PMDA update for post-Market Safety and Quality Management

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Chief Safety Officer
Pharmaceuticals and Medical Devices Agency
Contents

- Post-Market Safety
  - 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

Diagram:
- NDA Approval: 1 year
- Planning of RMP
- Condition of Approval
- Spontaneous ADR Reporting
- Real-world use survey
- If necessary PM Clinical Trial
- Periodical reporting
- EPPV
- 4-10 years
- Re-EX
- Re-EVA If necessary

If necessary
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

Drug A
ADR

Drug B
ADR

Drug B has higher frequency rate than the Drug A

Drug A

Number of ADRs / Number of Patients to be administered

Drug B

Discrimination of AEs from other factors

Drug A

Number of ADRs / Number of Patients to be administered or not

Drug B

Not administered

Drug A doesn’t relate to the AEs
“MIHARI” means a guard or a watch in Japanese.

MIHARI Project is:
- To utilize electronic healthcare records (EHR: health insurance claim data, medical records, etc) in order to evaluate possible safety issues more quickly and more securely.

In 2009-2013, more than 40 pilot studies were conducted to characterize the existing EHR databases and to develop phamacoepidemiological methodology to utilize EHR for quantitative risk evaluation of drugs.

In 2014, MIHARI project was formally launched as a regular safety assessment process of drugs.
Example: Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia

Overview of MID-NET System
Network of 10 hospital database from 23 hospitals

1. User/PMDA sends programs to 10 hospital consisting of 7 university hospital and 3 centers of 3 hospital groups.
2. Each hospital sends a result of analysis to data center.

3. User/PMDA access and analyzes the data using exclusive PC
   - Review results provided by hospitals
   - Conduct additional analysis by using these results
Data categories in the MID-NET system

- **Database**
  - HIS data
  - Claims data
  - DPC data

- **Outcome data**
  - Patient identifying data
  - Medical examination history data (including admission, discharge data)
  - Disease order data
  - Discharge summary data
  - Prescription order/compiled data
  - Injection order/compiled data
  - Laboratory test data
  - Radiographic inspection data
  - Physiological laboratory data
  - Therapeutic drug monitoring data
  - Bacteriological test data

- **HIS data**
In near future

**Quantitative risk assessment compared with control**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Number of patient with Hypocalcemia</th>
<th>Incidence proportion</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>190</td>
<td>93</td>
<td>0.489</td>
<td>1.35</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>245</td>
<td>89</td>
<td>0.363</td>
<td></td>
</tr>
</tbody>
</table>

Data from 3 hospitals (2013/7~12)

MID-NET will contribute to regulatory action (Trial analysis: Denosumab for Hypocalcemia)

**Spontaneous ADR reports** (~2012.8.31)
- serious Hypocalcemia: 32 cases
- death: 2 cases

**Dear healthcare professionals letter** (2012.9.12)

Launched (2012.4.17)
Challenges: Data quality, Cost and Human resources

1. Data quality
Matching rate between original data and MID-NET Data in A hospital

<table>
<thead>
<tr>
<th>Item</th>
<th>Rate before amendment</th>
<th>Rate after amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Name</td>
<td>99.1%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Prescription Order</td>
<td>67.0%</td>
<td>100%</td>
</tr>
<tr>
<td>Laboratory Test</td>
<td>55.8%</td>
<td>100%</td>
</tr>
</tbody>
</table>

2. Cost and Human resources
- Installation and system validation
- Maintenance
Full-scale utilization will start from FY2018

- Scope of the utilization of MID-NET
  Researches for drug safety, including B/R balance assessment, or receiving grants from the Gov.

- Users
  Regulators, Academia, Pharmaceutical companies and etc.

- Operational cost and user fee
  The user fee and procedures for utilization are discussed in the committee of MHLW.

MAHs can use MID-NET as one of the tools for the post-market surveillance. It is expected that a survey may become more scientific and results will be updated in each PBRER.
When do we need to consider Post-market surveillance, including MID-NET?

MAH will be able to use MID-NET as a Post-Market survey from 2018. Current NDA review time is around 1 year. MAH filing NDA should consider soon. PMDA consults for MID-NET utilization, if necessary.
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
- The revision of the guidance on description of PI is under processing.

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
The notification by MHLW will be published in near future with suitable term for preparation to revise PI by MAHs.
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>日本語</th>
<th>英語</th>
</tr>
</thead>
<tbody>
<tr>
<td>肝機能障害</td>
<td>Hepatic function dysfunction</td>
</tr>
<tr>
<td>肝障害</td>
<td>failure</td>
</tr>
<tr>
<td>不全</td>
<td>dysfunction</td>
</tr>
</tbody>
</table>
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  - 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)

North America
- U.S.A. 53
- Puerto Rico 11

EU
- France 17
- Denmark 18

Asia
- China 8
- Singapore 2
- Indonesia 3
- South Korea 1
- India 1

Other
- Belgium 1
- Finland 1
- Austria 1
- Italy 2
- England 4
- Netherland 4
- Ireland 5
- Spain 6
Inspection History 2: 2014.4～2016.3

On-site inspection

<table>
<thead>
<tr>
<th></th>
<th>APIs</th>
<th>Sterile</th>
<th>Bio</th>
<th>Radioactive</th>
<th>Packaging/Labeling</th>
<th>Testing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>148</td>
<td>85</td>
<td>95</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>363</td>
</tr>
<tr>
<td>%</td>
<td>41</td>
<td>26</td>
<td>23</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>100</td>
</tr>
</tbody>
</table>

About 40% of inspections were focused on APIs.

About 90% of inspections were held in Asia.
Inspection History 2-2: 2014.4~2016.3

On-site Inspection

※Foreign Countries (197 Applications, 20 Countries)

- China 69
- South Korea 33
- India 30
- Taiwan 18
- Indonesia 9
- Vietnam 3
- Thailand 1
- Malaysia 1
- Latvia 4
- Hungary 4
- Italy 5
- Belgium 3
- France 3
- Austria 1
- Germany 1
- Slovakia 1
- U.S.A. 6
- Turkey 2
- Spain 2
- Cyprus 1

North America

EU
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: Domestic Manufacturing sites manufacturing
  Plasma products, Vaccines, Biologics, and Placenta products

◆ Unannounced inspection other than above products may be conducted by
  unannounced, 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
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

Reconsider Fundamental Management System of GMP!
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 Annex1
- Data Integrity
- Classification of deficiencies
- ATMP Aide-memoire

Information Exchange
- Submit Inspection Schedule
- Exchange Inspection report
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 primal 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:
Thank you for your attention

Ask

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