Strategic Approach to Post-Marketing Safety Measures

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Today’s Topics

► Overview of Japanese Pharmacovigilance Framework

► Utilization of Electronic Healthcare Data
   - Update of MIHARI Project and MID-NET Project
Overview of Japanese Pharmacovigilance Framework

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

Planning of RMP for NME
Condition of Approval
Post-marketing observational survey
If necessary PM Clinical Trial
Periodical reporting
6-10 years
Spontaneous ADR Reporting
Re-examination If necessary
Early Post-marketing Phase Vigilance (EPPV)

- 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.
Spontaneous Serious ADR Reporting

- MHLW and PMDA gather ADR reports from drug companies and also directly from health care professionals.
- In FY2015, about 57,000 domestic serious ADR cases were reported.
Early Communication of Risk Under Review

- 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>
<tbody>
<tr>
<td>February 26, 2016</td>
<td>loxoprofen sodium hydate (oral solution)</td>
<td>Stenosis and obstruction of small intestine and large intestine</td>
<td>-</td>
<td>March 22, 2016 Revision of PRECAUTIONS</td>
</tr>
<tr>
<td></td>
<td>loxoprofen sodium hydate (tablets, fine granules)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>loxoprofen sodium hydate (tablets, fine granules)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTC drugs products containing loxoprofen sodium hydrate (oral dosage form)</td>
<td>Stenosis and obstruction of small intestine and large</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Safety Communication

► 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.
Post-marketing Surveillance for SAKIGAKE Drugs

- If an innovative new drug is approved under “SAKIGAKE” review system in near future, Japan will be the first country in the world which approves the drug.

- In that case, we have to 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.
Post-marketing activities for regenerative products approved under a new scheme

- 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.
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Limitations of spontaneous report

• Some events are unlikely to be reported.
• Causalities are difficult to determine by individual case safety report (ICSR) assessment.
• The incidence of ADR cannot be determined.

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 Project

► “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 have been 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.
Data Sources of MIHARI Project

- Health claims data
  - National Claims Database (NDB)
    - Provided by MHLW
    - Covering almost all Japanese citizens
  - Commercial Claims Database
    - Provided by commercial vendors

- Electronic medical records data
  - Medical Information Net-work (MID-NET)
    - Under development by MHLW/PMDA

PERCENTAGE OF ELECTRONIC CLAIMS

- Hosp ≥400 beds: 98.0%
- Hosp <400 beds: 98.7%
- Clinics: 97.5%
- Dentists: 95.4%
- Pharmacies: 99.4%

Electric: Paper:

0% 20% 40% 60% 80% 100%
Pharmacies
Dentists
Clinics
Hosp ≥400 beds
Hosp <400 beds
MID-NET Project

- MID-NET (Medical Information Database Network) project is a national project initiated by MHLW to establish the new DB network for MIHARI Project.
- 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>
<thead>
<tr>
<th>FY2011-2014</th>
<th>FY 2015</th>
<th>FY 2016</th>
<th>FY2017</th>
<th>FY2018</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

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Effective Use of “Big Data”

- NDB is a huge DB covering almost all Japanese people, but does not include outcome data like clinical laboratory test results.
  MID-NET is a small DB covering only 23 hospitals’ data, but include clinical laboratory test results.

- Each database has strengths and limitations. We should have enough knowledge about characteristics of each database and select the most appropriate database among several available databases for each purpose of an assessment.
Thank You

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