Strategic Approach to Post-Marketing Safety Measures

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<tr>
<th>Type of Financial Interest within last 12 months</th>
<th>Name of Commercial Interest</th>
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<td>☐ Grants/Research Funding</td>
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<td>☐ Stock Shareholder</td>
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<td>☐ Consulting Fees</td>
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<td>☐ Employee</td>
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<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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Today’s Topics

- Overview of Japanese Pharmacovigilance Framework
- Risk Management Plan (J-RMP)
- Utilization of Electronic Healthcare Data
  --- Update of MIHARI Project and MID-NET Project
Overview of Japanese Pharmacovigilance Framework

- **Approval**
  - Planning of RMP for NME
  - Condition of Approval

- **Spontaneous ADR Reporting**
  - EPPV: Early Post-marketing Phase Vigilance
    (6 months intensive monitoring)
  - Post-marketing observational survey
  - If necessary PM Clinical Trial
  - Periodical reporting

- **6-10 years**
  - RMP: Risk Management Plan
  - Re-EX: Re-examination

EPPV: Early Post-marketing Phase Vigilance
RMP: Risk Management Plan
Re-EX: Re-examination
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 health care professionals (HCP) and to collect ADR information intensively for the time frame by visiting hospitals periodically.

Early Post-marketing Phase Vigilance (EPPV)
MHLW and PMDA gather ADR reports from drug companies and also directly from health care professionals.

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 of ongoing evaluation is putted on PMDA website as a Risk Communications list.

### PMDA Risk Communications

### Drug Risk Information of Ongoing Evaluation

<table>
<thead>
<tr>
<th>Posted Date</th>
<th>Nonproprietary Name (Click on each drug name for more information on Package inserts) (only available in Japanese language)</th>
<th>Risk Information Ongoing Evaluation</th>
<th>Related Information</th>
<th>Investigation Results</th>
</tr>
</thead>
</table>
| February 26, 2016 | *Ioxoprofen sodium hydrate (oral solution)*  
                   *Ioxoprofen sodium hydrate (tablets, fine granules)*  
                   *Ioxoprofen sodium hydrate (tablets, fine granules)*  
                   *OTC drugs products containing ioxoprofen sodium hydrate (oral dosage form)* | *Stenosis and obstruction of small intestine and large intestine* | -                   | March 22, 2016  
Revision of PRECAUTIONS |
In case of important safety information, MHLW/PMDA request MAHs to disseminate “dear healthcare professionals letter (Yellow Letter, Blue Letter).”

PMDA promptly posts the letter on its website and sends it by e-mail to the subscribers of PMDA medi-navi.
Subscription of PMDA medi-navi

According to the survey conducted by PMDA in FY 2014, 77.3% of 4903 hospitals had one or more subscribers of PMDA medi-navi.

The ratios of hospitals having one or more subscribers was 95% for large hospitals (>500 beds) but 56% for small hospitals.
If an innovative new drug is approved under “SAKIGAKE” review system in near future, Japan will be the first country in the world which approved the drug.

In that case, we should be more careful to watch unexpected, serious ADRs in the post-marketing phase and so that EPPV for the drug is more important to detect such ADRs as early as possible.

The MAH for the drug will be required to conduct EPPV under the RMP.
Under the new expedited approval scheme for regenerative medical products, products will be authorized with conditions and for limited time if the safety is confirmed and the clinical benefit is likely to be predicted.

In that case, all treated cases using the approved products are registered, and a study to confirm efficacy and safety are required during marketing before re-application for the full-approval.
Today’s Topics

► Overview of Japanese Pharmacovigilance Framework

► Risk Management Plan

► Utilization of Electronic Healthcare Data
  --- Update of MIHARI Project and MID-NET Project
In order to conduct an appropriate management of risks of drugs throughout their life-cycle, J-RMP is required for new drugs since 2013 and for some generic drugs since 2014.

J-RMP is a compact document which consists of the following three elements;
- Safety specification
- Pharmacovigilance plan
- Risk minimization action plan.

177 J-RMPs have been posted on the PMDA website.
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, PMDA review team, and a risk manager of post-market surveillance team discuss and agree on the J-RMP before the approval.

PMDA has 14 risk managers for 12 review teams.
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.

J-RMP is a living document and should be reviewed at every milestone;
- Submission of periodical reports
- Completion of any post-marketing surveillance
- Taking additional safety measures
Development of J-RMP enhances collaboration between development teams and post-marketing safety teams in companies, and such collaboration contributes to planning and conducting more appropriate risk management.

J-RMP is also an useful and important document for HCPs because:

► HCPs can be aware of safety concerns not yet listed in Package Insert.
► HCPs can understand how they can cooperate with companies’ information gathering activities after approval.
► HCPs can recognize available risk minimization materials to protect safety of patients.
Utilization of J-RMP

- J-RMP is not yet well-known among HCPs according to the PMDA survey conducted in FY2014.
- Respondents who know RMP is only 22% totally.

<table>
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<tr>
<th>Bed Size (~)</th>
<th>Recognition of J-RMP</th>
<th>J-RMP Utilization by HCP who know well or to some extent</th>
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<tr>
<td>500 BEds</td>
<td>48</td>
<td>47.5</td>
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<tr>
<td>400 BEds</td>
<td>38.9</td>
<td>36.6</td>
</tr>
<tr>
<td>300 BEds</td>
<td>28.9</td>
<td>39.2</td>
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<tr>
<td>200 BEds</td>
<td>20.5</td>
<td>32.9</td>
</tr>
<tr>
<td>100 BEds</td>
<td>18</td>
<td>24.2</td>
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<tr>
<td>50 BEds</td>
<td>14.6</td>
<td>31.8</td>
</tr>
<tr>
<td>20 BEds</td>
<td>15.6</td>
<td>30.6</td>
</tr>
<tr>
<td>TOTAL (N=4903)</td>
<td>22.2</td>
<td>TOTAL (N=1087)</td>
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</table>
Today’s Topics

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- Risk Management Plan
- Utilization of Electronic Healthcare Data
  --- Update of MIHARI Project and MID-NET Project
Background & Objective of MIHARI Project

Limitations of spontaneous report

- Some events are unlikely to be reported
- Although reports are available, some causalities are difficult to determine by individual case safety report (ICSR) assessment

MIHARI Project（2009～）
- Medical Information for Risk Assessment Initiative-

To strengthen post-marketing drug safety measures in PMDA by developing new safety assessment framework using Japanese medical information databases
“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) project is a national project initiated by MHLW to establish the DB network for MIHARI Project to utilize electronic healthcare data for drug safety.

- Electronic healthcare data at 23 hospitals of 10 hub medical institutions will be retrieved and standardized for analysis and evaluation of ADR.
Data integration method from 23 hospitals

① PMDA sends query programs to 23 hospitals
② Each hospital sends an analysis result and/or anonymized individual data if necessary to the central data center.
③ PMDA accesses and analyzes the data using exclusive PC
  · Review results provided by hospitals
  · Combine 23 results
  · Conduct additional analysis by using these results
We are now checking data quality and verifying the operation of the MID-NET system. From this summer, we will conduct pilot studies using MID-NET data. Full-scale utilization will be started in 2018.

<table>
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<tr>
<th>FY2011-2014</th>
<th>FY 2015</th>
<th>FY 2016</th>
<th>FY2017</th>
<th>FY2018</th>
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<tbody>
<tr>
<td>Database developed</td>
<td>Data quality check</td>
<td>Verification and upgrade the system</td>
<td>Pilot studies</td>
<td>Full-scale utilization</td>
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Thank You

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Ask