Transformation towards a New Regulatory Paradigm

Risk Management Plan (RMP) on Biologicals and NCE

Junko SATO
International Coordination Officer
PMDA, Japan

Pharmaceuticals and Medical Devices Agency
Date of Establishment : April 2004

Kansai Branch

PMDA Homepage:
http://www.pmda.go.jp/english/index.html

Agenda

1. Introduction of PMDA
2. Background
3. Outline of J-RMP
4. Review process of J-RMP
5. Current situation and future challenges
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Our Philosophy (September, 2008)

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

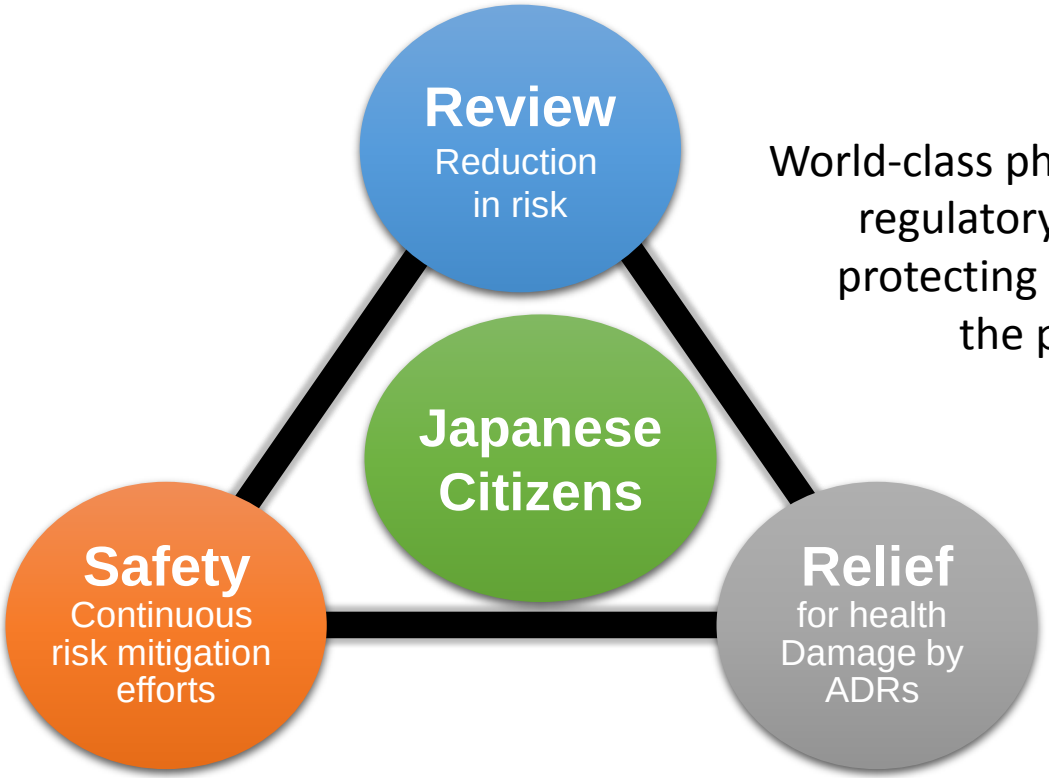
We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.

PMDA's Three Major Services

Safety Triangle

- Comprehensive risk management undertaken by three operations -



World-class pharmaceutical regulatory system for protecting the safety of the people

