Sentinel Initiative in Japan
- Utilization of Electronic Health Information in Pharmacovigilance -

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Background
Current environment of drug development and drug safety

• Expectation for innovative medicines
  - anti-body medicines, gene therapy, cellular and tissue-derived medicines, other innovation

• Enjoying benefit of new medicines at earliest possible
  - elimination of drug lag

  ➔ Limited knowledge and experience
  ➔ Difficulty to predict adverse events

NEED TO IMPLEMENT PROACTIVE AND PREVENTIVE SAFETY MEASURES
Current environment of drug development and drug safety

Global concern on safety of drugs
- Vioxx, IOM Report
- MHLW Committee on HCV Infection by Blood preparation

Difficulty of evaluation of post-approval safety of drugs
- Tamiflu, Anti-depressants

Limitation of spontaneous ADR reporting in safety evaluation

International harmonization
- Implementation of E2E

New technologies for drug safety
- Data mining
- Regulatory epidemiology

NEED TO MODERNIZE DRUG SAFETY PROGRAM:
USE OF ELECTRONIC HEALTH DATABASE
PMDA 2nd Midterm Plan (excerpt)

Reinforcement and enhancement of the system for safety information collection and evaluation

- Introduction of safety assessment team system according to therapeutic categories to realize advanced and specialized assessment of adverse drug reactions (ADRs). Stepwise increase of the number of teams.

- Utilization of data-mining methodology in safety assessment to enable early detection of ADRs and proactive safety measures to minimize risks.

- **Securing access to electronic medical record database including claim data to assess drug safety through ADR incidence survey and using a pharmacoepidemiological approach**

- Rationalization and effective implementation of PMS and surveys required by approval conditions including their timely review. Continuous evaluation of effectiveness and efficiency of PMS and post-approval surveys.

- Stepwise implementation of PMDA follow-up to ADR reporting by HCP.
Strengthening Office of Safety

Increasing the Number of Professional (regular) Staff by 100

**Office of Safety was divided into two Offices** (on July 1, 2009)

<table>
<thead>
<tr>
<th>Office of Safety I</th>
<th>Planning and Management Div.</th>
<th>Administration, Budget, etc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety Information Div.</td>
<td>Reception and dissemination of safety info.</td>
</tr>
<tr>
<td></td>
<td>Investigation and Guidance Div.</td>
<td>Guidance to industry and medical institutions</td>
</tr>
<tr>
<td></td>
<td>Pharmacoepidemiology Div.</td>
<td>Pharmacoepidemiological analysis</td>
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<tr>
<td></td>
<td>Surveillance and Analysis Div.</td>
<td>Access to e-Health Database “Sentinel”</td>
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<tr>
<td></td>
<td>Medical Devices Safety Div.</td>
<td>Device safety, Medication error</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Office of Safety II</th>
<th>Drug Safety Assessment Teams</th>
<th>Corresponding Offices of New Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Team 1</td>
<td>Office of New Drugs I</td>
</tr>
<tr>
<td></td>
<td>Team 2</td>
<td>Office of New Drugs II</td>
</tr>
<tr>
<td></td>
<td>Team 3</td>
<td>Office of New Drugs III</td>
</tr>
<tr>
<td></td>
<td>Team 4</td>
<td>Office of New Drugs VI, Offices of Biology I &amp; II</td>
</tr>
<tr>
<td></td>
<td>Team 5</td>
<td>Office of New Drugs V</td>
</tr>
</tbody>
</table>

- Streamlining/ enhancing communication and cooperation with Offices of New Drugs.
- Creation of Risk Management Staff (Pilot Implementation of Risk Management)
Sentinel Initiative in Japan
Signals: Data-mining vs Sentinel

Data-mining

Signal detection

Signal strengthening

Sentinel

Signal validation

Hypothesis testing in a formal pharmacoepi study
Possible purposes/benefits

- Detection of unknown ADR
- Estimation and evaluation of risk of drugs
- Evaluation of risks in subgroup and special population
- Comparison of AE incidence between new and existing drugs
- Comparison of AE incidence between use and non-use of a drug
- Analysis of impact and effectiveness of safety measures
FDA’s view on advantage of Sentinel Initiative

