New Streams of Risk Management

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PMDA Third Mid-term Plan for Safety (ctd.)

- Enhance Collection of ADRs
- Improve the System and Process of ADRs Evaluation
- Establish the System to Utilize Electronic Healthcare Data
- Enhance Feedback of Safety Information
- Enhance Dissemination of Information to the Patients
PMDA Third Mid-term Plan for Safety

► Promote Appropriate Safety Measures based on the J-RMP
► Enhance Post-marketing Safety Measures in Cooperation with Review Teams
► Improve Follow-ups of Safety Measures Conducted
Today’s Topics

► Overview of Japanese Pharmacovigilance Framework
► Risk Management Plan and Risk Managers
► New Initiatives for Safety Evaluation
  --- Utilization of Electronic Healthcare Data
  --- MID-NET Project
► New Regulation
  --- Notification of Package Insert
Overview of Japanese Pharmacovigilance Framework

EPPV: Early Post-marketing Phase Vigilance (6 months intensive monitoring)
RMP: Risk Management Plan
Re-EX: Re-examination

Approval

Planning of RMP for NME
Condition of Approval

Post-marketing observational survey
If necessary PM Clinical Trial

Spontaneous ADR Reporting

6-10 years

Re-EX

Periodical reporting

Re-evaluation If necessary
Early Post-market Phase Vigilance

- Monitoring ADRs is critical in the first 6 months after the launch of a new drug.
- Marketing authorization holders are required to provide the safety information to healthcare professionals and to collect ADR information intensively for the time frame by visiting hospitals periodically.

Visit each hospital before supply and after that periodically.

Provide information by visiting, sending letters, FAX or e-mails, or through retailers.
MHLW and PMDA gather the ADR reports directly from health care professionals, and via drug companies.

In FY2014, about 55,000 serious ADR cases were reported.
PMDA holds an experts meeting every 5 weeks to consider revisions of labelling. Drug risk information under consideration will be put on this PMDA Risk Communications list.

**Early Communication of Risk Under Review**

This webpage was developed to provide drug risk information which has undergone review by the PMDA/MHLW. Information provided here is as follows:

1. Risk Information was suggested by a certain amount of accumulated information on Adverse Drug Reactions (ADR) reports or Early Postmarketing Phase Vigilance (EPPV). Certain safety measures such as revision of Precautions section in the labelling of the product might be taken after the ongoing review.

2. Risk Information which has attracted attention in foreign drug regulatory agencies or academic societies and PMDA/MHLW has started its evaluation. Information provided here is still under review. If you are taking the following medicines, you should NOT stop taking them or reduce the dosage only on your own judgment. Consult your healthcare professional if you have any questions or concerns about these medications.

<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>Risk Information Ongoing Evaluation</th>
<th>Related Information</th>
<th>Investigation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>abiraterone acetate</strong></td>
<td>Hypokalaemia, thrombocytopenia, and rhabdomyolysis</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>montelukast sodium</strong></td>
<td>Thrombocytopenia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>telaprevir</strong></td>
<td>Precautions concerning a risk of renal impairment</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>memantine hydrochloride</strong></td>
<td>Hepatic dysfunction and jaundice</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>apixaban</strong></td>
<td>Interstitial pneumonia</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Risk Management Plan

- In order to ensure the safety of drugs, it is important to conduct an appropriate management of the risks of drugs throughout their life-cycle.
- J-RMP is a document summarizing the risk management for a drug.
- J-RMP is required for new drugs for which approval applications are submitted after April 1st, 2013, and for some of generic drugs after August 26, 2014.
J-RMP should be reviewed at every milestone;
Submission of periodical reports
Completion of any post-marketing surveillance
Taking additional safety measures
Risk Management Plan (ctd.)