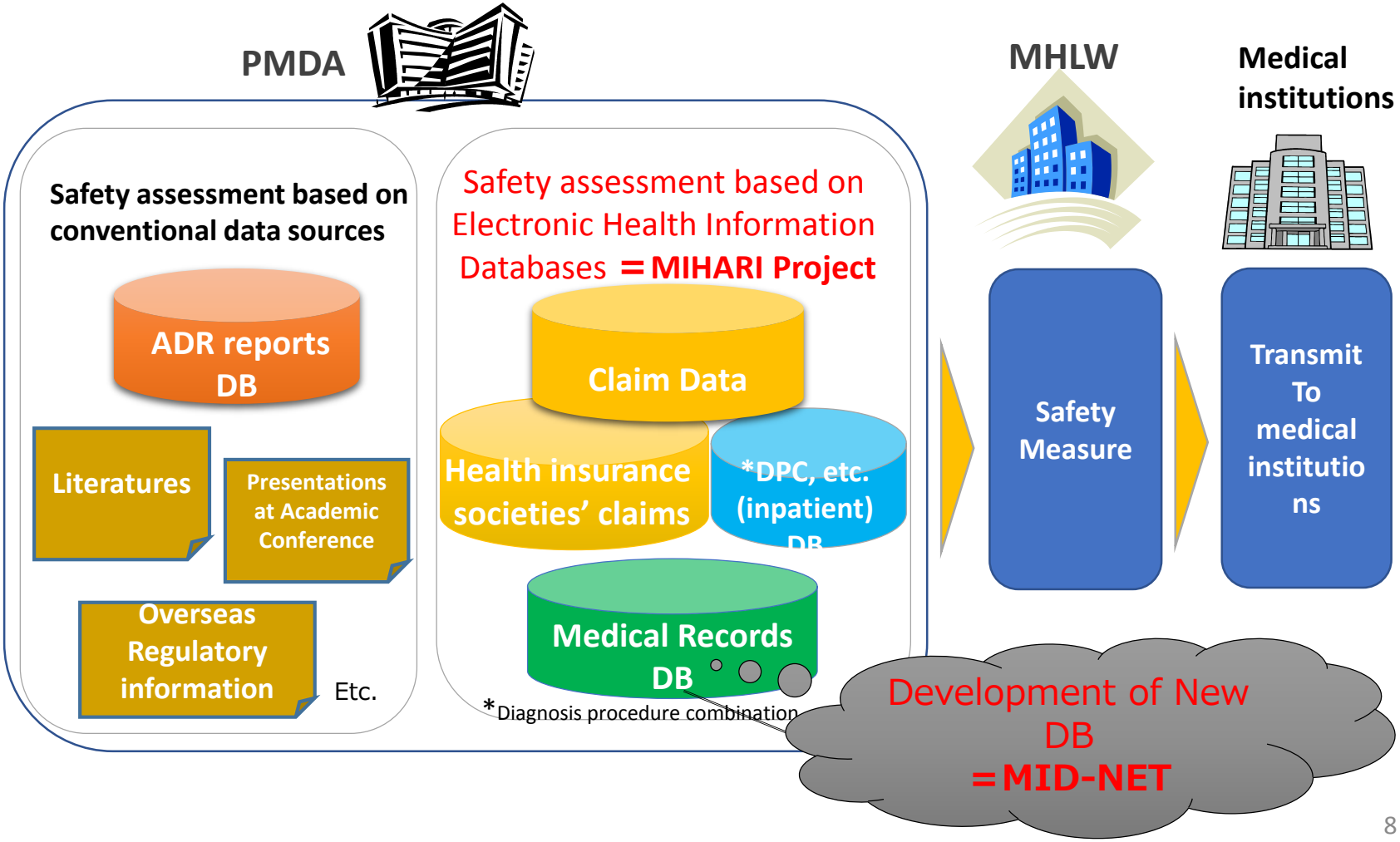
As the only regulatory authority in the world which plays three roles in an integrated manner, PMDA contributes to improve the standard of medical care by delivering safer and higher quality products faster to medical practice based on regulatory science

PMDA Third Mid-term Plan for Safety

- Enhance Collection of ADRs
- Improve the System and Process of ADRs Evaluation
- Establish the System to Utilize Electronic Healthcare Data
- Enhance Feedback of Safety Information
- Enhance Dissemination of Information to the patients

Sophistication of Safety measures

1. Medical Information for Risk Assessment Initiative(MIHARI Project)
2. Project for developing the medical information database infrastructure (MID-NET)



PMDA Third Mid-term Plan for Safety

- Promote Appropriate Safety Measures based on the J-RMP
- Enhance Post-marketing Safety Measures in Cooperation with Review Teams
- Improve Follow-ups of Safety Measures Conducted

