PMDA’s Recent Developments in Enhancement of Drug Safety Measures

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24th Annual EuroMeeting
26-28 March 2012
Copenhagen, Denmark
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“Safety” is one of the main targets of PMDA Second Mid-term plan (FY2009-FY2013)

“Strengthening and Improvement of Safety Measure Operations”
(Excerpt from Second Mid-term plan)
PMDA/MHLW Policy to enhance safety measures

System of sharing information for Proper use of drugs

Enhancement of Information Collection

Reinforcement of Scientific Safety Evaluation System

More Effective Dissemination of Safety information

Promotion of transparency

New Risk management system

Goal

- Prevention of serious drug safety-related crisis from Japan
- Effective encouragement of proper drug use.
- Ensuring credibility to post-market safety management system.
PMDA/MHLW Policy to enhance safety measures

System of sharing information for Proper use of drugs

Risk Management Plan Guidance (Draft)

Reinforcement of Scientific Safety Evaluation System

New Risk management system

Analysis

Transparency

Hypothesis

Evaluation

Crisis management

More Effective Dissemination of Safety information

Revision if necessary

Assessment of Safety measure effects

Planning and Implementation of Safety measures

Goal

- Prevention of serious drug safety-related crisis from Japan
- Effective encouragement of proper drug use.
- Ensuring credibility to post-market safety management system.

(1) MIHARI project
(2) EMR network project
1. MIHARI PROJECT
2. EMR NETWORK PROJECT
3. INTRODUCTION OF RISK MANAGEMENT PLAN
1. MIHARI PROJECT
2. EMR NETWORK PROJECT
3. INTRODUCTION OF RISK MANAGEMENT PLAN
What is the "MIHARI project"?

- THE PROJECT TO UTILIZE ELECTRONIC MEDICAL INFORMATION (HEALTH CLAIM DATA, MEDICAL RECORDS, ETC) FOR SAFETY MEASURES.
- LAUNCHED IN FY2009.
- "MIHARI" MEANS "MONITORING" IN JAPANESE. ALSO CALLED THE "MEDICAL INFORMATION FOR RISK ASSESSMENT INITIATIVE"
This MIHARI's logo is made from crossed 4 arrows colored blue and green. Two blue arrows show two types of data sources (claim data and medical record data) and two green arrows show two types of analysis methods (pharmacoepidemiological analysis and data-mining analysis), respectively. These 4 arrows indicate that various kinds of data are analyzed from many directions in the MIHARI project.
Background of MIHARI project

Strengthening and Improvement of Drug Safety Measure Operations in PMDA

Necessity of Drug Safety Analysis Using Expanded Data beyond Spontaneous Adverse Drug Reaction Reports

Establishment of the Framework for Drug Safety Analysis with Secondary Use of Electronic Health Information*

*Data from insurance claims and electronic medical records

<ADVANTAGES>
- Target population analysis
- Comparative evaluation
- Quantitative assessment
- Easier and prompt data collection (compared with primary data research)
MIHARI project - Objectives

- To ensure access to existing electronic health information (EHI) such as medical records and claim data
- To develop methodology and technique to use EHI for quantitative risk evaluation of drugs employing pharmacoepidemiological analysis
- To develop methodology and technique to use EHI for evaluation of impact of regulatory actions on drug safety.
- To establish framework for secondary utilization of EHI as a basis for taking safety measures.
Data Sources to be Examined

- Several data sources are examined at pilot studies in MIHARI
  - Health Insurance Claim Data
  - Diagnosis Procedure Combination (inpatient claim) Data
  - Electronic Medical Record Data
  
  etc.
Investigation Stages

Ensuring Access to Electronic Health Data
- Data collection scheme
- Data cleaning method

Evaluation of Data Characterization
- Data validation
- Data limitation

Data Utilization
- Epidemiological studies
- Interpretation of study results
Pilot Studies Using Claim Data

Signal Detection

Data mining
Primary detection of exhaustive combination of event and drug

Drug use survey
Survey for patient background or prescription trend in a specific population defined by diagnosis or drug

Evaluation of effects of regulatory actions
Survey for prescription trend or compliance of cautions after a regulatory action is taken

Signal Refinement

Alert detection
Secondary detection of specific combination of event and drug by pharmacoepidemiological methods

Risk estimation
Quantitative risk estimation for specific combination of event and drug by pharmacoepidemiological methods

Signal Evaluation

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Flow of a Pilot Study

Example:
Drug use survey and Evaluation of effects of regulatory actions

<table>
<thead>
<tr>
<th>Durations</th>
<th>Number of dispensing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>2,544</td>
</tr>
<tr>
<td>2 weeks</td>
<td>406</td>
</tr>
<tr>
<td>3-4 weeks</td>
<td>1,012</td>
</tr>
<tr>
<td>5-8 weeks</td>
<td>417</td>
</tr>
<tr>
<td>9-12 weeks</td>
<td>503</td>
</tr>
<tr>
<td>Over 12 weeks</td>
<td>72</td>
</tr>
</tbody>
</table>