- Safety issues can be identified and evaluated in near real-time

- Sentinel expands the capacity for evaluating safety issues
  - Improved access to subgroups, special populations
  - Improved precision of risk estimates due to expanded number of populations available for study

- Active surveillance can identify an increased risk of common AEs (e.g., MI, fracture) that health care providers may not suspect are related to medical products
Data/Data Source to be examined/referred

- Health insurance claim data (National database)

- Diagnosis procedure combination (DPC)

- Medical information system

- Drug Use Result Survey

- Adverse Drug Reaction Database

- Existing database (such as GPRD, i3)
Health Insurance Claim Data

- Japan has a national health insurance system.
- On-line electronic claim for reimbursement will be made obligatory by 2011.
- A National claim data database is planned to be constructed. The DB will be used primarily for research and analysis of medical economy.
- MHLW committee report discusses secondary use of DB by entities other than national government: pending: PMDA to be a secondary user of DB for drug safety analysis.
- **MHLW committee on reviewing hepatitis C cases and developing new regulatory structure to prevent relapse of ADR tragedies** recommended use of a national claim data DB for pharmacovigilance.
Diagnosis Procedure Combination (DPC)

- Inclusive reimbursement system for hospitalized patients with acute diseases.
- Electronic claim data with standardized data elements and codes are collected and put into DB by MHLW.
- DPC system started in 2003 with 82 hospitals.
- Number of DPC hospitals has been increasing.
- According to 2007 survey,

<table>
<thead>
<tr>
<th></th>
<th>Number of hospitals</th>
<th>Number of beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPC</td>
<td>1,283</td>
<td>434,231</td>
</tr>
<tr>
<td>All hospitals</td>
<td>8,862</td>
<td>913,234</td>
</tr>
</tbody>
</table>
2001 Grand Design for IT introduction in medical area (MHLW)
Target: Installation of electronic medical record system in 60% of hospitals with more than 400 beds by 2006

2005 Medical Institution Survey (9026 hospitals)
- Installation of electronic medical record system
  (All hospitals) Full installation 470 hospitals (5.2%)
  Partial installation 156 hospitals (1.7%)
  (Hospitals with more than 400 beds (722 hospitals))
  Full installation 129 hospitals (17.9%)
  Partial installation 23 hospitals (3.2%)

2006 New IT Renovation Strategy (Cabinet Office)
- Installation of integrated MIS (medical records and ordering system) in most hospitals with more than 200 beds by 2010
Partnership with MHLW and Research Group

MHLW: Consultation Meeting on the Utilization of Medical-area Database for Drug Safety Measures

MHLW-granted Research: Research on Creation of Pharmacoepidemiology Database Using medical Claim Data

PMDA: Expert Committee on Utilization of Electronic Health Database for Pharmacovigilance

Cooperation/Coordination
PMDA Expert Committee on Utilization of Electronic Health Information for Pharmacovigilance

- First Meeting in July 2009
- Chairperson: **Prof. Shigekoto Kaihara**, Vice-President, International University of Health and welfare, Tokyo
- Members: Experts in Medical Informatics, Data Management, Pharmacoepidemiology, Bio-statistics etc.
- Main objectives: to identify:
  > necessary infrastructure to ensure access to electronic health information such as e-medical records and e-insurance claim data.

  > methodology and technique to use electronic health information for quantitative risk evaluation of pharmaceuticals employing pharmacoepidemiology analysis.