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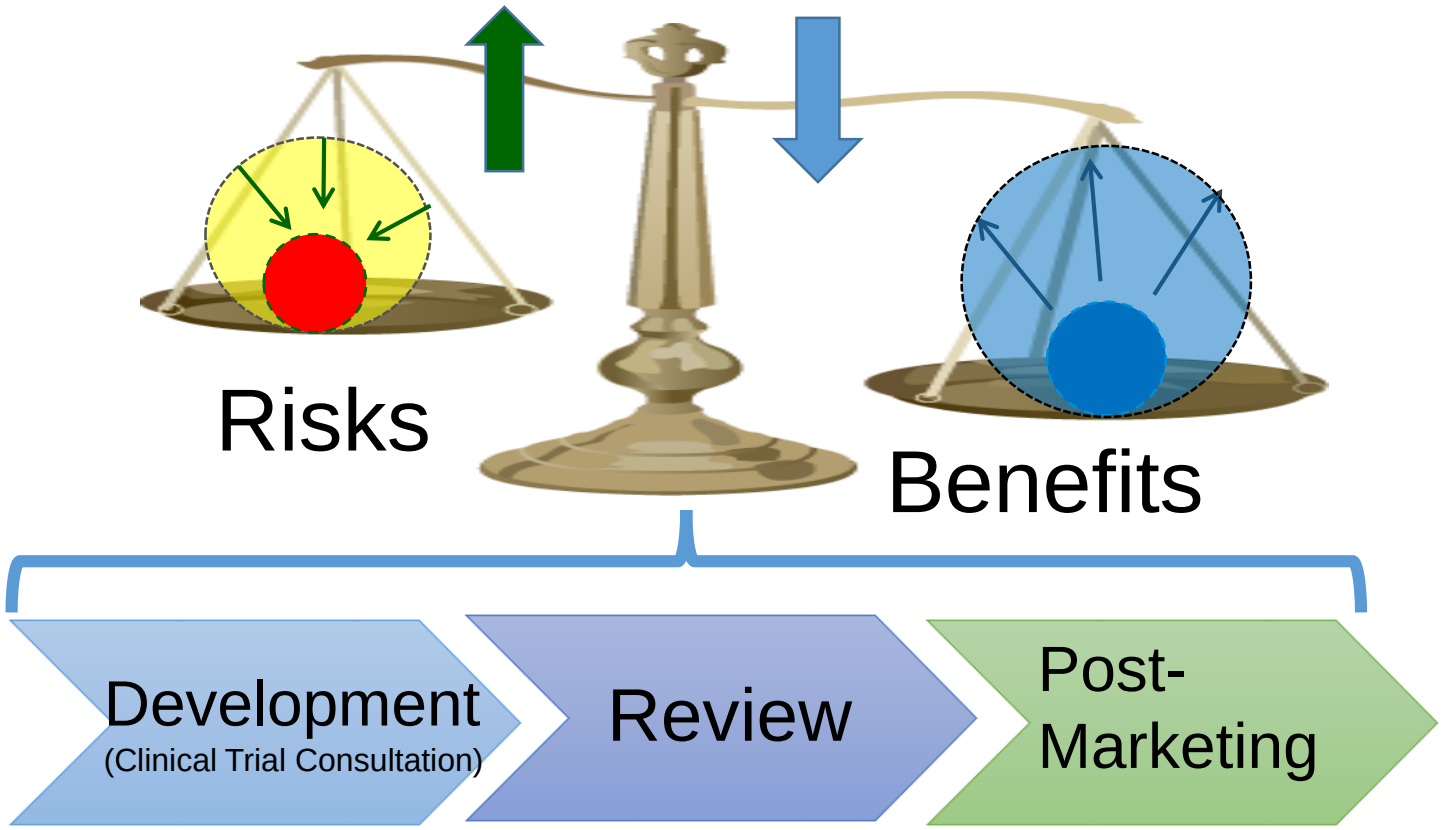
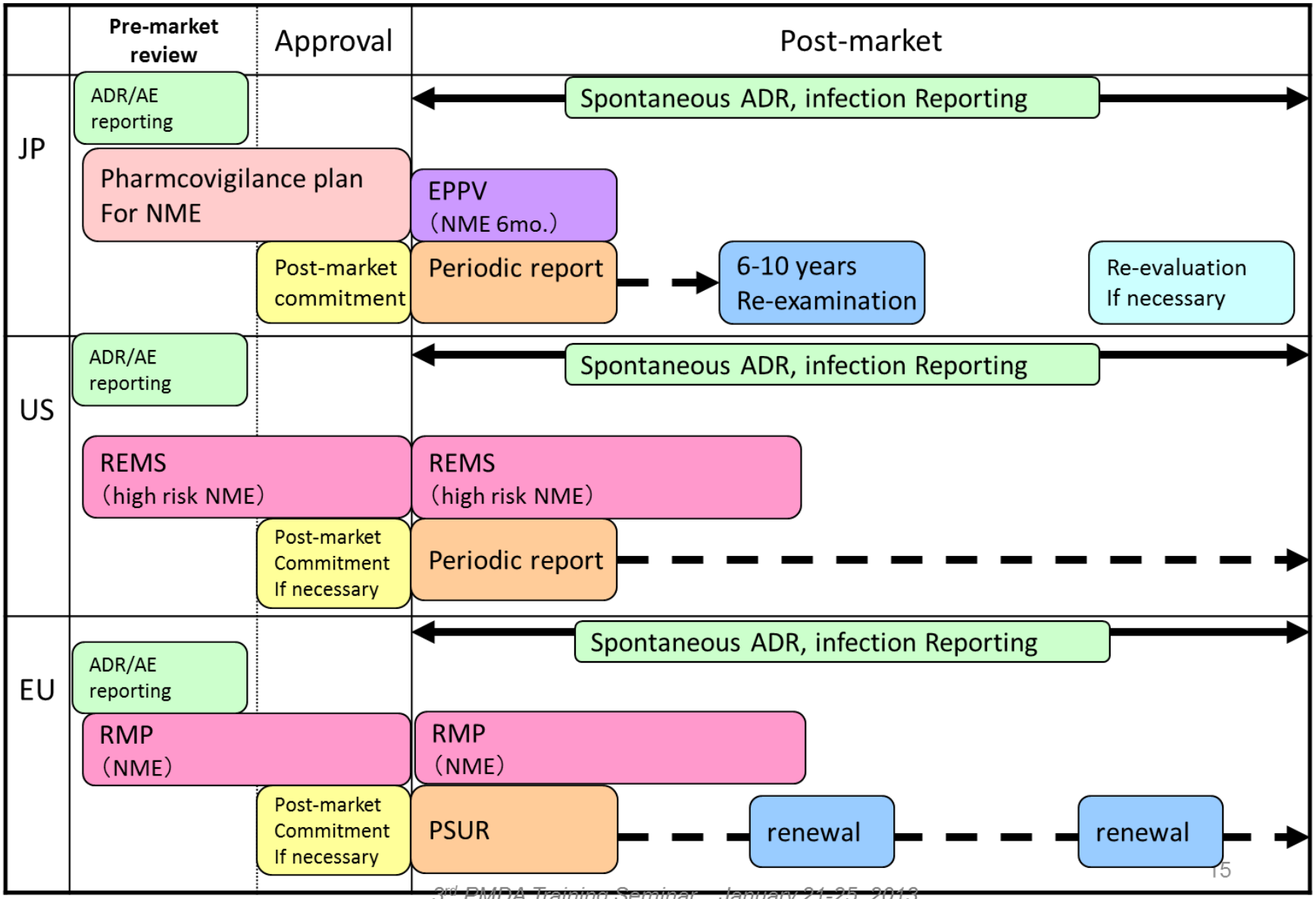
Continuous and Comprehensive B/R Evaluation through Life Cycle of Drugs

