PMDA’s Efforts in Safety Measures - Risk Management Plan (RMP) in Japan -

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Pharmaceuticals and Medical Devices Agency (PMDA), Japan

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Netherlands
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Background concept
Continuous and Comprehensive B/R Evaluation through Life Cycle of Drugs

Development (Clinical Trial Consultation) -> Review -> Post-Marketing

Risks

Benefits

Risks

Benefits

Review

Post-Marketing

25th Annual EuroMeeting Amsterdam 2013 | 4-6 March 2013 | RAI, Amsterdam, Netherlands
Continuous Improvement of B/R Valance Through Life-Cycle of Product

Evidence of efficacy

Unknown Risk

Early development Phase

Increase

Planning, Conduct, Analysis, Evaluation

Decrease/Reduction

Late development to Post-market Phase

Volume

Quality

Diversity

Convert unknown risk to known risk

Risk minimization
Benefit /Risk from Patient View Points

Improve B/R valance

Disease Risk

Drug Efficacy

ADR

Disease Risk

Drug Efficacy

ADR

Elimination of Drug = Patient disadvantage

Disease Risk

only
PhV updates in Japan
Pharmacovigilance measures JP, US, EU

Pharmacovigilance strategies including Pharmacovigilance Plan will be integrated into RMP.

**JP**
- Pre-market review
- Approval
- Post-market
  - ADR/AE reporting
  - Re-examination
  - Periodic report
  - Post-market commitment
  - If necessary

**US**
- ADR/AE reporting
- Spontaneous ADR, infection Reporting
- REMS (high risk NME)
- Periodic report
- Post-market commitment
  - If necessary

**EU**
- ADR/AE reporting
- Spontaneous ADR, infection Reporting
- REMS (NME)
- RMP (NME)
- PSUR
- renewal
- renewal
The Current Framework for Post-Marketing Safety Measures

Drug Approval

- 4-10 years (8 years)
- EPPV
- PMS
- ADR and Infection Reporting

Re-examination
## Numbers of Adverse Drug Reaction Reports

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</thead>
<tbody>
<tr>
<td>Companies: Japanese ADR</td>
<td>28,500</td>
<td>32,306</td>
<td>30,928</td>
<td>34,677</td>
<td>36,741</td>
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<tr>
<td>Companies: foreign ADR</td>
<td>95,036</td>
<td>116,662</td>
<td>141,386</td>
<td>170,021</td>
<td>220,455</td>
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<tr>
<td>Health Care Professionals</td>
<td>3,891</td>
<td>3,816</td>
<td>6,181</td>
<td>4,809</td>
<td>5,231</td>
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</tbody>
</table>
Risk Manager system
What is the Risk Manager?

Development → Review → Post-marketing

- Review Department (Review Team)
- Safety Department (Safety Team)
- Risk Manager (Act as Liaison)

- Development of early post-marketing phase vigilance plan
- Advice on Drug’s post-marketing safety measures
- Evaluation of the result of post-marketing survey
Risk Manager System in Japan

• For the continuous and comprehensive benefit-risk evaluation
  – Through life-cycle of product
    • From development stage to review period and post-approval stage
    • Integration of information of development and post-marketing stage.

• Enhancement of human resources in the safety department of PMDA began in fiscal 2009 (+100 person)
  → Risk Manager (RM) was realized!!
Roles and duties of Risk Manager

• For the continuous and comprehensive benefit-risk evaluation
  – Through life-cycle of product
    • From development stage to review period and post-approval stage
    • Integration of information of development and post-marketing stage
• 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)
• Liaison between clinical development and post-marketing safety measures
• 13 Risk Managers in different disease areas
• Risk Managers will be mainly in charge of RMP
Continues Risk Management through Product Life-cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>Regulatory Tool</th>
<th>Person in Charge</th>
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</thead>
<tbody>
<tr>
<td>Clinical Development</td>
<td>Development Safety Update Report (ICH E2F)</td>
<td>Review Team</td>
</tr>
<tr>
<td></td>
<td>Risk Management Plan (ICH E2E+α)</td>
<td>Review Team</td>
</tr>
<tr>
<td></td>
<td>Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))</td>
<td>Review Team</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety Team</td>
</tr>
<tr>
<td>NDA Review Phase</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Post-Marketing Phase</td>
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</tr>
</tbody>
</table>

- **Clinical Development Phase**: Development Safety Update Report (ICH E2F)
  - Development Safety Update Report (ICH E2F)
    - Jasen'in yaku no knaitei kaishūkan kantsu kōnen nichishigakuchū no genkan sekai٠kōhatsu to kaihatsu wo hōterroru
- **NDA Review Phase**: Risk Management Plan (ICH E2E+α)
  - Risk Management Plan (ICH E2E+α)
    - Kyōyaku no kaibetsu no kenkyū jikken kōhatsu to kaihatsu wo hōterroru
- **Post-Marketing Phase**: Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))
  - Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))
    - Kyōyaku no genkai no beneffito・rikusu proffaihen keiyō wo kōnshun suru tameni kiyoyaku no rikusu no kaihatsu wo jikken kōhatsu to kaihatsu wo hōterroru

- Review Team
- Review Team
- Review Team

**Key Dates**
- Apr. 2013 - Currently

**Additional Information**
- **Risk Manager**
- **Person in Charge**
- **Regulatory Tool**
- **Review Team**
Risk Management Plan in Japan
Looking for more efficient post-marketing survey

- In most of products, post-marketing surveys are required:
  - Are they sufficient and minimum?
  - Are purposes of data collection clear?

