Recent Trend on Utilization of Real World Data
- Challenges in Japan -

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Pharmaceuticals and Medical Devices Agency (PMDA)
Today’s Agenda

- Utilization of RWD for drug safety in PMDA
- New framework & infrastructure for reinforcing post-marketing drug safety measures by utilization of RWD
- Challenges for accelerating utilization of RWD
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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
Revised GPSP
Good Post-marketing Study Practice
(The Ministerial Ordinance, Implemented on April 1\textsuperscript{st} 2018)

Study frames in GPSP

- **Intervention**
  - Primary data collection
  - “Post marketing clinical trial”

- **Observation**
  - DB
  - “Post marketing database study”

- **Observation**
  - Primary data collection
  - “Post-marketing observational study with primary data collection”

**Newly created**

Revised GPSP clearly mentions that safety study based on database is acceptable for re-examination under the Japanese Pharmaceuticals and Medical Devices Law
Points to consider for ensuring the reliability in conducting post-marketing database surveillance (Notification No. 221, MHLW, Feb. 2018)

1. Scope of application

2. Definition of terms

3. Points to consider for ensuring the reliability in application documents for reexamination

App. Examples for DB vendors’ procedures about medical information databases for MAH to confirm

Pharmacoepidemiologic (PEpi) Assessment in PMDA

Role of Pharmacoepidemiologists

< In pre-approval >

• Review Risk Management Plan submitted by an industry to propose appropriate post-marketing studies etc.

< In post-approval >

• Conduct PEpi studies utilizing EMRs database for drug safety assessment

• Review PEpi data/reports submitted by industries etc.

Office of Safety (I and II)

Post-market evaluation

Office of New Drug (I - V)

Pre-market evaluation

Office of Medical Informatics and Epidemiology

Pharmacoepidemiologists

PMDA
post-marketing review/consult timeline for post-marketing database studies

- Identify Safety Specifications.
- Select the best pharmacovigilance (PV) activities to address safety concerns.
- Prepare and submit a draft RMP for agreement with PMDA.

- Develop protocols for post-marketing database studies.
  - feasibility analyses and validation studies may be conducted, if necessary
- PMDA provides scientific advice on a study protocol.
Procedures for Developing Post-Marketing Study Plan (January 23, 2018)

- Describes basic principle on how to plan a post-market study under Japanese pharmaceutical regulation
  - Four steps approach to plan an appropriate post-market study

Step 1~4 per each safety specification

Step 1. What is a concern to be clarified in post-approval?

Step 2. What is a suitable approach (i.e.; routine or additional PV)? If additional, what is the research question and suitable data source?

Step 3. If additional, which GPSP frame must be complied with? (clinical trial, observational study with primary data collection, database)

Step 4. If additional, creating a study protocol
Other related guidelines

• “Instructions for Post-marketing Database Study Protocols” (PMDA, Jan. 2018)

• A revision of “Case Examples of Risk Management Plan” (PMDA, Dec 2017), including a case of database study

• “Basic Principles on Use of Medical Information Databases in Post-marketing Pharmacovigilance” (Notification No. 609, MHLW, June 2017)

• “Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases” (PMDA, March 2014)

Many related guidelines focusing on Real World Data utilization were recently published in synchronization to the GPSP revision

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Data sources for post-marketing drug safety assessment

- **Conventional Information Sources**
  - Spontaneous ADR report DB
  - Overseas regulatory actions
  - Literatures
  - Presentation in Academic Conference
  - etc

- **Electronic Healthcare Data**
  - MIHARI
  - National claims DB
  - Other DB
  - Launched in 2009

- **PMDA**

- **MHLW**
  - Safety measures

- **Medical institutions**
  - Risk communication

**Data sources for post-marketing drug safety assessment**

**Conventional Information Sources**

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**PMDA**

**MHLW**

**Medical institutions**

**Risk communication**
The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently >4M patients).
- Officially launched in April 2018
- PMDA has led the project in cooperation with partner hospitals for establishing the high quality database
Key features of MID-NET®

• Distributed database in common data model format
• 23 medical institutions from 10 organizations
• 4 million patients in 2009-2017
• Real time update (every 1 week or 1-3M)
• MID-NET® holds medical records, claim data and prospective payment data for acute inpatient
• Standard codes available
• Laboratory test results available
• High data quality
MID-NET® common data model

- Local code of each content is mapped to standard code to analyze all hospitals data together.

