Regulator’s Utilisation of Big Data in Pharmacovigilance Activities

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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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<tr>
<td>☐ Grants/Research Funding</td>
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</tr>
<tr>
<td>☐ Stock Shareholder</td>
<td></td>
</tr>
<tr>
<td>☐ Consulting Fees</td>
<td></td>
</tr>
<tr>
<td>☐ Employee</td>
<td></td>
</tr>
<tr>
<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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Overview

► Great changes in the circumstances surrounding post-marketing drug safety measures from the end of 20th to the 21st century in Japan.

► PMDA has made efforts for implementing new framework & building new infrastructure for reinforcing post-marketing drug safety measures by utilizing Big RWD.

► Renovation of Good Post-Marketing Study Practice for utilizing Big RWD.

► Major future tasks for accelerating utilization of Big RWD.
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- Major future tasks for accelerating utilization of Big RWD.
Previously: Circumstances surrounding Post-Marketing Surveillance about a decade ago in Japan

More than half of new drugs were approved about 1 to 3 years behind the US.

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Lag (Median-Year)</td>
<td>1.2</td>
<td>2.4</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Review Time Lag (Median-Year)</td>
<td>1.2</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Drug Lag</strong> (Total of Above)</td>
<td>2.4</td>
<td>3.4</td>
<td>2.2</td>
<td>2.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Safety data in clinical practices (in foreign countries) were usually available for newly approved drugs in Japan.

Thus, a Japanese study in the post-market has been conducted for confirming there are **NO BIG DIFFERENCES** in safety between Japanese and Foreign population as well as between pre- and post approval.

Ando Y. et.al., GaBI Journal, 2013;2(1):41-4
Conventional approach for providing Post-Marketing Safety Measures

Drug Safety Assessment

- Spontaneous Adverse Drug Reaction report DB
- Literatures
- Overseas regulatory actions

Report

Safety Measures

Ministry of Health, Labour and Welfare

Risk Communication

Medical institutions
Entering an era of simultaneous approval in ICH regions

Median approval time for NASs approved by ICH agencies by approval year

Review time in Japan has shortened and is similar to US and EU time

faced with new challenge...

For a new drug approved in Japan, no experiences or a limited experiences in clinical practices were available in any countries.

Center for innovation in regulatory science (CIRS), R&D Briefing 62: “New drug approvals in ICH countries 2007 – 2016”
Big RWD in the field of health service has been emerged

- **Health insurance claims**: 98% are computerized!

- **Electronic medical records**: 77% of hospitals with over 400 beds are using!
  (Government's Goal: 90% by Mar. 2020)

> **PMDA had started to utilize those Big RWD as an additional data source for conducting more efficient and effective safety measures of new drugs.**
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Efforts for utilizing Big RWD in PMDA

**MIHARI Project**
To establish a new framework for promoting implementation of safety measures on the basis of quantitative risks provided by evaluation of electronic healthcare data available in Japan.
(Pilot phase 2009 - 2013. Since 2014 fully implemented!)

**MID-NET® Project**
(MID-NET®: Medical Information Database NETwork)
To establish a new distributed database system for utilizing in safety assessment, consisted of Hospital Information System (HIS) data managed by 23 hospitals of 10 medical institutions in Japan. (Development phase 2011 - 2017. Since Apr. 2018 fully implemented!)
Current framework for drug safety measures using RWD implemented by MIHARI Project

Drug Safety Assessment

- Conventional data
  - Spontaneous Adverse Drug Reaction report DB
  - Literatures
  - Overseas regulatory actions

- Real World Data
  - Health insurance claims DB
  - National claims DB

Report

Safety Measures

- Ministry of Health, Labour and Welfare
- Medical institutions

Risk Communication

NOW, We can use...

- Detailed
- Real Time
- Quality Managed

Medical Information Data!

Started full-scale operation since April 2018!
NOW, We can use...  

Detailed  

Real Time  

Quality Managed  

Medical Information Data!

Database in each hospital are converted to Common Data Model!

Various HIS data are available!

- Patient identifying data
- Medical examination history data (including admission, discharge data)
- Disease order data
- Discharge summary data
- Prescription order/compiled data
- Injection order/compiled data
- Laboratory test data
- Radiographic inspection data
- Physiological laboratory data
- Therapeutic drug monitoring data
- Bacteriological test data

Approximately 200 lab test results are available!

