Safety Measures of PMDA
- Risk Management Plan in Japan

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3rd 5-year mid-term plan of PMDA (FY2014-2018)

Major challenges

- Shortening the time to approval & High quality review/consultation services
- Enhancing safety measures
- Globalization

Specific measures

- Accelerated review process
  (Improvement of approval predictability)
- Improvement of prior assessment
  (substantial acceleration of approval review process)
- Readiness for introduction of risk management plan
- Globalization

- Introduction of approval system with condition/period for Regenerative Medicines
- Drastic improvement of consultation service
  - Improvement of pharmaceutical affairs consultation service on R&D strategy
  - Improvement of clinical trial consultation service
- Utilization of medical information database

Advanced Review/Consultation System

Human Resources with excellent skills 【751人→1065人】

Goal

- Development of Japan’s original innovative drugs and medical devices
- Marketing of cellular and tissue-based products
- Activation of the industry
- Extending health and life span of Japanese people
- Contribution to global medicine
Background concept of Safety Measures
Continuous and Comprehensive B/R Evaluation through Life Cycle of Drugs
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

Continuous Improvement of B/R valance Through Life-Cycle of Product
Benefit / Risk from Patient View Points

Disease Risk

Drug Efficacy

ADR

Elimination of Drug = Patient disadvantage

Disease Risk

Drug Efficacy

ADR

Disease Risk only
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

**Pre-market review**
- ADR/AE reporting
- Pharmcovigilance plan For NME
- Post-market commitment

**Approval**
- EPPV (NME 6mo.)
- Periodic report

**Post-market**
- Spontaneous ADR, infection Reporting
- 6-10 years Re-examination
- Re-evaluation If necessary

**JP**
- Pharmcovigilance plan For NME
- ADR/AE reporting
- Post-market commitment
- Periodic report

**US**
- REMS (high risk NME)
- REMS (high risk NME)
- Periodic report
- Spontaneous ADR, infection Reporting

**EU**
- RMP (NME)
- RMP (NME)
- PSUR
- renewal
- renewal

**Streamlined risk management strategies**
- 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 ADR Case Reports


- Domestic report
- Foreign report
- Physician report
Function of Risk Managers in PMDA
What is the Risk Manager?

Development

Review Department (Review Team)

Review

Risk Manager
(Act as Liaison)

Advice on Drug’s post-marketing safety measures

evaluation of the result of post-marketing survey

development of early post-marketing phase vigilance plan

Post-marketing

Safety Department (Safety Team)
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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<tbody>
<tr>
<td>Clinical Development Phase</td>
<td>Development Safety Update Report (ICH E2F)</td>
<td>Review Team (consultation)</td>
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<td>Risk Management Plan (ICH E2E+α)</td>
<td>Review Team (NDA review)</td>
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<td>Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))</td>
<td>Review Team (Re-examination) &amp; Safety Team</td>
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<td>NDA Review Phase</td>
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<tr>
<td>Post-Marketing Phase</td>
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Risk Management Plan in Japan
Burden on HCPs should be taken into consideration.

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

Need Additional measures? (Evaluation)※

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

- No
  - Spontaneous reporting
  - Research Report
  - Foreign actions report

**Pharmacovigilance Plan**

**Risk Minimization Action Plan**

**Routine**
- Spontaneous reporting
- Package Insert
- Booklet of Precaution for Use

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

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

※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策を検討することが重要です。

これまでにICH E2Eガイドラインで医薬品の既製承認のリスクや未知のリスク等を伴うと判定される「安全性検討事項」に取り上げ、医薬品安全性監視計画を作成することが求められていますが、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、承認審査から製造販売後の全ての期間において、ベンチマークとリスクの評価・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指しております。

概念図

RMP全体のイメージ

安全性検討事項

・重要な態度を示すリスク
・重要な潜在的リスク
・重要な不足事項

安全性監視計画

通常

・個別報告
  （副作用・感染症）
・研究報告
・研究報告

不要

・追加文書の作成・提出
・医薬品安全性監視
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

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.

PFSB/ELD Notification No. 0304-1
PFSB/SD Notification No. 0304-1
March 4, 2013

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
Challenges for the Future

- Evaluate after re-examination term
- Remove conditions of approval RMP
- Implement the RMP of generic drugs
Challenges for the Future

- We need more experiences about RMP review process between PMDA and MAHs
- Revise RMP by new information, if necessary
- Look for more efficient and meaningful post-marketing surveys
- Develop measures to minimize risks and to evaluate outcome of risk minimization activities
- It is important to achieve understanding of healthcare professionals
Benefit / Risk Evaluation and RMP
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 through life-cycle of the product
Coming era of PBRER from PSUR

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)
E2C(R2)

Just reached the step4!

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

各都道府県衛生主幹部（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

日米 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際に対通の基準となる「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ろしく御配慮願いたい。
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?
Initiative to Develop Infrastructure for Medical Information Database

Catch line: Provide safe and secure medical care by collecting 10 million patients scale medical information

- 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 2016.

<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.)

Cooperating medical institutions (10 University and group hospital sites)

Associated medical institutions of hub medical group

Utilization by PMDA and researchers

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

Kyushu U.
Saga U.

Kagawa U.

Tohoku U.
NTT Hospital (group)
U. Tokyo
Chiba U.
Kitasato U. (group)
Direction of Regulation Relating to Package Insert (For NDA)

**Current System**
- **Draft of PI**
  - Mandatory contents to be described in PI (Article 52)
  - Prohibition on Entries (Article 54)
- **Submission of draft PI**
  - The draft PI is to be submitted by the administrative direction
- **Approval**

**Revised System**
- **Draft of PI**
  - Mandatory contents to be described in PI (Article 52)
  - Prohibition on Entries (Article 54)
  - MAH shall develop the PI based on the latest scientific knowledge
- **Submission of draft PI**
  - The draft PI and its supporting document should be submitted together with application materials
- **Approval**
- **Notification of PI**
  - The notification of PI before marketing is now mandatory

**Check of compliance with the regulation**
- In case of non-compliance
  - Prevention of hazard (Article 77-4)
  - Order to improve management (Article 72-4)
  - Emergency Orders (Article 69-3)
- **Order to improve**
- **Penalty**

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All the players in good harmony

Thank you for your attention