# Pharmacovigilance in Asia: The Japanese Experience

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- 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.

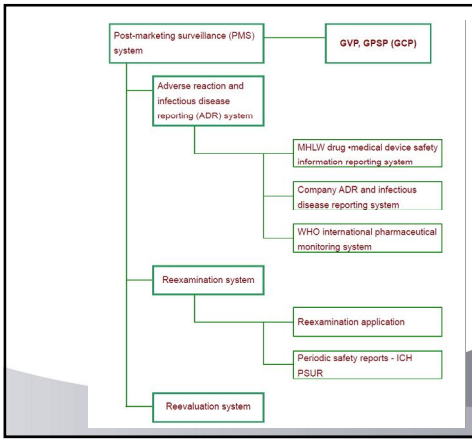


## Outline

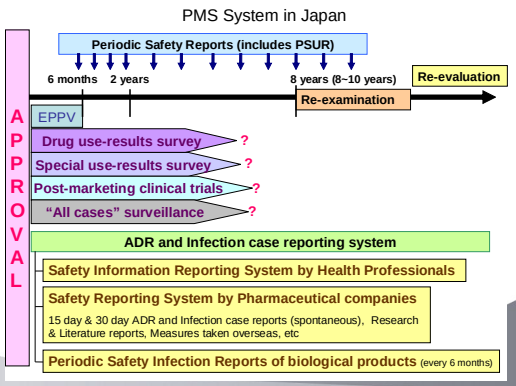
- Structure of the Japanese Pharmacovigilance System
- Post-marketing Surveillance Studies
- Expedited Reports
- Adverse Health Effect Relief
- Serious ADR Manuals



## Structure of Pharmacovigilance System in Japan





## 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

## Post-Market Studies

| | |
|---|---|
| Approvals 4/07-4/08 | 69 products |
| All-Case Surveillance | 22 |
| Actual Use Studies | 26 |
| Special Use Pediatrics | 2 |
| Pregnancy | 1 |
| Renal | 1 |
| Hepatic | 0 |
| Longterm | 20 |
| Other | 13 |
| No studies required | 2 |



## 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



## 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

## Use of Surveillance Study Data

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

This data is from Surveillance studies and so incidence is known

This data is from spontaneous reports and so incidence is unknown

(2) Other adverse reactions

| | ≥3% | 3% > ≥1% | <1% | Incidence unknown |
|---|---|---|---|---|
| Hypersensitivity[note] | | | Rash | Itchang |
| Gastrointestinal | | Anorexia and nausea | Vomiting, diarrhea, constipation, abdominal pain and salivation | Dysphagia and faecal incontinence |
| Psychoneurologic | | | Excitement, unrest, insomnia, sleepiness, libido increased, talkativeness and manic state | Nightmare, irascibility, hallucination, aggressiveness, delirium, delusion, mental depression, confusion, indifference and hyperkinesis |
| Central and peripheral nervous system | | | Poriomania, tremor, headache and dizziness | Stupor |
| Hepatic | Elevation of LDH | Elevation of AST (GOT), ALT (GPT), γ-GPT and Al-P | | |



## 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)

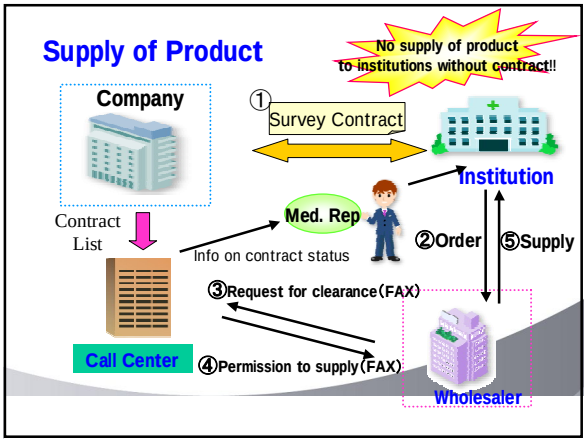
- Program of recording and following all exposures to a newly approved drug for a specific amount of time or number of exposures
  - Similar to a Registry
- As a condition of approval
- More likely if
  - Orphan drug
  - Perceived need for greater safety monitoring because new category of drug
  - Approval 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

## Expedited Reports

## 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



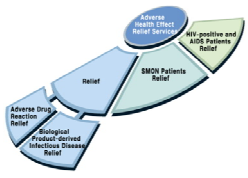
## Expedited Reporting in Japan

- 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"

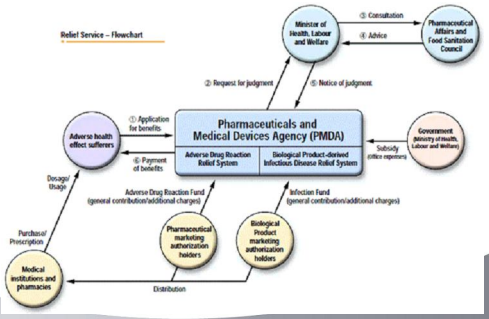


## Adverse Drug Reaction Relief System

- http://www.pmda.go.jp/english/healtheffect.html
- If a patient experiences an adverse drug reaction serious enough to require hospitalization or disability, they can apply for compensation/support
  - Must result from used of a prescribed medication within limits of the approved package insert
  - Prescription most 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



## Adverse Drug Reaction Relief System






## Most applications are accepted

Performance in Adverse Reaction Relief Service

| | FY 2004 | FY 2005 |
|---|---|---|
| Number of applications | 769 | 760 |
| Number of judged cases | 633 | 1,035 |
| Withdrawn (included in above) | 1 | 4 |
| Number of cases in progress* | 956 | 681 |
| Process time (Median) | 12.4 months | 11.2 months |



## Adverse Drug Reaction Relief System

Payment of Adverse Reaction Relief Benefit

| Type of benefit | FY 2004 | | FY 2005 | |
|---|---|---|---|---|
| | Number of cases | Amount of payment | Number of cases | Amount of payment |
| Medical expenses | 448 | 51,722 | 717 | 78,527 |
| Medical allowance | 472 | 42,711 | 757 | 70,073 |
| Disability pension | 24 | 592,028 | 33 | 653,143 |
| Pension for raising handicapped children | 4 | 17,810 | 17 | 40,639 |
| Bereaved family pension | 31 | 412,167 | 44 | 502,468 |
| Lump-sum benefit for bereaved family | 19 | 137,041 | 32 | 228,708 |
| Funeral expenses | 48 | 9,167 | 74 | 14,010 |
| Total | 1,046 | 1,262,647 | 1,674 | 1,587,567 |



## 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

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うっ血性心不全

英語名：Congestive Heart Failure
同義語：Chronic Heart Failure

A．患者の皆様へ




## 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

| 年度 | 副作用名 | 医薬品名 | 件数 |
|---|---|---|---|
| 平成18年度 | うっ血性心不全 | 塩酸ピオグリタゾン | 9 |
| | | シクロスポリン | 8 |
| | | アルプロスタジル | 5 |
| | | 塩酸エピルビシン | 4 |
| | | 塩酸ドキソルビシン | 3 |
| | | アリピプラゾール | 3 |



## Serious ADR Manuals

- Because specific drugs are listed in the “Serious ADR Manuals” you may see more reporting of those events from Japan
  - Higher physician awareness of that drug-event association
  - Because drugs are listed with event numbers there is a tendency to “rank” the drugs for risk
    - But the report numbers can’t adjust for differences in numbers of patients exposed



## 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