<table>
<thead>
<tr>
<th>Fe</th>
<th>FT3</th>
<th>KL-6</th>
<th>CK-MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>FT4</td>
<td>LAP</td>
<td>CRP</td>
</tr>
<tr>
<td>Ca</td>
<td>GOT(AST)</td>
<td>PIV-KA-Ⅱ</td>
<td>CYFRA</td>
</tr>
<tr>
<td>Na</td>
<td>GPT(ALT)</td>
<td>PRP</td>
<td>EPO</td>
</tr>
<tr>
<td>Mg</td>
<td>HBs (+/-)</td>
<td>T3</td>
<td>FSH</td>
</tr>
<tr>
<td>HbA1c</td>
<td>HBs (IU/ml)</td>
<td>T4</td>
<td>thrombocyte</td>
</tr>
<tr>
<td>GLU</td>
<td>HBs (ClO)</td>
<td>TPHA</td>
<td>monocyte</td>
</tr>
<tr>
<td>ALP</td>
<td>HB virus</td>
<td>TSH</td>
<td>lymphocyte</td>
</tr>
<tr>
<td>AMY</td>
<td>HC virus</td>
<td>TTT</td>
<td>acidocyte</td>
</tr>
<tr>
<td>ALB</td>
<td>hCG</td>
<td>ZTT</td>
<td>basocyte</td>
</tr>
<tr>
<td>HDL</td>
<td>hCG-β</td>
<td>γ-GTP</td>
<td>neutrophil</td>
</tr>
<tr>
<td>LDH</td>
<td>IgA</td>
<td>myoglobin</td>
<td>hematocrit</td>
</tr>
<tr>
<td>LDL</td>
<td>IgE</td>
<td>vitaminB₁₂</td>
<td>pH(blood)</td>
</tr>
<tr>
<td>TG</td>
<td>IgG</td>
<td>rheumatoid</td>
<td>pCO₂</td>
</tr>
<tr>
<td>Creatinine</td>
<td>IgM</td>
<td>folate</td>
<td>pO₂</td>
</tr>
</tbody>
</table>

: etc
NOW, We can use...

- Detailed
- Real Time
- Quality Managed

Medical Information Data!
NOW, We can use...

 Decorating
 Real Time

 Quality Managed Medical Information Data!

High quality and standardized data are available!

**Before Quality Management**

- Disease order data
  - Consistency: 99.1%
- Prescription order data
  - Consistency: 67.0%
- Laboratory test data
  - Consistency: 55.8%

**After Quality Management**

- Disease order data
  - Consistency: 99.9%
- Prescription order data
  - Consistency: 100.0%
- Laboratory test data
  - Consistency: 100.0%
MID-NET® can be utilized for various Post-Marketing Studies

**Drug utilization study**
- Investigate volume of prescriptions, days of prescriptions and interval of prescriptions

**Cohort study**
- Single Cohort (investigation of event occurrence and patient background)
- Double Cohort (Adjust covariates and investigate the relationship between risks and exposures)

**Interrupted time series**
- Investigate transitions before and after safety measures to evaluate impacts of the measures

**Nested case control study**
- Focusing on a specific outcome, investigate the risk by the presence or absence of risk factors
Example for interrupted time series analysis

Objective:

– To evaluate the risk of severe hypocalcemia and the effect of the regulatory action.
Proper selection of data source is essential for scientific safety assessment.

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Electronic Medical Records</th>
<th>Health Insurance Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Provider</td>
<td>10 Medical institutions</td>
<td>All health insurers in Japan</td>
</tr>
<tr>
<td>Covered patients</td>
<td>People provided medical service by each institution (~4 Million)</td>
<td>Entire Japanese population (120 Million)</td>
</tr>
<tr>
<td>Obtainable Health Information</td>
<td><strong>Detailed information in medical practices</strong> by each institution</td>
<td><strong>Standardized information relevant to reimbursement</strong></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Medical procedure</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Pharmacy Dispensing</td>
<td>YES (on-site pharmacy)</td>
<td>YES</td>
</tr>
<tr>
<td>Laboratory test result</td>
<td><strong>YES</strong></td>
<td><strong>NO</strong></td>
</tr>
<tr>
<td>OTC Drug</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

NATIONAL CLAIMS DB

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Role of Pharmaco-Epidemiologist in PMDA

**<pre-approval>**
- Review the Risk Management Plan of the new drug
- Propose appropriate post-marketing studies

**<post-approval>**
- Conduct pharmaco-epidemiological studies by utilizing Big RWD
- Review observational studies / reports submitted by MAHs
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Planning of Risk Management Plan

Purpose of re-examination: To reconfirm safety and clinical effectiveness of the new drugs at post-market stage after approval.

