

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

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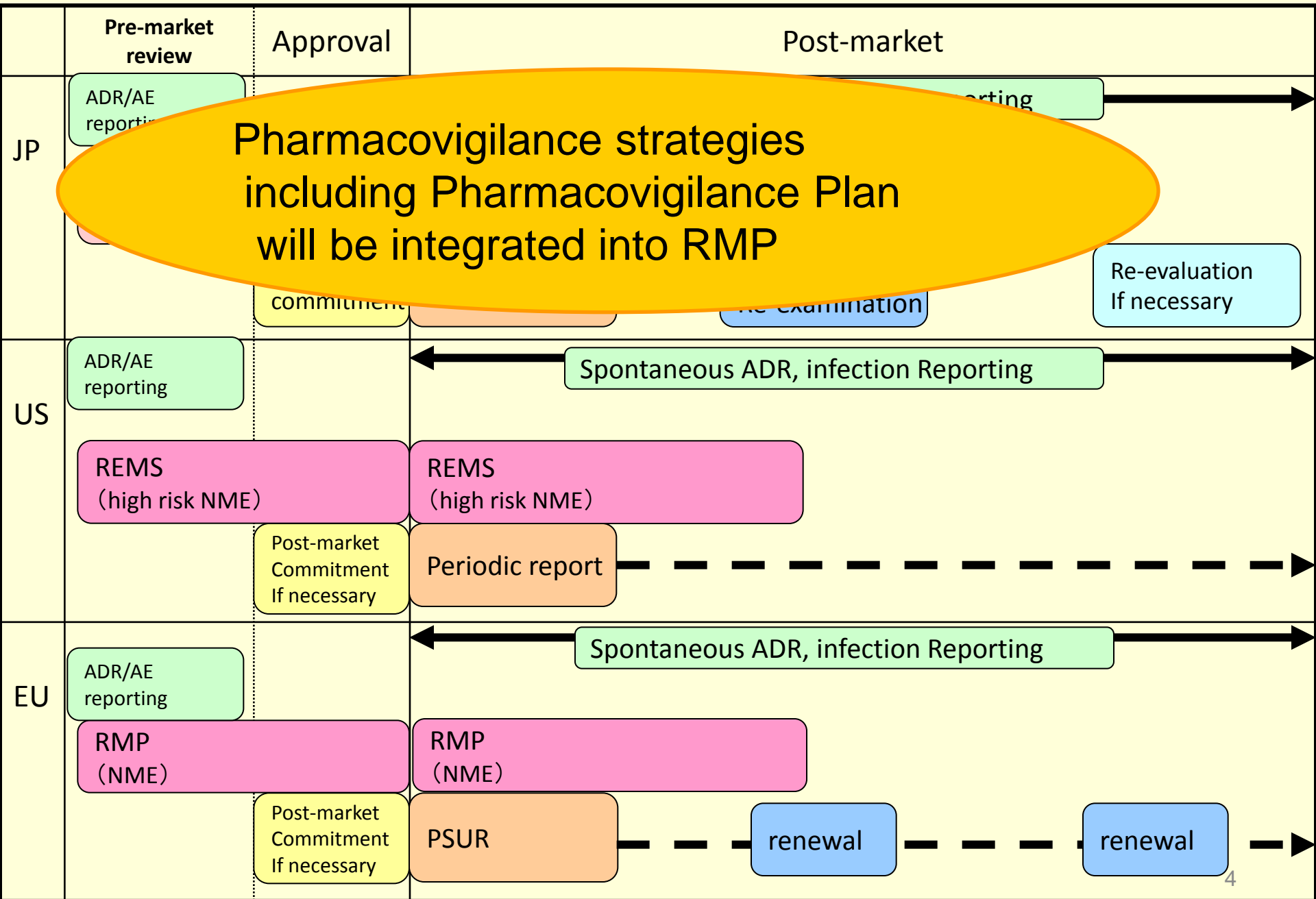


# Agenda

- Outline of Japanese PhV
- PhV updates in Japan
  - Risk Manager system
  - Development Safety Update Report in Japan
  - Risk Management Plan in Japan



# Pharmacovigilance measures JP, US, EU



# 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- Draft guidance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 20<sup>th</sup>-October 31<sup>st</sup> ,2011
  - Pilot execution of RMP
    - Collaboration with applicants
  - Revision by public comments
- Notification
  - [http://www.pmda.go.jp/english/service/pdf/mhlw/PFSB-SD\\_Notification120411-1.pdf](http://www.pmda.go.jp/english/service/pdf/mhlw/PFSB-SD_Notification120411-1.pdf)
  - Preparing format and Q&A



