PMDA update for post-Market Safety and Quality Management

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  - MID-NET: Full scale utilization from 2018 FY
  - Revision of Guidance for Description of PI
  - Promoting English Translation of PI

- Quality management
  - Status of on-site inspection
  - Participation in API Program
  - Activities related to PIC/S
Overview of the regulatory schemes of pharmacovigilance in Japan

EPPV: Early Post-marketing Phase Vigilance (6 months intensive monitoring)
RMP: Risk Management Plan
Re-EX: Re-examination
Re-EVA: Re-evaluation
Limitations of conventional PV data

- Under-reporting of ADR (Reporting biases)
- Lack of adequate denominator information of drug utilization for estimation of risk
- Not available of the comparative incidence rates between drugs in real-world use surveys that have no comparison group
- Sometimes difficult to distinguish ADR from events associated with underlying diseases or other factors

To strengthen post-marketing drug safety measures in PMDA by developing new safety assessment framework using Japanese medical information databases etc.
Advantages of utilizing EHR

I. Collecting information of ADRs not only for a targeted drug but also for other drugs and overall number of patients automatically
II. Comparing frequency of a certain AE among some drugs.
III. Discriminating AEs from disease-based symptoms.

Overall number of Patients

Comparison of frequency among Drugs

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ADRs / Number of Patients to be administered</td>
<td></td>
</tr>
</tbody>
</table>

Discrimination of AEs from other factors

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Not administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ADRs / Number of Patients to be administered or not</td>
<td></td>
</tr>
</tbody>
</table>

Drug B has higher frequency rate than the Drug A

Drug A doesn’t relate to the AEs
MID-NET® established by MHLW / PMDA is the real-time medical information DB network system for post-marketing drug safety studies.

Database in each hospital
Common data model
- Diseases
- Drugs
- Procedures
- Labo test
- Claims
- Others

Distributed databases
10 institutions (23 hospitals)

Tohoku Univ.
NTT Medical Center
Kyushu Univ.
Saga Univ.
Tokushukai Group
UTokyo Chiba Univ.
Kagawa Univ.
HUSM
Kitasato Inst.
Overview of MID-NET®

Onsite Center

User

① Create program

② Request for running program

⑦ View & Analysis

⑨ Send only summarized data (not individual data)

Central data center

⑧ Output

User

③ Approve the request

⑤ Approve to send data

⑥ Send data

Hospitals

Technical staff for MID-NET

④ Output

Original databases

Medical record

Labo test data

Claims

Others

Standardization Anonymization

Common data model database for MID-NET

SAS® etc

SAS® etc

SAS® etc

individual level data

Summarized data

SAS® etc

individual level data

Summarized data

AND/OR

Summarized data

Summary data

Send only summarized data

Send only summarized data (not individual data)
### MID-NET® Pilot study: Example 1: Risk of respiratory depression associated with Codeine

Patients with prescription of codeine-containing products (Excluding patients with cancer)  
\[ n = 7,267 \]

#### Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Age Range</th>
<th>Number of Patients</th>
<th>% of Total</th>
<th>% to Source Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1</td>
<td>&lt; 12 years old*</td>
<td>209</td>
<td>2.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td>12-18 years old*</td>
<td>199</td>
<td>2.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Subgroup 3</td>
<td>&gt;= 19 years old*</td>
<td>6,859</td>
<td>94.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Age at first prescription

---

**Number of patients (n)**  
- **Total**: 7,267  
- **Subgroup 1**: 209  
- **Subgroup 2**: 199  
- **Subgroup 3**: 6,859

**% to source population**  
- **Total**: 0.7  
- **Subgroup 1**: 0.2  
- **Subgroup 2**: 0.5  
- **Subgroup 3**: 0.8

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**MID-NET®** (2009～2015)

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*Excluding patients with cancer*
### MID-NET® Pilot study: Example 1:
Risk of respiratory depression associated with Codeine

Possible cases causing respiratory depression during administration of codeine-containing products

<table>
<thead>
<tr>
<th></th>
<th>Case (n)</th>
<th>Patients in the cohort (n)</th>
<th>%</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>24</td>
<td>7,267</td>
<td>0.3</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td><strong>Subgroup 1</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&lt; 12 years old</td>
<td>209</td>
<td>209</td>
<td>-*2</td>
<td>0.0-1.0</td>
</tr>
<tr>
<td><strong>Subgroup 2</strong></td>
<td>0</td>
<td>199</td>
<td>0</td>
<td>0.0-0.0</td>
</tr>
<tr>
<td>12-18 years old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup 3</strong></td>
<td>-</td>
<td>6,859</td>
<td>-</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>&gt;=19 years old</td>
<td>-*2</td>
<td></td>
<td>-*2</td>
<td></td>
</tr>
</tbody>
</table>