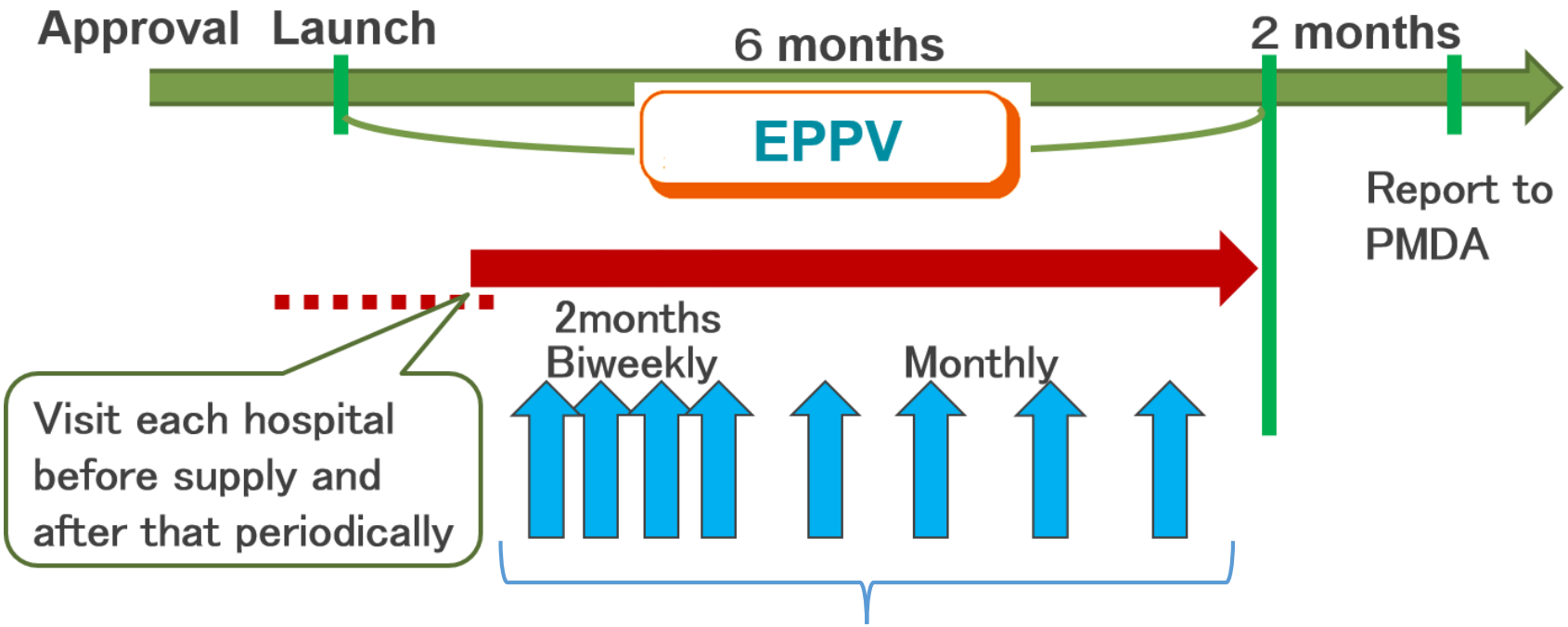


Current Pharmacovigilance measures



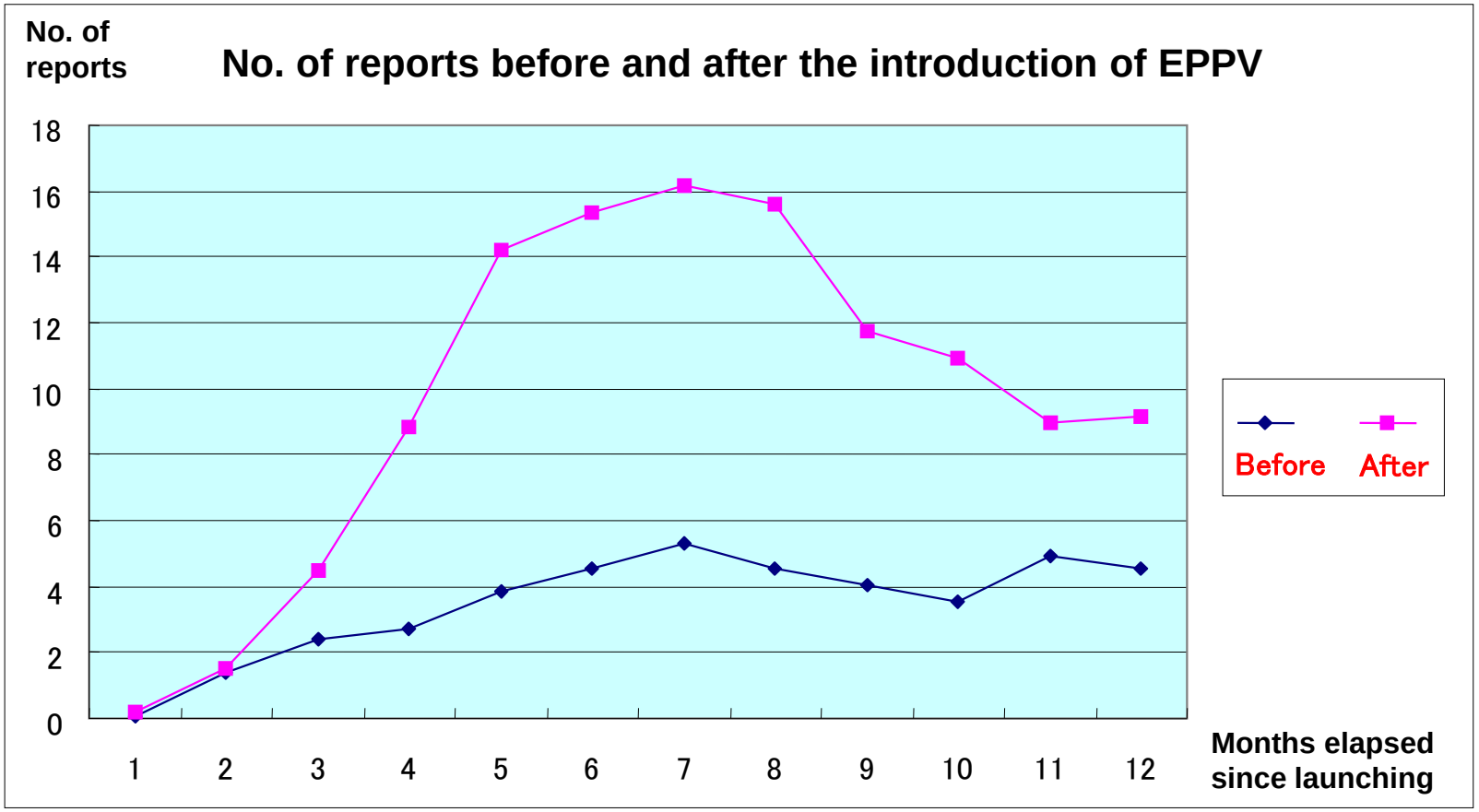
Early Post-market Phase Vigilance

- Monitoring ADRs is critical in the first 6 months after the launch of a new drug.



Periodical dissemination of safety information to the sites via visits, e-mails, letters, etc

Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV (avg/mo.)



EPPV was introduced in October 2001.
Number of before-EPPV is based on 30 new active ingredients launched between Apr. 2000 and Mar. 2001.
Number of after-EPPV is based on 22 new active ingredients launched between Oct. 2001 and Oct. 2002.

Re-Examination

- Aim: reconfirmation of the clinical usefulness of drugs after approval
- Timing of re-examination: designated by the MHLW at the time of their approval as new drugs.
  - new drug substance: 8 years (maximum 10 years)
- Surveys and studies required for reexamination applications: in compliance with the GPSP, GCP or GLP depending on their objective

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Risk Management Plan in Japan（J-RMP）

- Notification
  - **April 11, 2012:　Guidance of J-RMP**
  - April 26, 2012:　Format of J-RMP
  - September 7, 2012:　Q&A(1) of J-RMP
  - March 4, 2013:　Publication of J-RMP
  - March 6, 2013:　Q&A(2) of J-RMP
  - December 25, 2013:　Q&A(3) of J-RMP
  - August 26, 2014: Guidance of J-RMP for generic drugs

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.

Notification released on April 11, 2012, applying to all new drugs and follow-on biologics for which approval applications are submitted on or after April 1, 2013

PFSB/SD Notification No. 0411-1
PFSB/ELD Notification No. 0411-2
April 11, 2012

ural 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 of drugs on a consistent basis from the development phase to the post-marketing phase.