# Current RMP in Japan

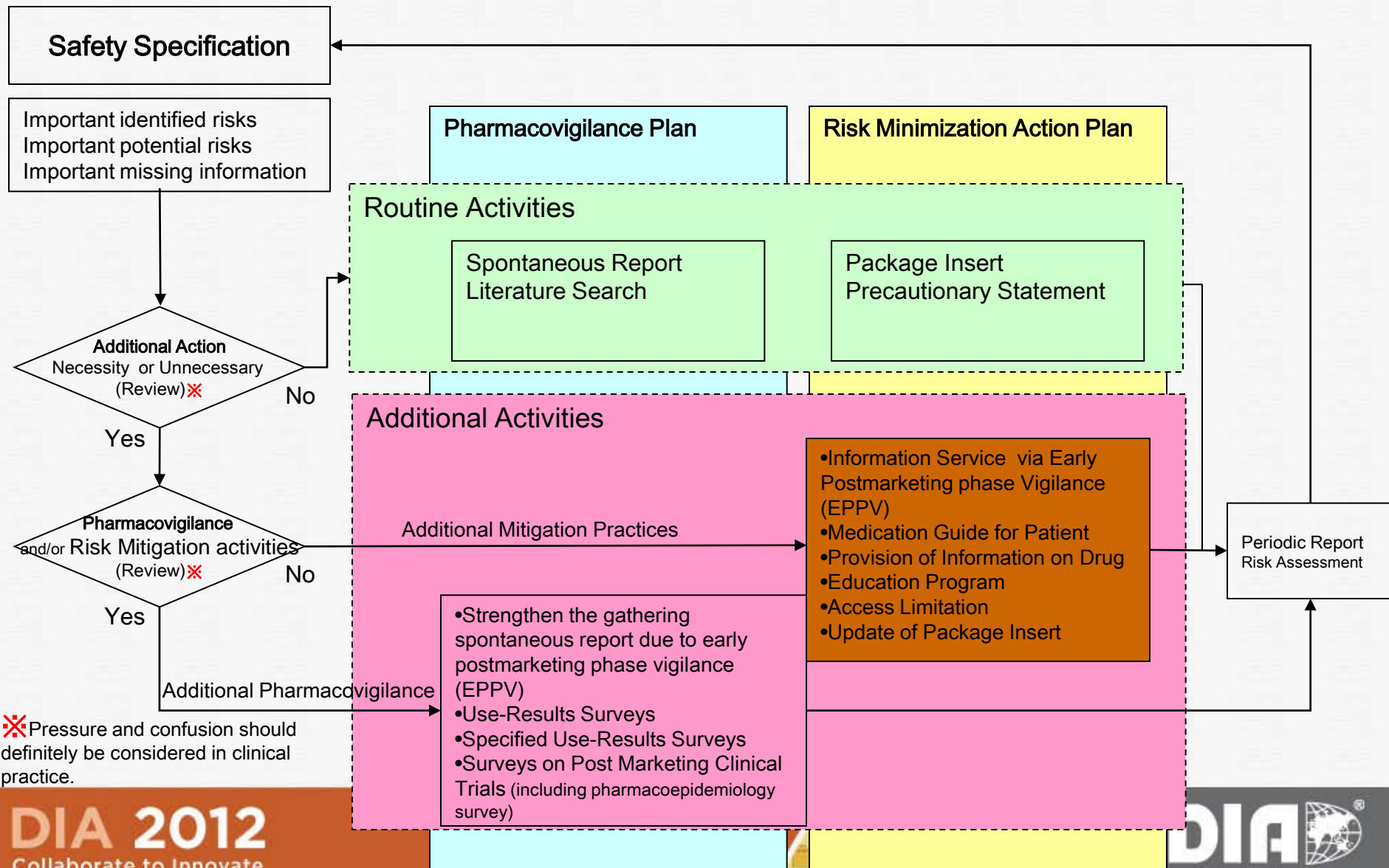
- Discussion & Agreement of RMP between PMDA and MAH before approval
  - Are Healthcare professionals involved?
- Most of products are required PMS.
  - Are they sufficient and minimum?
- Is RMP made based product's character ?
- Is purpose of RM/data collection clear ?