※1 Definition of respiratory depression
① Prescription of drugs for respiratory depression (i.e.; levallorphan, naloxon)
② Diagnosis with disease relating to respiratory depression (i.e.; dyspnea, acute respiratory failure, respiratory failure) and use of oxygen inhalation

※2 masked due to small sample size
MID-NET® Pilot study: Example 2: Effects of safety measures on hypocalcemia risk during denosumab prescription

Launched (2012.4.17)

Spontaneous ADR reports
- Serious Hypocalcemia: 32 cases
- Death: 2 cases
(〜2012.8.31)

Dear healthcare professionals letter (Blue letter) (2012.9.12)

Traditional process

Label change

Blue letter

Proportion (%)

Denosumab
Zoledronate
Risk ratio

Risk Ratio

MID-NET® - Driving insights to action
Current issues

- Current GPSP only cover primary data-collection studies, but not database researches
  - Most of all post marketing studies under GPSP are single cohort studies (usually 3,000 patients) with ambiguous research questions.

Amendment of GPSP is planned to be published in Autumn of 2017

- Database researches are clearly covered in the new GPSP.
  - comparative observational studies with clear research questions are required.
Full-scale utilization of MID-NET will start from FY2018. When do we need to consider Post-market surveillance, including MID-NET?

Current NDA review time is around 1 year. Pharmaceutical companies filing NDA should consider soon. PMDA consults for MID-NET utilization, if necessary. The user fee and procedures will be announced soon.
Revision of Guidance on Description of PI

Background & Purpose:
➢ The researches of Health Labour Sciences Research Grant recommended to make PI, package insert, more user friendly and easier to understand

1. Revision of items
➢ Delete “Relative contraindication” and “Careful Administration”
➢ Establish “Precautions for Specific population” such as Elderly, Pediatrics, Renal impairment and etc.

2. Introduction of Numbering
MHLW published the notification of the revision in this month with 5 years for preparation to revise PI by MAHs.
Promoting English Translation of PI

In order to strengthen international safety communication, Guidance for English translation of PI will be developed.

- Correct translation of the intention of the Japanese description
  Ex.「本剤投与を直ちに中止すること」: administration of this drug can/should be discontinued immediately
  The intention is much different between “can” and “should”.

- Unifying the fluctuation of the English translation of the adverse reaction

  - Two Japanese terms corresponding to an English word are available.
    As “Hepatic dysfunction" and “Hepatic failure” is not strictly used properly in Japanese, English terms are unified.
  
  - Two English terms corresponding to a Japanese term are available.
    Guidance to unify the terms according to different nuances by organ

<table>
<thead>
<tr>
<th>Japanese</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>不全</td>
<td>failure</td>
</tr>
<tr>
<td>肝機能障害</td>
<td>Hepatic function dysfunction</td>
</tr>
<tr>
<td>肝障害</td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Post-Market Safety

- MID-NET: Full scale utilization from 2018 FY
- Revision of Guidance for Description of Labeling
- Promoting English Translation of Labeling

Quality management

- Status of on-site inspection
- Participation in API Program
- Activates related to PIC/S
Inspection History 1: 2006.4～2008.3

On-site Inspection
※Foreign Countries
（139 Applications, 18 Countries）
### Inspection History 2: 2014.4～2017.3

**On-site inspection**

<table>
<thead>
<tr>
<th></th>
<th>APIs/Solid dosage form</th>
<th>Sterile</th>
<th>Bio</th>
<th>Radioactive</th>
<th>Packing/Labeling</th>
<th>Testing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>307</td>
<td>113</td>
<td>107</td>
<td>18</td>
<td>16</td>
<td>13</td>
<td>574</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>53</td>
<td>20</td>
<td>19</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

About 53% of inspections were focused on APIs/Solid dosage form.

