Pharmacovigilance in Asia: The Japanese Experience

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35th Brazilian Congress of Pharmaceutical Medicine

Disclaimer

• I am an employee of Eisai Co., Ltd. and I have received support from my employer to attend this meeting.
• I have a financial interest in Eisai Co., Ltd.
• The views expressed in this presentation are my own and do not represent the official position of my employer or of the MHLW or PMDA.
• I will not be presenting any information about unlabeled or unapproved uses of any drug in this presentation.

Outline

• Structure of the Japanese Pharmacovigilance System
• Post-marketing Surveillance Studies
• Expedited Reports
• Adverse Health Effect Relief
• Serious ADR Manuals

Structure of Pharmacovigilance System in Japan

PMS System in Japan

Re-evaluation

6 months - 2 years
5 years (6-10 years)

Drug use-results survey
Special use-results survey
Post-marketing clinical trials
"All cases" surveillance

ADR and infection case reporting system

Safety Information Reporting System by Health Professionals

Safety Reporting System by Pharmaceutical companies:
15-day & 20-day ADR and infection case reports (spontaneous), Research & Development, Literature, etc.

Periodic Safety Reports of biological products (every 6 months)
GPMSP, GVP and GPSP

- GPMSP: Good Post-Marketing Surveillance Practice
  - Standards for Post-marketing Surveillance
- GVP: Good Vigilance Practice
  - Standards for Post-marketing Safety Management
- GPSP: Good Post-marketing Study Practice
  - Implementation Standards for Post-marketing Investigations and Clinical Trials

GPSP

- Good Post-marketing Study Practice
  - Specifies items that are to be strictly complied with in order to achieve appropriate post-marketing surveillance and studies conducted by manufacturers/distributors
    - Must have written SOP’s
    - Designate a supervisor of post-marketing surveys
    - In-house inspections
    - Education & training
    - Preservation of records
    - Standards for Compliance with Reexamination and Reevaluation

GVP

- Good Vigilance Practice
  - Compliance is an assumed condition of approval for marketing
  - Establishes standards for post-marketing safety management
    - Collection, preparation, and study of proper use information on drugs, etc.,
  - Standards for the implementation of measures for safety assurance.

Reexamination

- Article 14-4 of PAL
  - Reexamination period ranges from 8 years up to 10 years (orphan drugs, pediatric) for new chemical entity
    - 4 years for additional indications, new dose, 6 years for new formulations/combination products, etc.
  - Data submitted for Reexamination must have been obtained according to GPSP
    - Clinical studies performed according to GCP standards in principle
    - But there are limitations on source data verification, etc. applied to "actual use" studies
    - Non-clinical studies must be performed according to GLP
  - During Reexamination period, a product effectively enjoys protection from generic competition

Surveillance Prior to Reexamination

- Conducted according to GPSP
  - “Actual Use Studies”
    - Observational study of safety and efficacy when used under conditions of approved package insert
  - Special Use Studies
    - Use in populations that may have been difficult to enroll during development program (elderly, renal or hepatic impairment, etc.)
  - Other PMS Clinical Studies
    - Under approved conditions of use

Reevaluation

- Article 14-6 of PAL
  - Efficacy and safety of an already approved drug are reconsidered on the basis of the current status of medical and pharmaceutical sciences
  - Addresses drugs which were approved when approval standards and medical practice was different
    - To eliminate drugs which may not have adequate efficacy or safety by today’s standards
Early Post-Marketing Phase Vigilance

- The company must repeatedly inform health professionals about the proper use of the new drug and collect information on serious adverse reactions.
- Concentrated period of vigilance during first 6 months after marketing.
  - For the first 2 months: Contact health professionals every 2 weeks (in principle).
  - For the following 4 months: Contact health professionals once a month (in principle).

Early Post-Marketing Phase Vigilance

- EPPV is not a clinical study nor is it a registry.
  - No protocol, reporting is still "spontaneous".
  - It is a system of encouraged (augmented) data collection.
  - Most companies do not classify reports received under this system as "solicited".
- At the conclusion of EPPV a report is submitted on the results of the data accumulated over that period.
  - Interview held to go over the results.

Post-Marketing Surveillance Studies

- "Actual Use Studies":
  - Observational study of safety and efficacy when used under conditions of approved package insert.
  - Typically 3000 subjects (varies by indication).
  - Typically 1000 enrolled per year.
  - 3000 allows detection of incidences of 0.1% for the period of exposure studied.
  - Performed under GPSP.
- Special Use Studies:
  - Use in populations that may have been difficult to enroll during development program (elderly, renal or hepatic impairment, etc.)
  - Observational trials.
  - Smaller patient numbers (typically 20-100).
  - Performed under GPSP.
- Other PMS Clinical Studies:
  - Under approved conditions of use.
  - Performed under GPSP and GCP.

Post-Market Studies

<table>
<thead>
<tr>
<th>Approvals 4/07-4/08</th>
<th>69 products</th>
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<tbody>
<tr>
<td>All Case Surveillance</td>
<td>22</td>
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<tr>
<td>Actual Use Studies</td>
<td>26</td>
</tr>
<tr>
<td>Special Use</td>
<td>2</td>
</tr>
<tr>
<td>Pediatrics</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0</td>
</tr>
<tr>
<td>Longterm</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
</tr>
<tr>
<td>No studies required</td>
<td>2</td>
</tr>
</tbody>
</table>

Why Surveillance Studies?

