Safety Measures of PMDA
- Risk Management Plan in Japan

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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
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

26th Annual EuroMeeting Vienna 2014
Benefit / Risk from Patient View Points

Disease Risk

Drug Efficacy

ADR

Improve B/R valance

Disease Risk

Drug Efficacy

ADR

Elimination of Drug = Patient disadvantage

Disease Risk only

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Pharmacovigilance
Update of Japan
Priority Issues to be Consolidated for Post-Marketing Safety Measures

1. Strengthening of information gathering on adverse drug reactions and malfunctions
2. Organization of information on adverse drug reactions and systemization of evaluation and analysis
3. Establishment of the medical information databases
4. Establishment of a post-marketing safety system through information feedback
5. Fulfilling information distributed to general public related to Pharmaceuticals and Medical Devices Safety
6. Appropriate safety measures based on the Risk Management Plan
7. Reinforcement of safety measures adapted to new review system as well as consistently monitoring the safety of drugs from the clinical trial stage to post-marketing stage
8. Strengthening and improvement of follow-up on implemented safety measures
9. Organizing, evaluating, and analyzing information gathered from Vaccine Adverse Reaction Reporting System
Pharmacovigilance measures JP, US, EU

<table>
<thead>
<tr>
<th></th>
<th>Pre-market review</th>
<th>Approval</th>
<th>Post-market</th>
</tr>
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<tbody>
<tr>
<td><strong>JP</strong></td>
<td></td>
<td>ADR/AE Reporting</td>
<td>RE-examination If necessary</td>
</tr>
<tr>
<td><strong>US</strong></td>
<td>ADR/AE Reporting</td>
<td>REMS (high risk NME)</td>
<td>Spontaneous ADR, infection Reporting</td>
</tr>
<tr>
<td><strong>EU</strong></td>
<td>ADR/AE Reporting</td>
<td>RMP (NME)</td>
<td>Spontaneous ADR, infection Reporting</td>
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Pharmacovigilance strategies including Pharmacovigilance Plan will be integrated into RMP.
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 ADR Case Reports

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Function of Risk Managers in PMDA
What is the Risk Manager?

Development → Review → Post-marketing

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

- Development of early post-marketing phase vigilance plan
- Advice on Drug’s post-marketing safety measures
- Evaluation of the result of post-marketing survey
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>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Development Phase</td>
<td>Development Safety Update Report (ICH E2F)</td>
<td>Review Team (consultation)</td>
</tr>
<tr>
<td>NDA Review Phase</td>
<td>Risk Management Plan (ICH E2E+α)</td>
<td>Review Team (NDA review)</td>
</tr>
<tr>
<td>Post-Marketing Phase</td>
<td>Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))</td>
<td>Review Team (Re-examination) &amp; Safety Team</td>
</tr>
</tbody>
</table>

Development Safety Update Report (ICH E2F)
治験薬に関して調査対象期間中に収集された関連する安全性情報の包括的かつ十分に検討された年次レビューと評価を提示する

Risk Management Plan (ICH E2E+α)
医薬品の開発段階、承認審査時から製造販売後のすべての期間において、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になることを目的。

Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))
製品の全体的なベネフィット・リスクプロファイル評価を可能にするため、医薬品のリスクに関して及び該当する場合には、承認された適応症に対するベネフィットに関して、新しい情報または明らかになりつつある情報の重要な分析を示すことにある。

Review Team (NDA review)

Review Team (Re-examination) & Safety Team

Currently PSUR

Apr. 2013 -

ICH step5 May. 2013

Risk Manager

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Risk Management Plan in Japan
**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

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

**Additional**
- Enhancement of spontaneous reporting by EPPV
- Drug use –results survey
- Specified drug use survey
- Post Marketing Clinical Study (Includes PharmacoEpi Study)
- etc

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

### Evaluation
- Additional PvP
- Additional RiskMAP

### (Evaluation)

**Risk Evaluation**

※Burden on HCPs should be taken into consideration.
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)

