POST-MARKETING SAFETY MEASURES IN JAPAN

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Mr. Akira Kawahara
Chief Safety Officer, PMDA, JAPAN

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Overview of PMDA

NAME: Pharmaceuticals and Medical Devices Agency

INAUGURATION: April 2004

MANAGEMENT: • Effective operation under “Medium Term Plan” for 5 years’ activities
  • Subject to regular evaluation of performance by the Evaluation Committee organized by MHLW

FINANCE: Corporate accounting method and subdivided accounts according to the functions

Financial resources:
• User fee (Review and Inspection)
• Contribution Funds (Post-marketing, Relief)
• Appropriation from Gov. budget
Organization of PMDA

PMDA’s Services

- Adverse Health Effect Relief Services
- Post-marketing Safety Operations
- Reviews and Related Operations
3 Pillars of Safety Operations

- Post-marketing Safety Operations for Drugs/Medical Devices
- Reinforced Safety Information (Database)
- Scientific Review and Research for Safety Information
- Information Provision (via the Internet), Pharmaceutical Consultation for Consumers
Post-Marketing Safety Scheme

MHLW

PMDA

PFSC*

- Review line-list of ADRs/Infectious diseases
- Make recommendations on safety measures, such as revision of package insert

Instruction of Safety Measures

Safety Information Dissemination

Medical Institutes, etc.

Reporting of ADRs/Infectious Diseases (3,609 cases, FY2006)

Reporting of ADRs/Infectious Diseases (26,309 cases, FY2006)

Safety Data Collection

Safety Information Dissemination

MAH

MHLW 143 staff --- Safety Div. 27 staff

PMDA 348 Staff --- Office of Safety 38 staff

PFSB 143 staff --- Safety Div. 27 staff

PMDA 348 Staff --- Office of Safety 38 staff

Safety Information Dissemination

Medical Institutes, etc.

Safety Data Collection

Safety Information Dissemination

* Pharmaceutical and Food Safety Council
Organization of Ministry of Health, Labour and Welfare

Ministry of Health, Labour and Welfare

Ministry Proper
- Minister’s Secretariat
- Health Policy Bureau
- Health Service Bureau

Pharmaceutical and Food Safety Bureau (PFSB) 143 staff
- Social Welfare and War Victim’s Relief Bureau
- Health and Welfare Bureau for the Elderly
- Equal Employment, Children, and Families Bureau
- Insurance Bureau
- Pension Bureau
- Director-General for Policy Planning and Evaluation

General Affairs Division
- Evaluation and Licensing Division
- Safety Division 27 staff
- Compliance and Narcotics Division
- Blood and Blood Products Division

Social Insurance Agency
FY2008 Budget for Pharmaceuticals
(Pharmaceutical and Food Safety Bureau, MHLW)

- FY2008 Budget ￥8,882mil./$88.9mil.
  (Safety Div. ￥249.6mil./$2.5mil)

- FY2007 Budget ￥8,916mil./$83.5mil.
  (Safety Div. ￥243.4mil./$2.4mil)

  - Difference △￥34mil./$0.32mil.
  - FY2008/FY2007 99.6%

NOTE: Japanese FY covers the period of Apr. 1 through Mar. 31.
$1=￥99.95 (as of Mar.19, 2008)
PMDA: Office of Safety

Chief Safety Officer

Office of Safety (38 regular staff)

- Planning & Management Div. (4 staff)
- Safety Info. Div. (4 Staff)
  - Info. Support Group
- Surveillance and Analysis Div. (6 Staff)
  - Drug Safety Div. (16 Staff)
  - Medical Device Safety Div. (7 Staff)
  - Medical Safety Info. Group

In addition, there are around 30 support staff and clerks as well as 5 part-time professional advisors (MD and statistician).
FY2008 Budget for Pharmaceuticals
(Office of Safety, PMDA)

• FY2008 income from MAHs est. ¥ 1,280 Mil.
• FY2008 MHLW subsidy est. ¥ 252 Mil.
• Others est. ¥ 4 Mil.
• (total ¥ 1,536 Mil.)