### Example of standard code

<table>
<thead>
<tr>
<th>Contents</th>
<th>Standard Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>ICD-10</td>
</tr>
<tr>
<td>Drug</td>
<td>YJcode, HOT9</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>JLAC10</td>
</tr>
<tr>
<td>Bacteriological test</td>
<td>JANIS</td>
</tr>
</tbody>
</table>

- 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
Overview of MID-NET® System

Onsite Center

User

① Create program

② Request for running program

③ Approve the request

④ Output

Hospital

Technical staff for MID-NET

⑤ Approve to send data

⑥ Send data

⑦ View & Analysis

⑧ Output individual level data

⑨ Send only summarized data (not individual data)

Central data center

User

SAS® etc

Common data model database for MID-NET

Standardization Anonymization

Original databases

Medical record

Lab test data

Claims

Others

Individual level data

Summarized data

Summarized data

User

Send only summarized data (not individual data)

Send data
Data Quality of MID-NET®

- PMDA has worked with partner medical institutions and IT companies for assuring data quality of MID-NET®.
- We have checked consistency between the original data and the standardized data stored in MID-NET®.

**Before** quality management

- Original data
- Disease order data: 99.1%
- Prescription order data: 67.0%
- Laboratory test data: 55.8%

**After** quality management

- Original data
- Disease order data: 99.9%
- Prescription order data: 100%
- Laboratory test data: 100%

• Periodic data check will be needed to maintain the high data quality of MID-NET®.
MID-NET® pilot: Case 1
Active monitoring of abnormal lab test results during drug administration

**Objective**

✓ To examine a possibility to use MID-NET® for active monitoring of abnormal liver function associated with a drug

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**Study Design**

- **Launch**
- **First analysis** at 6 M
- **Second analysis** at 12 M
- **Third analysis** at 18 M
- **Final analysis** at Certain years after launch

Data period for third analysis
**MID-NET® pilot: Case 1**

Active monitoring of abnormal lab test results during drug administration

**Cohort**: New users of Alogliptin Benzoate or Vildagliptin for type 2 diabetes mellitus.

- **Exposed group**
  - Alogliptin Benzoate (n=2,039)
  - Vildagliptin (n=2,039)

- **Control group**
  - Alogliptin Benzoate (n=2,039)
  - Vildagliptin (n=2,039)

**Outcome definition** (abnormal liver function test result)

- ALT, AST or ALP: > URL ×5

**Incidence rate per 1,000 person-years**

- Alogliptin incidence rate
- Vildagliptin incidence rate
- Rate ratio

**Time point of observation (every 6M)**

1. **MID-NET®** (FY2009〜2015)
2. 1:1 matching gender, age, t₀
3. Pilot study Unpublished data

**Active monitoring of abnormal lab test results during drug administration**
MID-NET® pilot: Case 2
Risk of Acute Myocardial Infarction Associated with Anti-Diabetes Drugs

- **Objective**
  - Cardiovascular events associated with anti-diabetes drugs are common risk in post-marketing phase.
  - To compare the risk of acute myocardial infarction (AMI) associated with DPP-4 inhibitors monotherapy to other anti-diabetes drugs monotherapy.

- **Outcome definition (AMI)**
  - Definitive diagnosis of AMI,
  - Admission* and
  - Elevation of cardiac biomarker values* (CK or CK-MB: ≥ URL × 2 or Troponin T: ≥ 0.1ng/mL)
  *during 30 days before and after the diagnosis date of AMI

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Incidence Rate per 1,000 Person-years</th>
<th>Adjusted Rate Ratio (95%CI)</th>
<th>Adjusted Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sulfonylurea insulin secretagogues</td>
<td>2.4</td>
<td>1 [ref]</td>
<td>1 [ref]</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>2.1</td>
<td>0.86 (0.25-2.90)</td>
<td>0.93 (0.08-10.80)</td>
</tr>
</tbody>
</table>

Table. Adjusted rate ratio and adjusted hazard ratio for AMI in the standardized population.
Validation of Outcomes

• A new project was launched in 2017 to promote the conduct of reliable pharmacoepidemiological studies utilizing electronic medical records.