  > methodology and technique to use electronic health information for evaluation of impact of regulatory actions for drug safety.
Academic Areas pertinent to Utilization of Electronic Health Information for Pharmacovigilance

- Biostatistics
- Pharmacoepidemiology
- Management of Medical Information
- Medical Informatics
Possible use of EHR for safety analysis

Hospital A
Data in EHR
- Diagnosis
- Prescription
- Lab tests
- Operation
- Hospitalization

Gateway DB

Standardization

Hospital B
Data in EHR
- Diagnosis
- Prescription
- Lab tests
- Operation
- Hospitalization

Gateway DB

PMDA
Dataset
- Diagnosis
- Prescription
- Lab tests
- Operation
- Hospitalization

ANALYSIS
Possible use of EHR for data collection for drug use result survey

Hospital A
- Data in EHR
- Patient
- Target drugs
- Efficacy
- AE
- Lab tests
- Operation
- Hospitalization

Hospital B
- Data in EHR
- Patient
- Target drugs
- Efficacy
- AE
- Lab tests
- Operation
- Hospitalization

Standardization

Clinical Research DB

Survey A
- Company A

Survey B
- Company B

Survey C
- Company C

Survey D
- Company D

PMDA
- Standardized Drug Use Result Survey DB

Companies:
- Company A
- Company B
- Company C
- Company D

Possible use of EHR for data collection for drug use result survey
Pilot study for examining the utility of electronic health database for the purpose of pharmacovigilance
Objective: To assess electronic health information whether it could be a innovative tool to strengthen our pharmacovigilance activities through characterization of electronic health information from two different data sources, investigation for the method to extract data regarding drug adverse reactions, and analysis of the data to estimate risks.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Medical Information System (MIS) study</th>
<th>DPC study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data source</td>
<td>Medical records</td>
<td>DPC (Claim data)</td>
</tr>
<tr>
<td>Investigation event</td>
<td>A) Pseudomembranous colitis / Antibiotics</td>
<td>A) Pseudomembranous colitis / Antibiotics</td>
</tr>
<tr>
<td></td>
<td>B) Stevens Johnson Syndrome / Antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C) Rhabdomyolysis / Statins</td>
<td></td>
</tr>
<tr>
<td>Number of participated hospital</td>
<td>1 (The same hospital for MIS study and DPC study)</td>
<td></td>
</tr>
</tbody>
</table>
Method

Study target populations prescribed antibiotics or statins were identified according to the criteria. Case patients were identified by the criteria of the events (A, B, or C). The extracted data was calculated, and exploratory analysis was adopted to Pseudomembranous colitis / antibiotics (event A) in MIS study.

Result

From MIS study, target populations were identified as 7,259 for antibiotics and 1,920 for statins. There were 55 cases of Pseudomembranous colitis, 1 case of Stevens Johnson Syndrome, and 1 case of Rhabdomyolysis. Proportion of the events were 0.76 %, 0.01 %, and 0.30 %, respectively.

From DPC study, target population was identified as 3,335 and there were 10 cases of Pseudomembranous colitis, therefore, the event proportion was 0.30 %.

Ethical consideration

This study followed ‘Ethical guideline for epidemiological studies’ which was provided by MHLW. As the guideline indicated, informed consent was not required in this study since it was an observation study only using existing documents.

The study plan was approved by ethical committee in the hospital where the study was conducted. The notice about this study had been posted at the hospital during the study period so that the people visiting doctors could have an opportunity to decline using their data.
### Criteria for Study target population

- Hospitalized during January 1, 2007 to December 31, 2007
- Older than 20 years at hospitalization
- Prescribed antibiotics (injection) during hospitalization

### Criteria for Case: Conditional expression (1 OR 2 OR 3) AND (4)

1. Have a corresponding diagnosis (ICD-10/A047)
2. Detected *C. difficile* by immunological assay
3. Prescribed oral Vancomycin
4. Drug exposure period: start date of prescription – end date of prescription PLUS 3 days
   
   Date of No. 1 or 2 or 3 (index date) are included in the drug exposure period.
Table 1. Number of target population and case

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Case</th>
<th>Percentage of the case</th>
</tr>
</thead>
<tbody>
<tr>
<td>7,259</td>
<td>55</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 2. Matched criteria of case

<table>
<thead>
<tr>
<th>Criteria of the case</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of pseudomembranous colitis (33)</td>
<td>X</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Positive result for C. Difficile test (42)</td>
<td>X</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Prescription of oral Vancomycin (18)</td>
<td>X</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>8 (15)</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>17 (31)</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 (100)</td>
</tr>
</tbody>
</table>
Pilot (MIS) Study: Event A: Pseudomembranous colitis / antibiotics = RESULT(2)