• FY2007 income from MAHs ¥ 1263 Mil.
• FY2007 MHLW subsidy ¥ 255 Mil.
• Others ¥ 5 Mil.
• (total ¥ 1,523 Mil.)

• Covering budget for Medical Devices Safety and partially for Quality (GMP/QMS and standard development)
For “Safer” Drugs / Devices

For “Safer” Drugs / Devices

ADR and Infectious Disease Report System

Various cases undetected even by doctors

Post-marketing Surveillance

Review and Approval

Early-phase Post-marketing Vigilance

Reexamination and Reevaluation

Review

Safety

Reinforce Risk Management

Inseparable Pair
Vigilance Operation Flowchart

Company

- Collect and study Information on Quality, Efficacy and Safety of Drug/Medical Device
  - Analysis
  - Consideration of Safety Measures
- Implementation of Safety Actions

PMDA

- Report
  - Receipt of Information on Quality, Efficacy and Safety of Drug/Medical Device
- Interviews
  - Company Interviews
- Data Collection, Analysis, Evaluation
- Instruction and discussion of Safety Measures
- Data Arrangement, Study Results
- Consultation with Experts

MHLW

- Grasp All Information
  - Extract Urgent & Significant Information
  - Administrative Considerations, Policy Planning for Safety Measures

Foreign Government Agencies, WHO

Academic Journals, etc.

Medical Institutes, Clinics, Pharmacies, etc. (ADRs)

Healthcare Providers, Mass Media, the Public

Safety Information Collection

Information Distribution

Instruction of Labeling Change, Quality improvement, Recall, etc.

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Information Distribution

Information Distribution
Outline of Information Flow (1) (MAH)

Collection of Safety Information

Information Source
- Healthcare providers
- Scientific journals or meetings
- Foreign Govs. etc.

PMS Manager
- Collection and analysis of safety info.
- Planning and execution of safety measures

PMS Management Dept.
- Healthcare providers
- Hospitals, pharmacies etc.
- PMDA

Execution of Safety Measures Report to PMDA

Marketing Supervisor General
- Direction, Decision

Quality Assurance Manager
- Coordination

MAH
Outline of Information Flow (2)

- Report from Company
  - Interview with company
    - Data collection, analysis, evaluation
  - Data collection, analysis, evaluation

- MHLW
  - Information from RA, WHO
  - Academic Journals
  - Report from HCPs

- PMDA
  - Grasp all information
  - Extract significant info.
  - Planning for safety measure

- Safety Actions
  (Administrative Advice for revision of package insert etc.)

RA: Regulatory Authority
JP Postmarketing activities

- PMS
  - Safety report
  - Re-examination
    - Periodic Safety Report
      - Incl. PSUR
    - Re-evaluation
  - Risk Minimization
    - Risk Communication
  - EPPV

- Expedited
- Periodic
- Drug Use Investigation
- Drug Use Investigation of Special Population
- Postmarketing Clinical Trial
- Periodic
- Ad hoc
- Quality
Electronic Reporting transmitted by internet

Reporting by FD

Reporting by paper documents
ADR Report from HCP

- voluntary basis
  - since 1967: designated medical institutions
  - since 1984: designated pharmacies
  - since 1997: all medical institutions and pharmacies
- stipulated in PAL
  - since 2003
- HCPs shall report to MHLW when
  - detect occurrence of any disease suspected to be caused by adverse reactions
  - confirm that it is necessary to prevent occurrence or spread of hazards
ADR Reporting by Med. Inst.