<table>
<thead>
<tr>
<th>Country</th>
<th>Asia</th>
<th>Japan</th>
<th>EU</th>
<th>North America</th>
<th>South America</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Inspection “APIs only”</strong></td>
<td><strong>190</strong></td>
<td>40</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>251</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>76</td>
<td>16</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

About 76% of inspections were held in Asia.
Inspection History 2-2: 2014.4～2017.3

On-site Inspection

※Foreign Countries （293 Applications, 21 Countries）

EU

China [値]
India [値]
Asia

South Korea [値]
Taiwan [値]

North America

U.S.A [値]

Japan

Turkey [値]
Spain [値]
Austria [値]
Latvia [値]
Belgium [値]
France [値]
Hungary [値]
Malaysia [値]
Singapore [値]
Thailand [値]
Vietnam [値]
Indonesia [値]
Cyprus [値]
Slovakia [値]
Germany [値]
Unannounced Inspection

Notification issued: January 15, 2016
Yakushokukanmahatsu 0115-2 Manager of Compliance and Narcotics Division
Pharmaceutical Safety and Environmental Health Bureau, MHLW

“To be exhaustive to conduct Regular Inspections for Pharmaceutical Products”

**Purpose:** Prevent fraud and confirm GMP compliance condition

**Scope sites:** Manufacturing sites for
- Plasma products, Vaccines, Biologics, and Placenta products

◆ Unannounced inspection other than above products may be conducted, if necessary
What did Unannounced Inspection revealed?

**Necessary to improve Data and Process Authenticity**

1. Operator uses own memos instead of approved SOP
   ⇒ Insufficient SOP and records & Insufficient training (OJT etc.)
2. Re-test conducted without deviation or OOS procedure.
   First test records weren’t keep as a GMP document.
   ⇒ Risk that rejected results change to pass
3. Test samples which has no clear usage and no record of quantity
   ⇒ Risk that use those for re-test
4. Raw data and records are rewriting and make a fair copy
   ⇒ Not raw data & Lack of understanding of GMP records
   ⇒ Issuance of test records management is insufficient

**Reconsider Fundamental Management System of GMP!**

5. Records and documents which has no indication were kept in warehouse and office
   ⇒ Documents and records are without control
   ⇒ No traceability
   ⇒ Not complying with documents retention period
6. Leave disposal
November 24, 2016, Japan joined ongoing collaboration on GMP inspections of active-pharmaceutical-ingredient (API) manufacturers between EMA and its international partners.

- Enhancing quality, safety and efficacy of medicines globally
- Sharing information on inspections, including planning, policy and reports, for manufacturers of APIs that are located outside the participating countries.
- Increasing cooperation and mutual reliance between regulators participating in the initiative, as well as to ensure the best use of inspection resources worldwide.

Member: EMA, EU Member States and the European Directorate of the Quality of Medicines and Healthcare (EDQM), US-FDA, the Australian Therapeutic Goods Administration (TGA), Health Canada and the World Health Organization
Activates related to PIC/S

**Conference, meetings held in Japan**
- **2014.12**
  - QRM (Quality Risk Management) Expert Circle
- **2016.12**
  - GMP Inspection seminar organized by PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) with the support of PIC/S at Toyama

**Guideline WG**
- Revision of Annex 1
- Data Integrity
- Classification of deficiencies
- ATMP Aide-memoire

**Information Exchange**
- Submit Inspection Schedule
- Exchange Inspection report
PMDA-ATC

PMDA-ATC (PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs)

GMP Inspection Seminar (Mock Inspection)
December 5th–9th, 2016 Toyama, Japan
Cooperate with JPMA

Specially skill up and harmonize GMP inspector’s skills within Asia

Risk based Inspection Planning
Understand Product Quality Risk
Data Integrity

Improve GMP levels of Manufacturing sites within Asia

PMDA-ATC GMP Inspection Seminar 2016
(From PMDA Website)

Introduction
The Pharmaceuticals and Medical Devices Agency (PMDA) is pleased to announce the holding of the PMDA-ATC GMP Inspection Seminar 2016. This Seminar is organized by PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) with the support of PIC/S.

This "PMDA-ATC GMP Inspection Seminar 2016" will be a five-day seminar for GMP inspectors from regulatory authorities, held in Toyama prefecture, Japan.

The principal object of this Seminar will be Risk-based Inspection and Data Integrity. We will offer practical training in the form of a mock inspection.

Target participants will be GMP inspectors at beginner or intermediate level. This Seminar will enable Inspectors to conduct risk-based GMP inspection.

Participation from many regulatory authorities is welcomed.

Key Seminar Objectives
The Seminar is designed to address three key areas:
PMDA update for post-Market Safety and Quality Management

Thank You

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