• Information page of RMP for company (in Japanese)
  http://www.info.pmda.go.jp/rmp/to_company.html
医薬品リスク管理計画（RMP: Risk Management Plan）について

目的

医薬品の安全性と信頼性を保つためには、開発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ICH-E2E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を含めて「安全性検討事項」として取り上げ、医薬品安全性監視計画を作成するよう求められましたが、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。

今般、医薬品安全性監視計画に加えて、医薬品のリスクの低減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の策定について」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」がとりまとめられました。

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、これまで以上により明確な見通しが求められ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
・重要な既知のリスク
・重要な不確実情報

安全性監視計画

通常

・自己報告
（副作用・感染症）
・研究報告
・国内測定報告

不要

リスク最小化計画

・治癒療法の作成・改訂
・患者への医薬品ガイド
Please Visit PMDA English website
Risk Management Plan Guidance

Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Translated by Office of Safety I,
Pharmaceuticals and Medical Devices Agency

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

PFSE/SD Notification No. 0411-1
PFSE/ELD 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...
Publication of Risk Management Plan

To: Directors of Prefectural Health Departments (Bureaus)

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

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

Publication of Risk Management Plan

The Ministry of Health, Labour and Welfare (MHLW) previously issued notifications

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?
# Table of Contents of RMP Guidance

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 necessary.
• Transparency among stakeholders
  – Comprehensive information collection & risk management thorough life-cycle of the product
Benefit / Risk Evaluation and RMP
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
薬食審査発0517第1号
平成25年5月17日

各都道府県衛生主管部（局）長 殿
厚生労働省医薬食品局審査管理課長
（公印省略）

定期的ベネフィット・リスク評価報告（PBRER）について

日本EU医薬品規制調和国際会議（以下「ICH」という。）が組織され、品質、安全性及び有効性の各分野で、ハーモナイゼーションの促進を図るための活動が行われているところである。

今般、ICHにおける三極の合意事項として、販売後の医薬品のベネフィットとリスクに関する情報を定期的に報告する際に共通の基準となる「定期的ベネフィット・リスク評価報告（PBRER）」が取りまとめられ、その作成のための標準的な方法（原文）を別添の通り翻訳したので、貴管下関係業者等に周知よく御配慮願いたい。
2.7 Benefit-Risk Evaluation

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks. 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, and to consider whether steps need to be taken to improve the benefit-risk balance through risk minimisation activities, e.g., labelling changes, communications with prescribers, or other steps.

- 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?
Tohoku U.  
NTT Hospital (group)  
U. Tokyo  
Chiba U.  
Kitasato U. (group)  
Hamamatsu U.  
Sch. Of Med.  
Kagawa U.  
Kyushu U.  
Saga U.  

- Build database hubs at 10 cooperating medical institutions nationwide such as university hospitals.  
- Target is to make more than 10 million patients data ready for use in 2015.

<Expectations>
Faster and more appropriate safety measures by utilizing the database for safety study.  
(Ex. Understanding of adverse reaction ratio, risk assessment, evaluation of safety measure effects, etc.)

Utilization by PMDA and researchers

Data collected at 10 hub medical institutions will be retrieved and studied for analysis and evaluation of adverse reactions.

Cooperating medical institutions  
(10 University and group hospital sites)

Associated medical institutions of hub medical group
The notification of PI before marketing is now mandatory.

The draft PI and its supporting document should be submitted together with application materials.

MAH shall develop the PI based on the latest scientific knowledge.

The draft PI and its supporting document should be submitted together with application materials.

In case of non-compliance, the following orders and penalties apply:

- **Order to Improve**
  - Prevention of hazard (Article 77-4)
  - Order to improve management (Article 72-4)
  - Emergency Orders (Article 69-3)

- **Punitive Clause** (Articles 84, 86, and 90)
All the players in good harmony

Thank you for your attention