Table 3. Characteristics of case and target population

<table>
<thead>
<tr>
<th></th>
<th>Case Number of patients (%)</th>
<th>Target Population Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (0.83)</td>
<td>3620</td>
</tr>
<tr>
<td>Female</td>
<td>25 (0.69)</td>
<td>3639</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average +/- SD</td>
<td>70.1±18.02</td>
<td>63.2±18.59</td>
</tr>
<tr>
<td>Lowest quartile</td>
<td>62</td>
<td>50</td>
</tr>
<tr>
<td>Median</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Highest quartile</td>
<td>83</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 4. Numbers of case and target population classified by the group of antibiotics prescribed

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Case Number of patients (%)</th>
<th>Target Population Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Beta-lactams Broad-spectrum</td>
<td>8 (1.26)</td>
<td>633</td>
</tr>
<tr>
<td>2 Beta-lactams Cephalosporins</td>
<td>6 (4.23)</td>
<td>142</td>
</tr>
<tr>
<td>3 (1st generation) Cephalosporins</td>
<td>12 (0.53)</td>
<td>2277</td>
</tr>
<tr>
<td>4 (2nd generation) Cephalosporins</td>
<td>12 (0.48)</td>
<td>2507</td>
</tr>
<tr>
<td>5 (3rd generation) Cephalosporins</td>
<td>21 (1.06)</td>
<td>1990</td>
</tr>
<tr>
<td>6 Monobactams</td>
<td>0 (0)</td>
<td>5</td>
</tr>
<tr>
<td>7 Carbapenems</td>
<td>37 (4.45)</td>
<td>832</td>
</tr>
<tr>
<td>8 Aminoglycosides</td>
<td>10 (4.81)</td>
<td>208</td>
</tr>
<tr>
<td>9 Fosfomycins</td>
<td>2 (6.45)</td>
<td>31</td>
</tr>
<tr>
<td>10 Vancomycins</td>
<td>12 (6.63)</td>
<td>181</td>
</tr>
<tr>
<td>11 Teicoplanins</td>
<td>2 (4.35)</td>
<td>46</td>
</tr>
<tr>
<td>12 Tetracyclines</td>
<td>4 (1.29)</td>
<td>309</td>
</tr>
<tr>
<td>13 Lincomycins</td>
<td>7 (3.33)</td>
<td>210</td>
</tr>
<tr>
<td>14 New quinolones</td>
<td>6 (4.41)</td>
<td>136</td>
</tr>
<tr>
<td>15 Sulfamethoxazole/Trimethoprim</td>
<td>0 (0)</td>
<td>4</td>
</tr>
</tbody>
</table>
Pilot Study : Conclusion

• Only one hospital participated in this study, however, some progresses were made -

  – ADR information could be identified from both medical records (Medical Information System) and DPC.
  – A framework to characterize medical records and DPC was successfully developed.
  – The health records have potential to become a useful tool for pharmacovigilance.

• The level of available information depends on data sources, therefore, the way we use each data source should be different. Further investigation is needed in order to establish procedures that will help us to utilize electronic health records as a new tool to strengthen pharmacovigilance in PMDA.
Establishment of Scientific Evaluation System for Post Market Safety of Medical Devices

- Registry of PCI (DES and BMS) and CABG in Coronary Artery Disease (with a focus on late/very late stent thrombosis)

- Japanese Registry for Mechanically Assisted Circulatory Support – J-MACS (equivalent to INTERMACS)
FDA’s Sentinel Initiative
THE SCIENCE OF SAFETY