Ex.1 Dispensing Duration

Ex.2 Distribution of age

Ex.3 Trend of prescription

Boxed Warning

Results
Necessity of Data Source Variety

- **Claim data**
- **Drug Use Result Survey data**
- **DPC data**
- **ICSR data**
- **Medical Record data**

**Data base size**

- Detailed ADR information
  - ADRs
  - Suspected drugs
  - Event Dates

- Standardized and many data elements
  - Diseases with severity
  - Dates of prescriptions
  - Surgeries

- Longitudinal data

- Detailed medical information
  - Lab test results

**All data sources are not perfect and have limitations**

**Necessity to select the most appropriate data source, depending on a purpose**
Web Pages of MIHARI

• Japanese
  – Reports from pilot studies are available
  http://www.info.pmda.go.jp/kyoten_iyaku/mihari.html

• English
  http://www.pmda.go.jp/english/service/mihari_project.html
1. MIHARI PROJECT
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Outline of EMR Network Project

- Development of an electronic medical record (EMR) data utilization network with collaborative hospitals and PMDA
- Establishment of standardized database and analytic system in each hospital
- Establishment of common work space for analysis accessible to collaborative hospitals and PMDA
- Aim to expand the network to wider hospitals in the future
- Utilization of EMR data for accurate and prompt benefit/risk assessment by applying epidemiological methods
Objective

- Securing access to 10 million individual’s EMR data in order to strengthen drug safety

- Enable to collect accurate and detailed safety data which have not been spontaneously reported by pharmaceutical companies
Electronic Medical Record Network Project for Drug Safety

- Budget approved FY2011 Governmental to initiate “Safety 10Mil. Data project”
- The network construction will be completed by FY2013.

Desired Outcomes:
- Promote risk & benefit review of medical technologies and provide safer healthcare.
- Enable the government to take rapid and appropriate measures for drug safety.
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Risk Management Plan Guidance

- Risk Management Plan (RMP) Guidance (Draft) was made available for public consultation on April 20, 2011 (Period of public consultation: by October 31, 2011)

- This guidance is intended to propose a standard concept for “Pharmacovigilance Plan” and “Risk Minimization Plan” By MAH (marketing authorization holder)

RMP Guidance is expected to be finalized and Notified early FY2012
Introduction of RMP - Background

• In Japan, various kind of risk management strategies have already been taken to ensure post-marketed drug safety. (…and have been fairly effective. ) (eg. Spontaneous reporting system, Use result survey, EPPV, revision of package insert, Preparation and provision of Medication guide for patients)

• However, these safety measures are not necessarily taken systematically and consistently. (No explicit guidance which measure should be taken for what kind of drug)
**Pharmacovigilance measures JP, US, EU**

<table>
<thead>
<tr>
<th></th>
<th>Pre-market review</th>
<th>Approval</th>
<th>Post-market</th>
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<tr>
<td><strong>JP</strong></td>
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<td></td>
<td>ADR/AE reporting</td>
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<td>Spontaneous ADR, infection Reporting</td>
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<tr>
<td><strong>US</strong></td>
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<td>REMS (high risk NME)</td>
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<td></td>
<td>Post-market Commitment If necessary</td>
<td>Periodic report</td>
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<td><strong>EU</strong></td>
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<td>RMP (NME)</td>
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<td>Post-market Commitment If necessary</td>
<td>PSUR</td>
<td>renewal</td>
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**Pharmacovigilance strategies including Pharmacovigilance Plan will be integrated into RMP**

- **REMS** (high risk NME) will be integrated into RMP
- ADR/AE reporting
- Spontaneous ADR, infection Reporting
- Periodic report
- Post-market Commitment If necessary
- RMP (NME)
- PSUR
- renewal
Features of RMP guidance draft (1)

- MAH should identify safety issues of drug as Safety Specification according to the characteristics of each drug (e.g., treatment population, target disease)

- MAH should develop “Pharmacovigilance plan” and “Risk Minimization Plan” based on Safety Specification.
MAH should consider to collect information on drug efficacy/effectiveness by conducting post-market surveillance/study on efficacy/effectiveness.

Timely and appropriate assessment of impact, and revision of RMP if necessary.
Risk Minimization Plan
Pharmacovigilance Plan

Routine

- Spontaneous Report
- Literature search

Additional

- Detailed examinations of Pharmacovigilance Plan and/or Risk Minimization Plan?
- Additional measures necessary? (Assessment)※

Additional Risk Minimization plan
- Revision of precautions
- Information dissemination by EPPV
- Medication guide for patients
- Educational program
- Limiting access
- Post-market Clinical Trial

Additional vigilance plan
- Enhancement of Spontaneous Report Collection by EPPV
- Use result survey
- Specified use result survey
- Post-market Clinical Trial

Safety Specification

- Important Specified Risks
- Important Potential Risks
- Important missing Information

Additional measures Necessary? (Assessment)※
- No

※: In deciding the measures to be taken, good consideration is required to avoid excess burdens and confusion in real clinical settings.
Introduction of RMP – Expectations

- Enhancement of post-marketing drug safety
- Promotion of Benefit-risk evaluation of post-marketed drugs.
- Improvement of Safety measure operations through evaluation based on benefit-risk analysis.
Thank you for your kind attention!