THE BENEFIT/RISK BALANCE DURING THE LIFE CYCLE OF DRUGS IN JAPAN

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1. Balancing Benefit and Risk
2. Risk Manager
3. Risk Management Plan (RMP)
4. PMDA’s view on Pharmaceutical Affairs
1. Balancing Benefit and Risk
PMDA’s Safety Triangle

**Review**
Risk reduction

**People**

**Safety**
Continuous risk mitigation efforts

**Relief**
Relief measures for health damage caused by risk factors
Improving Estimation (Efficacy & Safety)

Balancing Various Factors
  e.g. Benefit / Risk
  Social Impact

Developing New Tools

Three Pillars of Regulatory Science

Regulatory Science (RS):
“the science aimed at the optimal introduction of new products of science, such as discovered substances and new scientific tools/technologies and knowledge/information into society.”

Regulatory science as a bridge between Science and society.
Continuous and Comprehensive B/R Evaluation through Life Cycle of Drugs

Benefits

Risks

Development
(Clinical Trial Consultation)

Review

Post-Market
Responsibilities of Companies and Regulators

- Evidence for efficacy and safety of medical products should be produced by the companies.
- Regulators instruct the companies to produce and visualize scientific evidence of medical products.
- Medical Products should be so used that their Risk can be minimized and their Benefit maximized.

Basis for Regulatory Decision

RMP and Collaborative Post Market Measures
B/R Evaluation throughout Life Cycle of Drugs and Pharmacovigilance Strategies

(New Approach)

- **Companies’ effort**
  - RMP

- **PMDA’s effort**
  - Risk Manager system
  - MIHARI project
  - EMR network project

- Spontaneous reporting system
- Use result survey
- Early Post-marketing Phase Vigilance (EPPV)
- Revision of package insert
- Preparation and provision of Medication guide for patients

(Existing Approaches)

- Development stage
- Review stage
- Post-approval stage
2. Risk Manager
12 Risk Managers (RMs) in different disease areas

RMAs are liaison between clinical development and post-marketing safety measures

RMAs contribute to life cycle monitoring of drug safety, and to more appropriate and timely safety actions to be taken.
Risk manager in PMDA review team

Advise to developing product;
- To clarify the safety issues
- To make safety measure before approval
- To identify issues to collect post-marketing data
- To avoid misuse
- To make user friendly information (incl. labeling)

*Responsible for coordinating review and safety departments
development of early post-marketing phase vigilance plan

Advice on Drug’s post-marketing safety measures

evaluation of the result of post-market survey

[Case of Dabigatran]

Risk Manager

Risk Manager throughout Drug Life Cycle

Development

Review

Post- market

Review Department

Safety Department

(Act as Liaison)
3. **Risk Management Plan (RMP)**
1. **Aim**
   1. Life-cycle Risk Management
   2. Follow-up specified known/unknown Risks
   3. Help applicants produce evidence on safety and efficacy
   4. Clarification of evidences to get applicants involved
   5. Help to evaluate benefit/risk strategically

2. **Procedure**
   1. Companies submit Draft RMP with NDA (Apr. 2013-)
   2. Discussion and agreement on RMP b/w PMDA and companies before approval
   3. Revision after marketing at safety events
Conceptual Diagram of RMP (workflow process)

Safety Specification
- Important Specified Risks
- Important Potential Risks
- Important missing Information

Pharmacovigilance Plan
- Routine
  - Spontaneous Report
  - Literature search
- Additional
  - Additional Risk Minimization practices
    - Enhancement of Spontaneous Report Collection by EPPV
    - Use result survey
    - Specified use result survey
    - Post-market Clinical Trial

Risk Minimization Plan
- Package Insert
- Precautions
- Information dissemination by EPPV
- Medication guide for patients
- Educational program
- Limiting access
- Revision of precautions

Risk Assessment (Periodical reports)

Additional action Necessary? (Assessment) ※ No

Additional Pharmacovigilance and/or Risk Minimization activities? (Assessment) ※

※: In deciding the measures to be taken, good consideration is required to avoid excess burdens and confusion in real clinical settings.
Characteristics of Japanese RMP

• Optimal risk management and data collection
  – Incl. generic drug
• Start discussion at the development stage
• Set up milestones
  – Obvious goal of surveillance
  – Revision of RMP by new information, if necessary.
• Transparency among stakeholders
  – Comprehensive information collection & risk management thorough life-cycle of the product
Guidance for RMP

Guidance for RMP was issued Apr. 11, 2012

Provides basic ideas for companies to prepare Risk Management

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PMDA’s view on Pharmaceutical Affairs

- **Purpose of Pharmaceutical Affair** is to **improve the public health** through regulations to **secure quality, efficacy and safety** of drugs and medical devices and taking necessary measures to **promote R&D**, where the **reliability** must be verified.

- Medical Service: *Individual Medicine/Health*
- Pharmaceutical Affairs: *Public Medicine/Health*
- **Ultimate Medical Ethics**
Scientific Integrity/Honesty

Academic Science

Absolute Values
Relative Values

Regulatory Science

Applying "Academic Science" to the Society through "Regulatory Science"

Contribution to the World and the Society
Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced scientific technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.

Basic Research

Seeds of new drug / medical devices originated in Japan

Pharmaceutical consultation on R&D Strategy

Clinical Trial Consultation

Review

POC / After POC

Non-clinical tests

Quality Tests

CT

Approve

Office of Review Innovation

Establishment of the Science Board

Academia

Board members

PMDA

Offices of review : Drugs & Medical Devices

Practical use

Innovative medical products
Collaboration among Industry, Government, Academia, and People with recognition of each parties’ obligations and responsibilities
Ultimate medical ethics is exemplified in pharmaceutical affairs.

Regulatory Science helps to practice medical ethics.