Risk Management Plan in Japan （J-RMP）

- RMP guidance has been implemented since April 1, 2013
- In the revised Good Vigilance Practice (GVP) enforced on October 1, 2014, RMP is required as a condition for approval if necessary

Safety measures in Japan from April 1, 2013

- Drug risk should be managed based on RMP

What is RMP?

- A set of pharmacovigilance activities designed to minimize the risks of drugs based on the identified safety issues of individual drugs.
- The activities include investigations and information collection through use-results surveys and Early Post-marketing Phase Vigilance, etc., as well as additional information provision to healthcare professionals.
- Mandatory for new drugs and biosimilars/follow-on biologics, and for some of generic drugs.

Safety measures in Japan from April 1, 2013

- Drug risk should be managed based on RMP

Basic Points of J-RMP

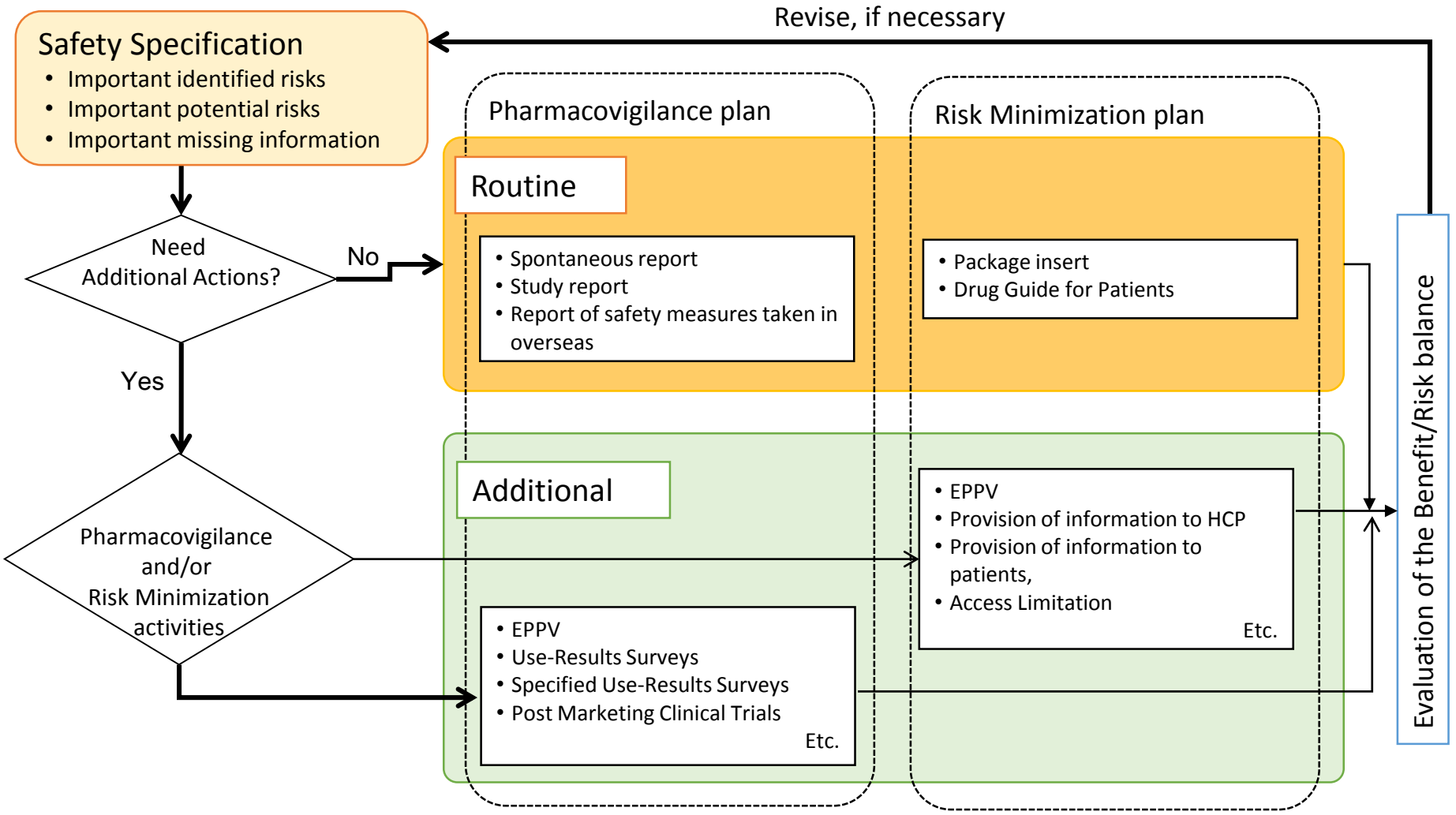
- Pharmacovigilance activities and risk minimization activities should be performed based on Safety Specification.
- RMP should be evaluated at respective milestones and the result should be reported to the PMDA.
- RMP should be revised based on the evaluation of RMP.