Electronic Reporting

① FAX

Medical Institutes

Postal Mail

② MHLW (Paper and Electronic Reports)

④ Investigation

Pharm. Company

ADR Reporting by Company

⑤ PMDA

③ Feedback
### ADR Reporting Rule (Drug)

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Predictability</th>
<th>Time frame of report to PMDA</th>
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<tbody>
<tr>
<td>Serious</td>
<td>Not predictable</td>
<td><strong>15 days</strong></td>
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<tr>
<td></td>
<td>Predictable</td>
<td>- Death etc.* 15 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Others 30 days</td>
</tr>
<tr>
<td>Not serious</td>
<td>Not predictable</td>
<td><strong>Annually</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Annual Cumulative Report)</td>
</tr>
<tr>
<td></td>
<td>Predictable</td>
<td>-</td>
</tr>
</tbody>
</table>

- Reporting time frame depends on seriousness and predictability of the case. (Article 253 of the Ministerial Ordinance on PAL)

- No timeframe defined for HCP reporting

* - Death
  - ADR caused by new drug ingredient within 2 years after approval
  - ADR detected by Early Phase Post-marketing Vigilance (EPPV)
Reported ADR / Infectious Disease Cases

![Graph showing reported ADR and infectious disease cases from 1996 to 2006.]

Note: Foreign reports by drug makers are not included in and before FY03'.
Course of Post-marketing Safety Measures

- After-the-Fact Measures (Measures taken after the incidence of ADR)
- Prognostic Measures (Measures taken for drugs/patients with possible incidence of ADR)
- Preventive Measures (Measures taken for high-risk situation (high-risk patients etc.))
Safety Measures

- Revision of a package insert
- Recall/withdrawal, suspension of the sale
- Improvement of the products to prevent reoccurrence of the AE

- Administrative Instruction/Advice by PMDA/MHLW to MAH to revise safety information in package insert; “Precautions for Use,” “Boxed Warning,” etc.
- Dissemination of information on ADR/AE incidents and measures against them (e.g., publication of “Pharmaceuticals and Medical Devices Safety Information” and “Urgent Safety Information” by MHLW) etc.
Early Phase Post-marketing Vigilance (EPPV)

• Promote proper use of new drugs
• Detect serious ADRs earlier
• Take safety measures quickly

• Protect patients from ADRs
Early Post-Marketing Phase Vigilance : EPPV

Enforced on Oct 1, 2001

1. To ensure necessary information for appropriate use (contraindication, careful administration etc) is explained to the medical institutions 2 weeks before delivery.

2. To request medical institutions to use the drugs carefully and report serious ADRs, if occurred, immediately to pharmaceutical companies.

3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.
Early Phase Post-marketing Vigilance, EPPV

- Preparation of the protocol of EPPV
- Sale
- Delivery of new drugs to medical institutions
- Giving information by visiting, letters, FAX, E-mail etc.
- Reports of Adverse Reaction
- Sale
- 0-2 months
- Every 2 wks
- Once a month
- 6 months
- 8 months
- Report to MHLW
Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV (average per month)

EPPV was introduced in October 2001.
Number of before-EPPV is based on 30 new active ingredients launched between Apr. 2000 and Mar. 2001.
Information on approvals of Drugs/Devices

Package Inserts for Pharmaceuticals or Medical Devices

Reports of suspected adverse events or suspected Defects

Doctor letters and Safety Information

Information for the Health Care Professionals

Recalls

Information about the free mail system provided by PMDA

Pharmaceutical Guidance for patients

Consultation on Drugs/Devices

Measures against the Serious Adverse Events

Q&A on Pharmaceutical

For Patients and the general public

For Health Care Professionals

Package Inserts for OTC Drugs

Information for the general public
Information distributed by MHLW/PMDA

• Revision of package insert by MHLW
• Documents of Committees/Working groups available on the MHLW website (Japanese only)
• Pharmaceuticals and Medical Devices Safety Information by MHLW (PMDSI English version to be available by PMDA)
• Pharmaceuticals and Medical Devices Information Website (PMDInfoWeb, Japanese only) by PMDA
  – Package insert, guidance for patients, rules of ADR reporting, pieces of ICSRs and etc.
Improvement of Safety Measures

Safety Measures Based on a Series of Cases

Case 1

Case 2

Case 3

Case X

MHLW Implementation of Safety Measures

Prospective/Preventive Safety Measures

PMDA

Data Mining Technique

Sentinel Medical Institution Network (In Specific Area)

