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

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Background concept

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

- Risks
- Benefits

Development (Clinical Trial Consultation) → Review → Post-Marketing
Continuous Improvement of B/R valance Through Life-Cycle of Product

Evidence of efficacy

Volume
Quality
Diversity

Increase
Planning, Conduct, Analysis, Evaluation

Decrease/Reduction

Late development to Post-market Phase

Convert unknown risk to known risk
Risk minimization

Benefit /Risk from Patient View Points

Disease Risk

Improve B/R valance

Drug Efficacy
ADR

Disease Risk

Drug Efficacy

Elimination of Drug = Patient disadvantage

Disease Risk only

Disease Risk

ADR

Disease Risk

ADR
Pharmacovigilance measures JP, US, EU

<table>
<thead>
<tr>
<th></th>
<th>Pre-market review</th>
<th>Approval</th>
<th>Post-market</th>
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<tbody>
<tr>
<td><strong>JP</strong></td>
<td>ADR/AE reporting</td>
<td></td>
<td>Spontaneous ADR, infection Reporting</td>
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<tr>
<td><strong>US</strong></td>
<td>ADR/AE reporting</td>
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<td>Spontaneous ADR, infection Reporting</td>
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<td></td>
<td>REMS (high risk NME)</td>
<td>REMS (high risk NME)</td>
<td>Periodic report</td>
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<tr>
<td><strong>EU</strong></td>
<td>ADR/AE reporting</td>
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<td>Spontaneous ADR, infection Reporting</td>
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<td>RMP (NME)</td>
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<td>PSUR renewal</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

- Domestic report
- Foreign report
- Physician report

<table>
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<tr>
<th>Year</th>
<th>Domestic Report</th>
<th>Foreign Report</th>
<th>Physician Report</th>
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<td>0</td>
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<td>FY2009</td>
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<tr>
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<td>300000</td>
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<td>FY2012</td>
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</table>
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**

<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></td>
<td>Risk Management Plan (ICH E2E+α)</td>
<td>Review Team (NDA review)</td>
</tr>
<tr>
<td>NDA Review Phase</td>
<td>Periodic Benefit-Risk Evaluation Report (ICH E2C(R2))</td>
<td>Review Team (Re-examination) &amp; Safety Team</td>
</tr>
<tr>
<td>Post-Marketing Phase</td>
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**Notes:**
- DSUR: Development Safety Update Report
- RMP: Risk Management Plan
- PBRER: Periodic Benefit-Risk Evaluation Report
- ICH step5: International Conference on Harmonisation step 5
- ICH step5: May, 2013
Risk Management Plan in Japan

Burden on HCPs should be taken into consideration.

Concept of J-RMP

Safety Specification
- Important Identified Risk
- Important Potential Risk
- Important Missing Data
- Need for additional measures?
  - Yes
  - No

Pharmacovigilance Plan
- Spontaneous reporting
- Research Report
- Foreign actions report
- Package Insert
- Booklet of Precaution for Use

Risk Minimization Action Plan
- Info Dissemination by EPPV
- Info for Health Professionals
- Drug Guide for patients
- Access restriction
- etc

Additional
- 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
Please Visit PMDA English website

Risk Management Plan Guidance

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

April 30, 2013

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

Publication of Risk Management Plan

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
RMP & B/R evaluation

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
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 ....
Our effort to improve B/R Balance is endless!!

All the players in good harmony

Thank you for your attention