- The number of Japanese patients exposed to a new drug during clinical development is limited.
- Foreign data is often included in the new drug application.
- Desire for information on incidence of adverse reactions during "actual use" (real world) conditions.
- Desire for information from high-risk and under-studied patient populations such as elderly, renal impaired, hepatic impaired.
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Use of Surveillance Study Data

- This information is used to update the Japanese PI with adverse reaction incidence information

This data is from spontaneous reports and so incidence is unknown

Problems with Surveillance Studies

- Usually there is no comparator group
  - Attribution of causality cannot be determined
- Report rates of “reactions” not just rates of “events”
  - Bias in evaluating causality for an open-label study?
- Data collection is not as robust as during clinical development
  - No rigorous source data verification
  - Data typically collected by Medical Representatives

All Cases Surveillance (Zenrei-chousa)

- Program of recording and following all exposures to a newly approved drug for a specific amount of time or number of exposures
  - Similar to a Registry
- As a condition of approval
- More likely if
  - Orphan drug
  - Perceived need for greater safety monitoring because new category of drug
  - Approval is largely based on foreign data
  - Frequent serious adverse reactions
  - High risk of off-label use
- Generally means limiting the institutions which can use the product
  - Institutions contract to participate in the monitoring program

Zenrei-Chousa Methods

- Methods of implementing a Zenrei-Chousa resemble those for a restrictive Risk Minimization Action Plan
  - Limit supply to institutions with certain facilities (e.g. ability to treat an acute, known ADR) or staff
  - Limit supply to institutions which contract with the company to participate in the monitoring program
  - Limit supply to physicians who meet certain requirements (specialty association, agreement to implement monitoring, etc.)
  - Limit supply to patients who give informed consent, show knowledge of safety risks

Issues for “All Cases Surveillance”

- Lower reporting rates for adverse events in these surveillance studies compared to clinical development
  - Under-reporting or selected patient population?
- Some reports that patients in these surveys are younger or have less severe disease than overall patient population (within that indication)
  - Are the results applicable to the wider population?
- Restriction in facilities which can participate means that drug supply is restricted
  - Creates considerable burden for physicians & patients participating
  - But there are fewer provisions to assure data quality
Spontaneous Reports in Japan

- Most spontaneous reports come from health professionals via Medical Representative (MR)
- Initial reports are generally written by MR
- Follow up is also made through MR
  - Important new events may be followed through site visit by company’s pharmacovigilance staff
- Follow up (detailed) reports are generally written by health professionals
  - Generally well-documented

E2B Reporting

- Electronic reporting for both pre-approval (clinical trial) and post-approval expedited reports
- Essentially all reporting of individual adverse reactions is electronic
  - Encrypted e-mail
  - Physical delivery of electronic media

Expedited Reporting in Japan

- Expedited reporting to regulator is done electronically
- Different rules for reports which originate from Japan compared to foreign reports
  - Japanese reports are more likely to be expedited
- Category of report for “Actions taken abroad”
  - Japanese MHLW wants to be informed of international safety actions taken
- Special categories of reports for “infection reports” and “research reports”

Adverse Health Effect Relief

副作用救済制度
“Adverse Health Effect Relief Services”
Adverse Drug Reaction Relief System

- If a patient experiences an adverse drug reaction serious enough to require hospitalization or disability, they can apply for compensation/support:
  - Must result from use of a prescribed medication within limits of the approved package insert
  - Prescription must be for an approved indication
- Patient or their family sends to PMDA report from their physician on the diagnosis and evidence of drug prescription
- The application may be rejected but usually is accepted
- The patient or their family is awarded financial support for medical therapy costs, disability compensation or death benefit
- System is financially supported by pharmaceutical companies but companies have no influence on outcome

Most applications are accepted

<table>
<thead>
<tr>
<th>Performance in Adverse Reaction Relief Service</th>
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<tbody>
<tr>
<td>FY 2004</td>
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<tr>
<td>Number of applications</td>
</tr>
<tr>
<td>Number of adverse cases</td>
</tr>
<tr>
<td>Number of cases included in above</td>
</tr>
<tr>
<td>Process time (Median)</td>
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Excluded

- Damage as a result of statutory immunization (a separate public relief system is available). Damage resulting from the voluntary receipt of immunization will qualify.
- When the marketing authorization holder of the pharmaceutical and/or biological product are obviously liable for the damage.
- When the pharmaceutical was used for the purpose of saving the life of the patient even though the possibility of health damage was recognized.
- The adverse reaction to the pharmaceutical or the infection/other adverse health effect from a biological product caused only minor damage to health, or the valid period for requesting relief has already expired.
- In case of improper usage of pharmaceutical or biological product.
- In case of adverse health effects caused by pharmaceuticals not designated under the relief system (only applies to Adverse Drug Reaction Relief System)

Serious ADR Manuals
Serious ADR Manuals

- Version for patients
- Version for Healthcare Professionals
  - Information on diagnosis and treatment
  - Lists of approved medications for which the reaction is mentioned in the package insert
  - Recent experience in numbers of reports received

<table>
<thead>
<tr>
<th>年度</th>
<th>原因</th>
<th>列挙品名</th>
<th>件数</th>
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<tbody>
<tr>
<td>20XX年度</td>
<td>1. 副性心不全</td>
<td>電解質補充剤</td>
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<tr>
<td></td>
<td></td>
<td>キロスタシル</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td>アルピラクシル</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<td>他類</td>
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<tr>
<td></td>
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Summary

- A rigorous program of surveillance is performed under GPSP for each new drug approval
- Several aspects of the current PMS system in Japan fulfill the objectives of Risk Management and Risk Minimization
- There is a public relief system for adverse health effects from medications in Japan
- Publication of manuals on serious adverse effects improves public awareness of these conditions