**Pharmacovigilance Plan**
Plan for activities of collecting information of individual risks
- Routine: Collecting information of ADRs
- Additional: EPPV
  - Post-marketing observational studies
  - Post-marketing clinical trials
  - Pharmacoepidemiologic studies, etc

**Risk Minimization Action Plan**
Plan for safety measures taken to minimize individual risks
- Routine:
  - Package insert
  - Patients Drug Guide
- Additional:
  - EPPV
  - Additional communications to HCP
  - Additional communications to patients
  - Special management of use
  - Special education of physicians, etc

**Safety Specification**
- important identified risks
- important potential risks
- important unknown risks due to missing information
At the time of approval application of new drugs and a part of generic drugs, a draft of J-RMP is required to submit to PMDA. Then, the applicant and PMDA review team and a risk manager discuss and agree on the J-RMP before the approval.
Development of J-RMP

► When PMDA judges that additional activities are necessary, MAH is required to conducting appropriate post-marketing safety measures based on the agreed J-RMP as a condition of an approval.

► Sharing a J-RMP document among healthcare professionals is important to ensure post-marketing safety of drugs.

► J-RMP is made public via PMDA website at the earliest availability.
Risk Managers in PMDA

- Risk Managers are liaison officers between the review teams and the post-market safety teams to develop the suitable safety measures.
- PMDA has 14 risk managers for 12 review teams.

Diagram:
- Development
- Review
- Post-marketing

Review Team:
- Development of early post-marketing phase vigilance plan
- Advice on post-marketing safety measures
- Evaluation of the result of post-marketing survey

Safety Team

Risk Manager (Act as Liaison)
“MIHARI” means a guard or a watch in Japanese.

MIHARI Project is

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

Launched in FY2009.
Since 2009, we have conducted pilot studies to ensure access to existing electronic healthcare data (EHD) such as medical records and health insurance claim data. To develop pharmacoepidemiological methodology and technique to use EHD for quantitative risk evaluation of drugs and for evaluation of impact of regulatory safety actions.
MID-NET Project

MID-NET (Medical Information Database Network) is a national project initiated by MHLW to establish the DB network for MIHARI Project to utilize electronic healthcare data for drug safety.
MID-NET Project

► Electronic healthcare data at 10 hub medical institutions will be retrieved and standardized for analysis and evaluation of ADR.

► A standardized database of EHD and an analysis system has been already established in each of 10 co-operating medical institutions.

► Data quality check and system validations are now being conducted.

► Full-scale utilization of the MID-NET data is expected to start in 2018.
A new regulation on notification and publication of product safety information has been introduced into the Pharmaceuticals and Medical Devices Law and came into effect in November, 2014.

MAHs are required to make prior notification of product safety information at the start of marketing and at the time of their revisions.

After the notification, MAHs shall immediately publish the package insert on the PMDA website.
Items to be notified

Among sections in package insert, sections listed below by red and underlined letters shall be notified.

| 1 Date of preparation or revision |
| 2 Japan Standard Commodity Classification Number |
| 3 Therapeutic category |
| 4 Regulatory classification |
| 5 Name |
| 6 Warnings |
| 7 Contraindications |
| 8 Description |
| 9 Indications |
| 10 Dosage and administration |
| **11 Precautions** |
  * Precautions related to the indications |
  * Precautions related to the dosage and administration |
  * Careful administration |
  * Important precautions |
  * Drug interactions |
  * Adverse reactions |
| 12 Pharmacokinetics |
| 13 Clinical studies |
| 14 Pharmacology |
| 15 Physicochemistry |
| **16 Precautions for handling** |
  * Geriatric use |
  * Use during pregnancy, delivery or lactation |
  * Pediatric use |
  * Effects on laboratory tests |
  * Overdosage |
  * Precautions concerning use |
  * Other precautions |
| 17 Conditions for approval |
| 18 Packaging |
| 19 References and request for literature should be made to: |
  * Name and address of manufacturer or importer |
The contents of product safety information are reviewed by a review team and a risk manager during approval review, and after approval, they are revised based on the consultation between PMDA and MAH based on the information collected in post-marketing surveillance.
Based on the consultation with PMDA, MAHs notify the package insert including product safety information to PMDA electronically via the Internet and then the package insert is published on the PMDA website.
PMDA English Website

Thank You

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