• PMDA and the partner medical institutions conduct validation studies on approximately 20 health outcomes.
  • To establish a clinically valid and reliable definition for an outcome based on the electronic codes in database.

<table>
<thead>
<tr>
<th>anaphylaxis</th>
<th>interstitial pneumonia</th>
<th>heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutropenia</td>
<td>rhabdomyolysis/myopathy</td>
<td>cerebral infarction</td>
</tr>
<tr>
<td>cerebral hemorrhage</td>
<td>acute coronary syndrome</td>
<td>acute/late-onset hepatic failure</td>
</tr>
<tr>
<td>severe skin disease</td>
<td>pulmonary thromboembolism</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>ventricular arrhythmias</td>
<td>supraventricular arrhythmia</td>
<td>bradyarrhythmia</td>
</tr>
<tr>
<td>acute pancreatitis</td>
<td>gastrointestinal perforation</td>
<td>Intestinal obstruction</td>
</tr>
</tbody>
</table>
Electronic Healthcare Databases in Japan

- **Electronic Medical Records Database**
  - Medical Information, Claims data etc
- **Dispensing Claims Database**
  - Claims data
- **Medical Institutions**
- **Dispensing Pharmacy**
- **Examination payment facility**
- **Insurer**
  - Claims data
- **Subscriber**
  - Healthcare Delivery
  - Issue Insurance cards
  - Copayment
  - Insurance Fee
- **Health Insurance Association’s Claims Database**
- **National Claims Database**
- **Ministry of Health, Labour and Welfare (MHLW)**

Image 1: Health Insurance Association's Claims Database

Image 2: National Claims Database

Image 3: Electronic Medical Records Database

Image 4: Dispensing Claims Database

Image 5: Medical Institutions

Image 6: Dispensing Pharmacy

Image 7: Examination payment facility

Image 8: Insurer

Image 9: Subscriber

Image 10: Healthcare Delivery
# Major Characteristics of Healthcare Data in Japan

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Electronic Medical Record data</th>
<th>Claims data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Health Insurance</td>
</tr>
<tr>
<td>Main Data Provider</td>
<td>Medical institutions</td>
<td>Insurers</td>
</tr>
<tr>
<td>Obtainable Health Information</td>
<td>Detailed information on medical practices by each institution</td>
<td>Standardized information relevant to reimbursement</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Medical procedure</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Pharmacy Dispensing</td>
<td>YES(on-site pharmacy)</td>
<td>YES</td>
</tr>
<tr>
<td>Laboratory test result</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Covered patients</td>
<td>People provided medical service by each institution</td>
<td>People enrolled in each health insurance system</td>
</tr>
</tbody>
</table>
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### Challenges and Actions for Accelerating Adequate Utilization of RWD

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conducting scientifically appropriate PMS</td>
<td>✓ Publish regulatory guidelines to promote post marketing studies utilizing RWD</td>
</tr>
<tr>
<td></td>
<td>✓ PMDA Consultations for planning PEpi Study</td>
</tr>
<tr>
<td>Ensure the quality of study plan &amp; results</td>
<td>✓ Amendment of GPSP and regulatory inspections</td>
</tr>
<tr>
<td></td>
<td>✓ Publish regulatory guideline on the reliability of post-marketing studies utilizing RWD</td>
</tr>
<tr>
<td>International cooperation</td>
<td>? More collaborations for sharing experiences and knowledge about utilization of RWD for regulatory purpose</td>
</tr>
<tr>
<td></td>
<td>? International harmonization on standards for data quality and analytical methods in utilizing RWD</td>
</tr>
</tbody>
</table>

*Scientific approaches and careful considerations in utilizing and evaluating RWD are the key to promote RWD utilization for regulatory purpose*
Active utilization of RWD toward advanced medical care

**Regulatory decisions based on better scientific evidences**
- Proper safety assessment utilizing RWD in addition to the traditional approaches

**RMP implementation utilizing RWD**
- Efficient risk management
- Better quality of safety information

**Provide leading-edge Medical Therapy with ensuring Safety**
- Scientific and speedy safety measure

**Better quality of Medical Care**
- Maximize benefit/risk ratio
• PMDA web site


Thank you very much for your kind attention !!