1961)

- Re-examination system (6 years after approval) was introduced
- Re-assessment system was legislated
- ADR reporting system from MAH was legislated (duty)
- Introduction of emergency order such as temporarily stop the sale or recall
Re-evaluation

• Aim: reconfirmation of the quality, efficacy and safety of approved drugs based on the present level of medical and pharmaceutical science.
• Drugs to be re-evaluated: designated by MHLW if needed.
• Rationale for necessity of Re-evaluation: when the usefulness of an approved drug is evaluated by the present standard, the usefulness sometimes disappears because more effective and/or safer drugs might be approved over time.
• Results of Re-evaluation are following;
  1. Withdrawal
  2. Restriction or modification of indications
  3. No action
### Disease registries currently being developed by National Centers (NC)

<table>
<thead>
<tr>
<th>NC</th>
<th>Targeted disease areas</th>
<th>Main registration</th>
<th>Number of participating institutions</th>
<th>Target number of patients and registration period</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Center</td>
<td>orphan cancer (soft tissue sarcoma, cutaneous tumor, childhood tumor)</td>
<td>Registered clinical trial information</td>
<td>56</td>
<td>100-150 patients/year</td>
</tr>
<tr>
<td>National Cerebral and Cardiovascular Center</td>
<td>adult congenital heart disease, stroke, heart failure, fetal arrhythmia</td>
<td>Age, gender, registered (main) name of disease, date of administration and discharge from the hospital, severity of disease, lab results, treatment history, comorbid disease, medications, stage, family history, clinical trial information, lifestyle, etc.</td>
<td>100</td>
<td>2000-3000 patients/year</td>
</tr>
<tr>
<td>National Center of Neurology and Psychiatry</td>
<td>psychiatric disorder, Parkinson('s) disease, inherited muscle disorder including muscular dystrophy</td>
<td></td>
<td>31</td>
<td>15000 patients (End FY2018)</td>
</tr>
<tr>
<td>National Center for Global Health and Medicine</td>
<td>diabetes mellitus</td>
<td></td>
<td>200</td>
<td>1 million patients (End FY2019)</td>
</tr>
<tr>
<td>National Center for Child Health and Development</td>
<td>Orphan Diseases, intractable diseases in children</td>
<td></td>
<td>33</td>
<td>30000 patients</td>
</tr>
<tr>
<td>National Center for Geriatrics and Gerontology</td>
<td>mild cognitive impairment, sarcopenia</td>
<td></td>
<td>22</td>
<td>More than 4000 patients</td>
</tr>
</tbody>
</table>