# Risk Management Program (RMP)

## Workflow Process



# PMDA website ( <http://www.pmda.go.jp/> )



The screenshot shows the PMDA website interface. At the top, there is a logo for PMDA (Pharmaceuticals and Medical Devices Agency, Japan) and a language selector set to 'Japanese'. Below the logo, there are navigation links for 'Contact', 'Access', 'Links', 'Site Map', and a search bar. The breadcrumb trail indicates the current page is 'Safety Information announced by MHLW'. On the left, a navigation menu lists various services, with 'Drug and Medical Device Review' highlighted. A red arrow points from this menu item to the first entry in the table below.

## Safety Information announced by MHLW

Date	Title
<b>New</b> April 11, 2012	 Risk Management Plan Guidance
February 14, 2012	 PFSSB/SD Notification 0214-9 "Call attention to the Precautions of anti-influenza virus drugs"
August 12, 2011	Press Release:  Warnings and Alerting Severe haemorrhages in patients treated with an anticoagulant "Prazaxa capsules (dabigatran etexilate)"
August 2, 2011	 Risk Management Plan (RMP) Guidance (Draft) (This draft guidance was issued to invite public comment by MHLW)



**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/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

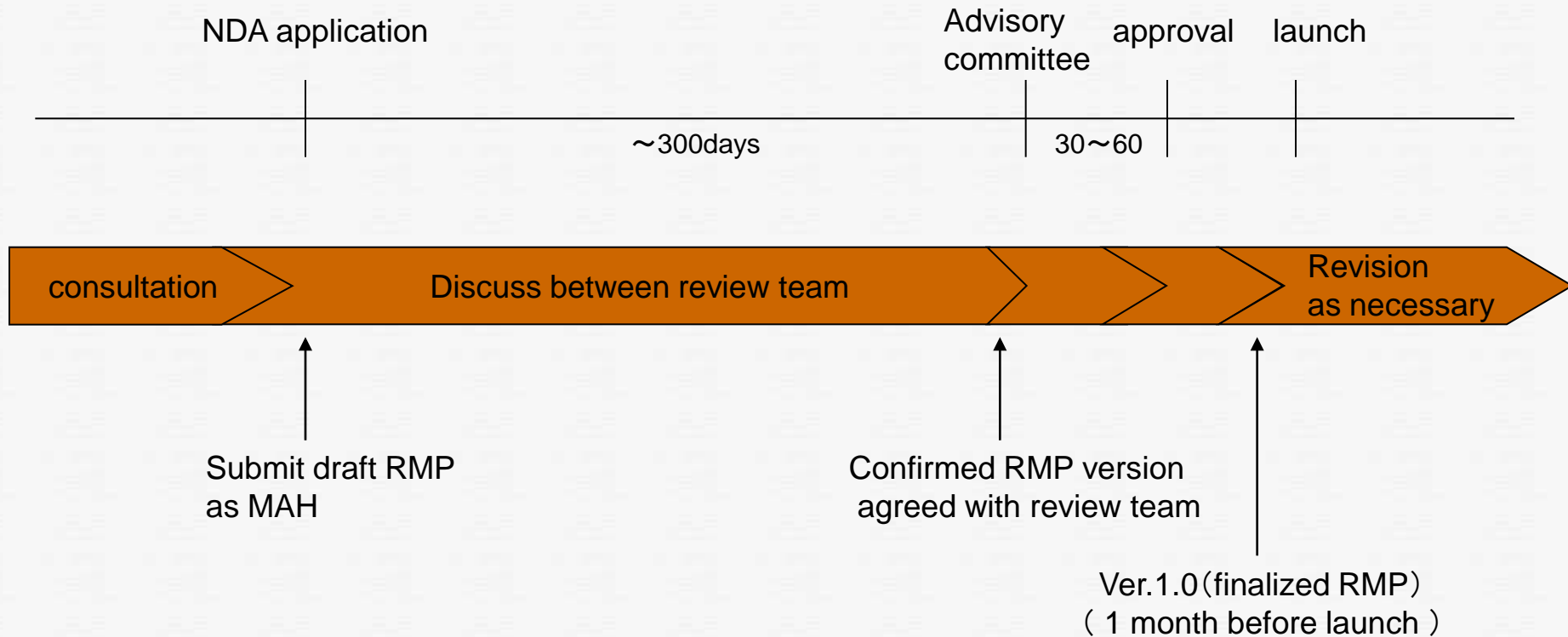


# Characteristics of Japanese RMP

- 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 ecessary.
- Transparency among stakeholders
  - Comprehensive information collection & risk management thorough life-cycle of the product



# Development and revision of RMP





# 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

<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>



# 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

