Pharmacovigilance in Japan and Risk Management Plans (RMP); Regulator Perspective

Kazuhiko Mori,
Chief Safety Officer
Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Disclaimer

• The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

• These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, Drug Information Association Inc., DIA and DIA logo are registered trademarks. All other trademarks are the property of their respective owners.
Agenda

• Outline of Japanese PhV
• PhV updates in Japan
  – Risk Manager system
  – Development Safety Update Report in Japan
  – Risk Management Plan in Japan
Pharmacovigilance strategies including Pharmacovigilance Plan will be integrated into RMP
Risk Manager (RM) 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) → RM was realized!!
Risk Manager (RM)

• 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

• **12 Risk Managers** in different disease areas
RMP in Japan

• Draft guidance
  – Public consultation; April 20th-October 31st, 2011
  – Pilot execution of RMP
    • Collaboration with applicants
  – Revision by public comments

• Notification
  – Preparing format and Q&A
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?
Risk Management Program (RMP)
Workflow Process

Safety Specification
- Important identified risks
- Important potential risks
- Important missing information

Additional Action
- Necessity or Unnecessary (Review)

Pharmacovigilance and/or Risk Mitigation activities (Review)

Routine Activities
- Spontaneous Report
- Literature Search

Additional Activities
- Additional Mitigation Practices
  - Strengthen the gathering spontaneous report due to early postmarketing phase vigilance (EPPV)
  - Use-Results Surveys
  - Specified Use-Results Surveys
  - Surveys on Post Marketing Clinical Trials (including pharmacoepidemiology survey)

Risk Minimization Action Plan
- Package Insert Precautionary Statement

- Information Service via Early Postmarketing phase Vigilance (EPPV)
- Medication Guide for Patient
- Provision of Information on Drug
- Education Program
- Access Limitation
- Update of Package Insert

Periodic Report Risk Assessment

※ Pressure and confusion should definitely be considered in clinical practice.
PMDA website (http://www.pmda.go.jp/)
PFSB/SD Notification No. 0411-1
PFSB/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 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
2. Risk Management Plan

- Development of Risk Management Plan
- Points to Consider in Development of Risk Management Plan
- Setting of Milestones in Risk Management Plan
- Review of Risk Management Plan
- Safety Specification
- Identification of Safety Specification
6. Risk Minimization Plan

6.1 Routine Risk Minimization Practices

6.2 Additional Risk Minimization Activities
   6.2.1 Provision of Additional Information to Healthcare Professionals
   6.2.2 Provision of Information to Patients
   6.2.3. Establishment of Conditions of the Use of the Drug
   6.2.4 Other Activities

6.3 Implementation Plan for Additional Risk Minimization Activities
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
Development and revision of RMP

- NDA application
- Advisory committee approval launch
  - ~300 days
  - 30~60

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)
Development Safety Update Report

• ICH-E2F
  – Step 4; August, 2010
  – Step 5;
    • EU: Adopted by CHMP, September 2010, issued as EMA/CHMP/ICH/309348/2008
    • MHLW: To be notified
    • FDA: Published in the Federal Register, 23 August 2011, Vol. 76, No. 163, p. 52667-8

Implementation of DSUR in Japan

- Still ongoing.....
Safety report begins with development stage and next stage

- Safety report throughout from development phase to post-marketing phase
  - ICH-E2C(PSUR)
  - ICH-E2F(DSUR)
- The NEXT STAGE ⇒ ICH-E2C(R2)
  - Benefit / Risk evaluation PBRER
Summary

• Comprehensive Risk Management
  – Through life-cycle of products
  – Involve all related stakeholders
  – Transparency

• Data collection based on available data
  – Based on character of product

• Utilization of existing data
  – Safer, more beneficial, and more optimal