Risk Extraction

Scientific Analysis/Evaluation

MHLW Implementation of Safety Measures
Application of Data Mining Method to Post-marketing Safety Operations

Diagram:
- All Adverse reactions information
  - Adverse reactions information which needs further investigations
  - Adverse reactions information which needs response/measure

Analysis operations:
- Line List analysis
- Signal detection
- Case analysis

Consideration on the need of hearing with companies and experts

Database of adverse reaction reports:
- Line list (Weekly, daily)
- Detection results by data mining (Signal detection technique)
- Case cards
Sentinel Medical Institution Network for Oncology Combination Therapy Surveillance

Academic society

Cooperating hospitals
  - Patient Registry
  - ADR case report

Follow up Inquiry

ADR feedback

PMDA
  - ADR Frequency Monitoring
  - Analysis of collected data

PMDA

External Experts

MHLW

Safety Action

Companies

Info.

ADR cooperation

Info.

Prescription

Patient
Present situation of “Drug Lag”

1,417 days (approx. 4 years)

Average days to launch 100 world best selling products in each country after their first launch. Because different combinations of 100 world best selling products are marketed in different countries, average days are calculated based on the products actually marketed in each country.

Research paper No. 31
Measures and policies to reduce the drug lag
Target Setting FY 2007 ~ 2011 (5 years)

Aims: To reduce the “drug lag” by a total of 2.5 years by 2011 through 1.5 year and 1.0 year reductions respectively in the development and approval times; and to cut down the marketing lag to 500 days in line with the U.S.

Development time
Current time lag of application between Japan and US/ EU: 4.3 years (median)

Approval review time
Present total review time of standard products: 22 – 24 months (median)

To reduce current time lag of application between Japan and US/ EU by 1.5 years

To reduce Total TC (median) for standard products applied after FY2004 by 1.0 year

To reduce a total of 2.5 years
Total risk management system for Consultation, Review and Safety

Present

- Clinical trial consultations etc.
  - Correction and addition of data
  - Rejection of inadequate data
  - Advice on development strategy
  - Global clinical trial consultation
  - Advice and instruction on Pharmacovigilance

Future

- Clinical trial consultations etc. (prior evaluation)
  - Advice on development strategy
  - Global clinical trial consultation
  - Advice and instruction on Pharmacovigilance

Review

Safety

(Application with inadequate documents will be rejected)

I. Enhancement of CT consultation
   - Conduct the review of toxicity and pharmacology etc. beforehand as a part of consultation
   - Advice on development strategy at the early stage of development, clarification of review policy
   - Enhanced measures for global collaborative clinical trial and state-of-the-art science and technology

II. Review with selected focuses
   - Focused on essential evaluation of efficacy and safety

III. Enhancement of safety measure
   - Start giving advice and instruction on Pharmacovigilance from the consultation stage
Cooperation between review and safety (Current)

Offices of New Drugs

- New drug application
- Initial Interview
- Expert discussions on review
- Meeting on items for the council

Council (committee/executive session)

- Approval
  - Use-results surveillance, Special use-results surveillance and Protocol of Post-market clinical trial
  - Report of the result of early phase post-marketing phase vigilance

- Safety update
  - Consideration of need for package insert revision

Office of Safety

- Collection of safety issues
- Consideration of the need and issues for early post-marketing phase vigilance
- Consideration of the draft package insert

Reexamination

- Reports of use-results surveillance, Special use-results surveillance and the Post-marketing clinical trial
Future Perspective:

Total Management of Safety Information from developing stage to Post Marketing Phase

- to create a system in PMDA to manage all safety information from development and review stage to post marketing phase by strengthening cooperation between OND and Office of Safety with a view to giving timely and effective guidance and advices on safety measures

- Contribute to Life Cycle Management of Drugs
  - Identification of Safety Specification of New Drugs
  - Design of Post Market Studies and Investigations to address the specification
  - Assessment of the results of studies and investigations
Our Mission (MHLW／PMDA)

To Ensure **Faster** Access to **More Effective** and **Safer** Pharmaceuticals, Medical Devices for the Public

Improving Public Health