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 from early development to approval
  - “Zero” review time lag Support for elimination of development time lag
- Enhancing safety measures
- Accelerated review process (Improvement of approval predictability)
- Improvement of prior assessment (substantial acceleration of approval review process)
- Enhanced overseas inspection system
- Drastic improvement of consultation service
  - Active involvement from the early development phase
- Appropriately accommodate the most advanced technologies including personalized medicine and regenerative medicine

**Prerequisites:**
- US/EU-equivalent system and human resources with excellent skills

**Goal**
- Activation of the industry
- Extending health and life span of Japanese people
- Contribution to global medicine
- Responding to social needs such as Japan Reconstruction Strategy and Health/Medical Care Strategy
Background concept of Safety Measures
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

Increase
Planning, Conduct, Analysis, Evaluation

Decrease/Reduction

Volume Quality Diversity

Late development to Post-market Phase

Unknown Risk

Convert unknown risk to known risk
Risk minimization

Continuous Improvement of B/R valance

Early development Phase
Benefit /Risk from Patient View Points

Improve B/R valance

Disease Risk

Drug Efficacy

ADR

Drug Efficacy

Drug Efficacy

Elimination of Drug = Patient disadvantage

Disease Risk only
Pharmacovigilance
Update of Japan
<table>
<thead>
<tr>
<th></th>
<th>Priority Issues to be Consolidated for Post-Marketing Safety Measures</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Strengthening of information gathering on adverse drug reactions and malfunctions</td>
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<tr>
<td>2.</td>
<td>Organization of information on adverse drug reactions and systemization of evaluation and analysis</td>
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<tr>
<td>3.</td>
<td>Establishment of the medical information databases</td>
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<td>4.</td>
<td>Establishment of a post-marketing safety system through information feedback</td>
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<tr>
<td>5.</td>
<td>Fulfilling information distributed to general public related to Pharmaceuticals and Medical Devices Safety</td>
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<td>6.</td>
<td>Appropriate safety measures based on the Risk Management Plan</td>
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<tr>
<td>7.</td>
<td>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</td>
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<tr>
<td>8.</td>
<td>Strengthening and improvement of follow-up on implemented safety measures</td>
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<td>9.</td>
<td>Organizing, evaluating, and analyzing information gathered from Vaccine Adverse Reaction Reporting System</td>
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</tbody>
</table>
### Pharmacovigilance measures JP, US, EU

<table>
<thead>
<tr>
<th>Pre-market review</th>
<th>Approval</th>
<th>Post-market</th>
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</thead>
<tbody>
<tr>
<td>ADR/AE reporting</td>
<td></td>
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<tr>
<td>REMS (high risk NME)</td>
<td></td>
<td>Post-market Commitment If necessary</td>
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<tr>
<td>Periodic report</td>
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<tr>
<td>EPPV (NME 6mo.)</td>
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</tbody>
</table>

- **Pharmacovigilance strategies including Pharmacovigilance Plan will be integrated into RMP**

**JP**
- ADR/AE reporting
- REMS (high risk NME)
- Post-market Commitment If necessary
- Periodic report
- EPPV (NME 6mo.)
- Renewal

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

**EU**
- ADR/AE reporting
- RMP (NME)
- Post-market Commitment If necessary
- PSUR
- Renewal
The Current Framework for Post-Marketing Safety Measures

Drug Approval

Re-examination

4-10 years (8 years)

EPPV

PMS

ADR and Infection Reporting
Numbers of ADR Case Reports

- FY2007
- FY2008
- FY2009
- FY2010
- FY2011
- FY2012

Legend:
- domestic report
- foreign report
- physician report
Function of Risk Managers in PMDA
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
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

### Phase
- **Clinical Development Phase**
- **NDA Review Phase**
- **Post-Marketing Phase**

### Regulatory Tool
- **DSUR**
  - 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。

- **RMP**
  - 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。

- **PBRER**
  - 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に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関するベネフィットに関して、新しい情報または明らかに新たな情報の重要な分析を示すことににある。

### Person in Charge
- **Review Team (consultation)**
- **Review Team (NDA review)**
- **Review Team (Re-examination) & Safety Team**

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**ICH step 5**
- **Apr. 2013 -**
- **Currently PSUR**
- **ICH step 5 May. 2013**
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
- Enhancement of spontaneous reporting by EPPV
- Drug use –results survey
- Specified drug use survey
- Post Marketing Clinical Study
  (Includes PharmacoEpi Study)
  etc

PvP and / or RiskMAP?
- Additional PvP
- Additional RiskMAP

Need Additional measures?
- No
- Yes

(Evaluation)※

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

Periodic Reporting
- 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
http://www.info.pmda.go.jp/rmp/to_company.html
Risk Management Plan Guidance

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.
<table>
<thead>
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<th>Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare</th>
<th>Translated by Office of Safety 1, Pharmaceuticals and Medical Devices Agency</th>
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*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 thorough 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 薬局規制調和国際会議（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方よろしく御配慮願いたい。
• 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 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
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.
All the players in good harmony

Thank you for your attention