Routine Pharmacovigilance Activities
- Spontaneous ADR reporting
- Continuous monitoring of safety profile (signal detection) etc.

Additional Pharmacovigilance Activities
- EPPV (6 months)
- Post-Marketing Surveillance
- Post-Marketing Clinical Trial if necessary

EPPV: Early Post-marketing Phase Vigilance

Re-examination period (4-10 years)
Renovation of Good Postmarketing Study Practices

- Nov. 2017: Amendment of the Good Postmarketing Study Practices (GPSP) 
  “Post-marketing Database Surveillance” was newly defined.

**Old GPSP**
Primary data collection was only mentioned as a post-marketing study of new drugs

**Renovated GPSP**
Secondary use of database is allowed as a post-marketing study in addition to the primary data collection.

Selectable design for post-marketing study
- Primary data collected from hospitals
- Post-marketing Clinical Trial

Selectable design for post-marketing study
- Primary data collected from hospitals
- Real World Data provided by database holder (including patients registry)
- Post-marketing Clinical Trial
Guidelines & notifications for utilizing RWD by MAH

- “Points to consider for ensuring the reliability in conducting post-marketing database surveillance” (Notification No. 221, MHLW, Feb. 2018)
- “Points to consider for planning Pharmacovigilance activities” (PMDA, Feb. 2018)
- “Contents and format of a study protocol for Post-marketing Database Surveillance” (PMDA, Jan. 2018)
- A revision of “Case Examples of Risk Management Plan” (PMDA, Dec. 2017), including a case of database study
- “Basic principles in utilizing medical information database on Pharmacovigilance” (Notification No. 609, MHLW, June 2017)
Planning Steps for RMP/Pharmacovigilance Activities

- **Step 1.** Clarification of serious concerns about post-marketing safety and/or effectiveness.
- **Step 2.** Selection of scientific approaches as Pharmacovigilance activities.
- **Step 3.** Understanding obligation to comply with regulatory requirements.
- **Step 4.** Making a detailed plan for Pharmacovigilance activities, including a planning of study protocol.

**Oct. 2017, PMDA started a new consultation service for planning Pharmacoepidemiological study as a Pharmacovigilance activity**
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Challenges and Actions for Accelerating Adequate Utilization of RWD

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conducting scientifically appropriate PMS</td>
<td>☑ Publish regulatory guidelines to promote post marketing studies utilizing RWD</td>
</tr>
<tr>
<td></td>
<td>☑ PMDA Consultations for planning Pharmaco-Epi Study</td>
</tr>
<tr>
<td>Ensure the quality of study plan &amp; results</td>
<td>☑ Amendment of GPSP and regulatory inspections</td>
</tr>
<tr>
<td></td>
<td>☑ Publish regulatory guideline on the reliability of post-marketing studies utilizing RWD</td>
</tr>
<tr>
<td>International cooperation</td>
<td>? More collaborations for sharing experiences and knowledge about utilization of RWD for regulatory purpose</td>
</tr>
<tr>
<td></td>
<td>? International harmonization on standards for data quality and analytical methods in utilizing RWD</td>
</tr>
</tbody>
</table>

*Scientific approaches and careful considerations in utilizing and evaluating RWD are the key to avoid causing chaos and unrest on RWD utilization*
PMDA

**Regulatory decisions based on better scientific evidences**
- PMDA had started routine use of medical information data for assessing safety concerns on daily clinical practice in Japan.

Industries

**Risk Management Plan implementation utilizing Big RWD**
- Rapid, effective and efficient risk management
- Better quality of safety information

Medical Institution

**Provide leading-edge medical therapy with ensuring safety**
- Scientific and speedy safety measure

Public

**Better quality of medical care**
- Maximize benefit/risk ratio