- Discussion & Agreement of Post-marketing survey between PMDA and MAH before approval
  - Healthcare professional’s opinion have been involved in the review process, however,
  - Are the results of current post-marketing surveys useful for Healthcare professionals?
Concept of J-RMP

Safety Specification
- Important Identified Risk
- Important Potential Risk
- Important Missing Data

Pharmacovigilance Plan
- Spontaneous reporting
- Research Report
- Foreign actions report

Risk Minimization Action Plan
- Package Insert
- Booklet of Precaution for Use

- Additional RiskMAP
- Info Dissemination by EPPV
- Info for Health Professionals
- Drug Guide for patients
- Access restriction
  - etc

Routine
- Need Additional measures? (Evaluation)
  - No
  - Yes

Additional
- PvP and / or RiskMAP? (Evaluation)
  - Additional RiskMAP
  - Additional PvP

※ Burden on HCPs should be taken into consideration.
Development and revision of RMP

NDA application

Advisory committee approval

launch

~300 days

30~60 days

Consultation

Discuss between review team

Revision as necessary

Submit draft RMP as MAH

Confirmed RMP version agreed with review team

Ver.1.0 (finalized RMP) (1 month before launch)
Information about the RMP

• About drug risk management plan (in Japanese)
  – Objective
  – Conceptual diagram
  – Relevant documents
  – Case Described of drug risk management plan
    http://www.info.pmda.go.jp/rmp/to_company.html

• Risk Management Plan Guidance (in English)

• We are now preparing for providing information of RMP to HCPs and general public including patients
医薬品リスク管理計画（RMP：Risk Management Plan）について

目的

医薬品の安全性の確保を図るためには、開発の段階から製造販売後まで常にリスクを適正に管理する方針を検討することが重要です。

これまでのH・E2ガイドラインでは、医薬品の既知のリスクや未知のリスク等を対象として「安全性検討事項」として取り上げ、薬品安全性監視計画を作成することを求めていましたが、医薬品のリスクを低減するための方法については記載されていませんでした。

今回、医薬品安全性監視計画に加えて、医薬品のリスクの確認を図るためのリスク最小化計画を含めた医薬品リスク管理計画（RMP：Risk Management Plan）を策定するための指針「医薬品リスク管理計画指針について」及び具体的な計画書の様式、提出などの取り扱い「医薬品リスク管理計画の策定について」がどうなるか。

この指針の活用により医薬品の開発段階、承認審査時から製造販売後の全ての期間において、ベネフィットとリスクの評価・見直しが行われ、これまで以上に明確な見通しを持った製造販売後の安全対策の実施が可能となることを目的としております。

概念図

RMP全体のイメージ

安全性検討事項

・重要な既知のリスク
・重要な潜在的なリスク
・重要な不確実性

安全性監視計画

・自覚症状
・研究報告
・外国情報

リスク最小化計画

・医薬品の内容改訂
・患者とい薬品の対応

# PMDA English website

## Safety Information announced by MHLW

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
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<tbody>
<tr>
<td>April 11, 2012</td>
<td>Risk Management Plan Guidance</td>
</tr>
<tr>
<td>February 14, 2012</td>
<td>PFSE/SD Notification 0214-3 “Call attention to the Precautions of anti-influenza virus drugs”</td>
</tr>
<tr>
<td>August 12, 2011</td>
<td>Press Release: Warnings and Alerting Severe haemorrhages in patients treated with an anticoagulant “Pazaxa capsules (dabigatranetoxilat)”</td>
</tr>
<tr>
<td>August 2, 2011</td>
<td>Risk Management Plan(RMP) Guidance (Draft)</td>
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</table>

This draft guidance was issued to invite public comment by MHLW.

PFSB/SD Notification No. 0411-1
PFSB/ELO Notification No. 0411-2
April 11, 2012

To: Directors of Prefectural Health Departments (Bureaus)

From: Directors of Safety Division
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Risk Management Plan Guidance

To ensure the safety of drugs, it is important to consider the ways to manage the risk.
Current RMP in Japan

- Discussion & Agreement of RMP between PMDA and MAH before approval
  - Are Healthcare professionals involved?
- Most of products are required PMS.
  - Are they sufficient and minimum?
- Is RMP made based product’s character?
- Is purpose of RM/data collection clear?
1. Introduction

2. Risk Management Plan

3. Safety Specification

4. Pharmacovigilance Plan

5. Plan for Survey/Study on Efficacy

6. Risk Minimization Plan

7. Evaluation of Risk Management Plan and Report to PMDA
Characteristics of Japanese RMP

• Optimal risk management and data collection
  – Incl. generic drug

• Start to discussion at the submission of NDA

• Set up milestones
  – Obvious goal of surveillance
  – Revision of RMP by new information, if ecessary.

• Transparency among stakeholders
  – Comprehensive information collection & risk management thorough life-cycle of the product
Please Visit PMDA English website
RMP & B/R evaluation
Coming era of PBRER from PSUR

Periodic Benefit-Risk Evaluation Report (PBRER)

E2C(R2)

Just reached the step 4!

Current Step 4 version
dated 17 December 2012
• As new information about the drug emerges during marketing experience, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks ....
B/R Balance becomes inevitably worse after Approval?
Questions from seven years ago

Conventional drug → Little difference between individuals or between subgroups

Targeted therapy drug → Large difference between individuals or between subgroups

Even though they show a similar average value, then do you consider that B / R balance is the same?
For reliable quantitative assessment

- Randomized controlled trials are essential
- Placebo vs. Active comparator
- Data Quality Management
- Standardization of method, data format, etc.
- Validity of the weighting of each element
- Generalizability of evaluation results
- Individual optimization vs. average data
- Continuous reassessment is essential
All the players in good harmony

Thank you for your attention