We are seeing the emergence of a science of safety. This science combines the growing understanding of disease and its origins at the molecular level (including understanding of adverse events resulting from treatment) with new methods of signal detection, data mining, and analysis, enabling researchers to generate hypotheses about, and confirm the existence and causal factors of, safety problems in the populations using the products. In addition, personalized medicine is generating information about the unique genetic and biologic features of each person that some day will help determine how he or she responds to treatment. Using these tools, FDA has increasingly adopted a life-cycle approach to product development and evaluation. This kind of approach should be used for all medical products so that safety signals generated at any point in the process can be evaluated along with relevant benefit-risk data to inform treatment choices and regulatory decision making. FDA regards improving risk and benefit analysis to be one of the important facets of the science of safety that urgently requires additional development.
FDA’s Sentinel Initiative (2)

Sentinel Overview

• Develop an active electronic safety monitoring system to
  – Strengthen FDA’s ability to monitor postmarket performance of medical products
  – Augment, not replace, existing safety monitoring systems
  – Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)

• Data remains with data holders behind existing firewalls

• Data holders would run queries—FDA-requested, or other—(or could opt out)
  – Convey results summaries for review
  – According to strict privacy and security safeguards
FDA’s Sentinel Initiative (3)  Issues being examined

**Scientific Operations**
1. Defining and Evaluating Possible Database Models
2. Evaluation of Existing Methods for Safety Signal Identification
3. Evaluation of Timeliness of Medical Uptake for Surveillance in Healthcare Databases

**Governance**
4. Developing a Governance and Operations Structure for Sentinel Initiative

**Data and Infrastructure**
5. Evaluation of Potential Data Sources for Sentinel Initiative
6. Evaluating Potential Sentinel Network Data Sources for Blood and Tissue Product Safety Surveillance and Studies
7. Evaluation of Potential Data Sources for a National Network of Orthopedic Device Implant Registries-

**Privacy**
8. Engagement of Patients, Consumers, and Health Care Professionals in Sentinel Initiative
The way Forward
## 5-Year Road Map

<table>
<thead>
<tr>
<th></th>
<th>FY2009</th>
<th>FY2010</th>
<th>FY2011</th>
<th>FY2012</th>
<th>FY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Claim Data</strong></td>
<td>Small scale pilot study</td>
<td>Expansion of data source</td>
<td>Implementation in PMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DPC</strong></td>
<td>DPC pilot study</td>
<td></td>
<td></td>
<td>Implementation in PMS</td>
<td></td>
</tr>
<tr>
<td><strong>Oversees DB</strong></td>
<td></td>
<td>Analysis of oversees DB</td>
<td>Evaluation report</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical Information System</strong></td>
<td></td>
<td>Small Scale Pilot Study</td>
<td></td>
<td>Expansion of No. of hospitals</td>
<td>Implementation in PMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Examining technical issues</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>ADR DB</strong></td>
<td></td>
<td>Examining technical issues</td>
<td></td>
<td>Provision of DB</td>
<td></td>
</tr>
<tr>
<td><strong>DB for drug use result surveys</strong></td>
<td></td>
<td>DB creation</td>
<td></td>
<td>Implementation in PMS</td>
<td>Provision of DB</td>
</tr>
<tr>
<td></td>
<td>Discussion on policy, objectives, requirements</td>
<td>Pilot use</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Other technical issues</td>
<td></td>
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</tbody>
</table>
Plan for 2009 and after

<Claim data>

> Small scale pilot study using commercially available claim DB (relatively small number of subjects).

> To conduct actual analysis on an AE and a medicine on DB.

> To identify characteristic and usability of claim data.

<Medical Information System> <DPC>

> To obtain medical records in a standardized format from a small number of hospitals.

> To conduct actual analysis of a specific AE and a specific medicine on HIS data.

> To identify characteristic and usability of MIS data.

> Same study for DPC data as appropriate
Plan for 2009 and after

<Existing DB abroad>
  > To study existing DB in the US and Europe.

  > Also to study how regulatory agencies such as FDA/EMEA use those DB for epidemiological analysis and for regulatory consideration and action.

<ADR Database>
  > To start consideration of
    - improving content and presentation of ADR line listing on PMDA website.
    - providing ADR data available for researchers etc. for data-mining and other analysis

<Drug Use Result Survey Data>
  > To start consideration of
    - promoting feedback and use of drug use result survey data including provision of a database
Thank you very much for your kind attention