Scope of J-RMP

Development of the J-RMP should be considered at the following milestones:

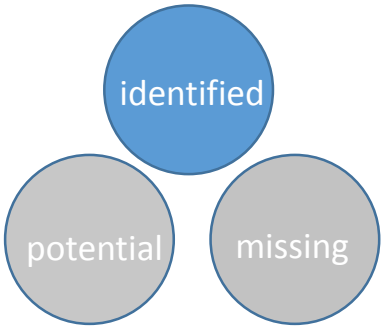
- At the time of submission of approval application for new drugs and biosimilars
- At the time when new concerns regarding safety have been identified in the post-marketing phase
- At the time of submission of approval application for generic drug versions of the original drugs for which additional pharmacovigilance activities or additional risk minimization activities are being performed

RMP Conceptual Diagram



Identification of “Safety Specifications”

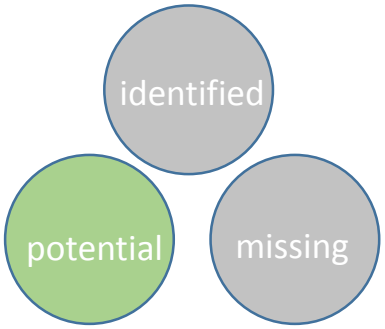
Important identified risks



- DEFINITION:
  - Risks for which the association with the drug is known

- EXAMPLES:
  - ✓Adverse reactions that occurred more significantly in the drug group in clinical studies
  - ✓Adverse reactions for which causal relationship is suggested by temporal relationship derived from many spontaneous reports

Important potential risks



- DEFINITION:

  Risks for which the association with the drug has been suspected but not been sufficiently confirmed

- EXAMPLES:
  - ✓Adverse reactions that are predicted from the pharmacological effect of the drug, etc. but have not been clinically confirmed
  - ✓Adverse reactions that have been observed in the drugs of the same class with the same indications

Important missing information

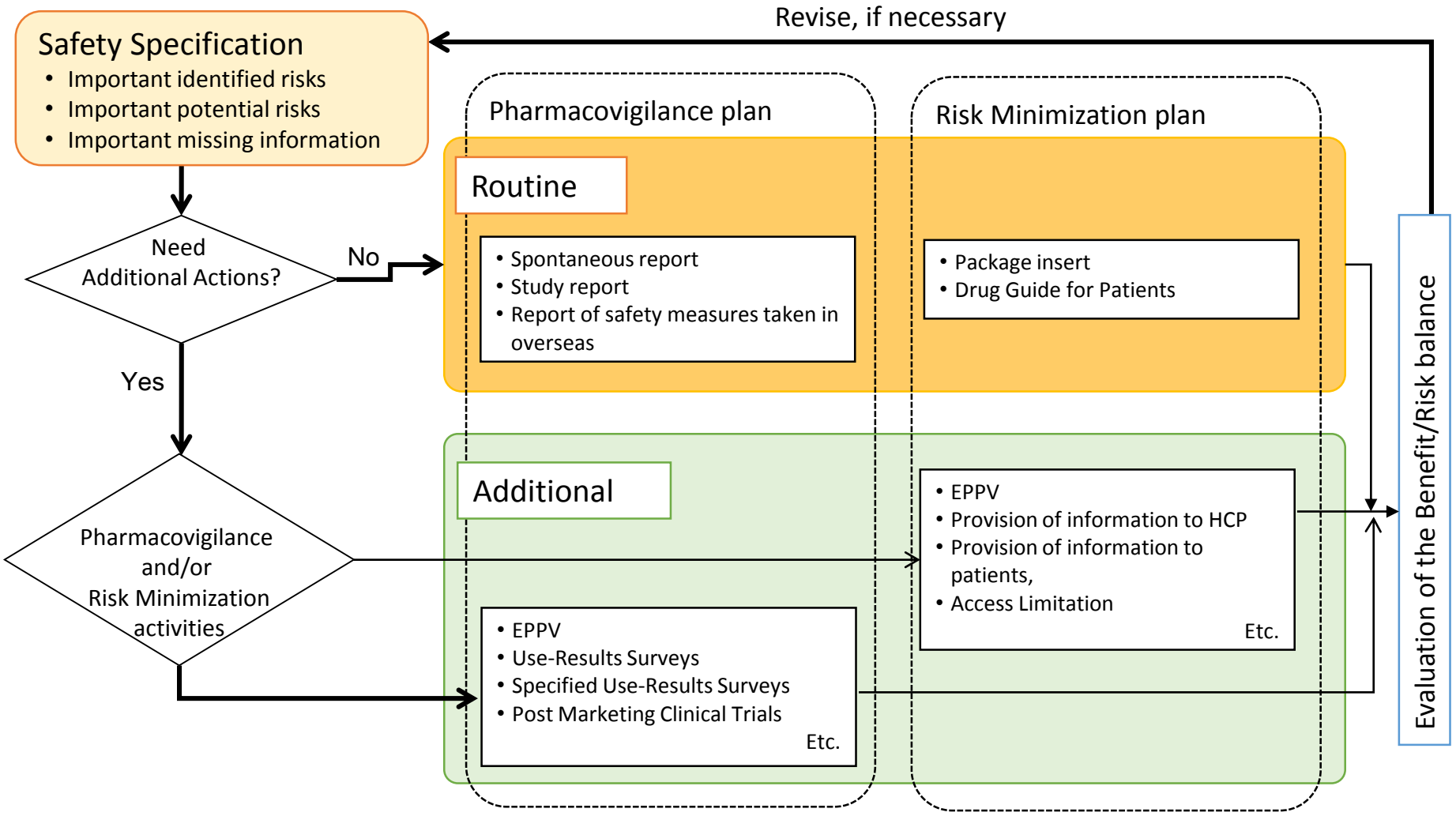
- DEFINITION:

  Risks for which sufficient information has not been obtained to predict the safety

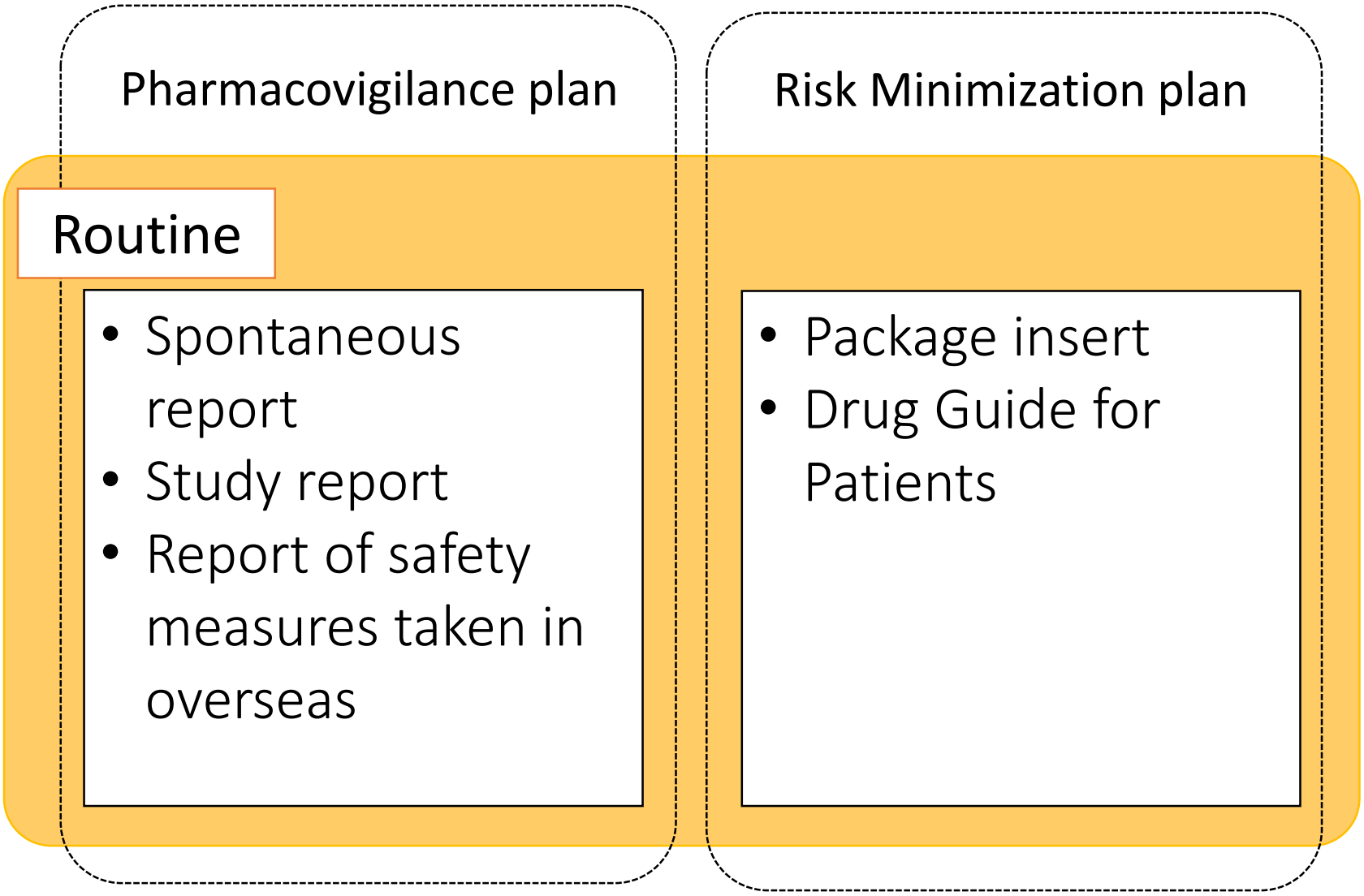
- EXAMPLES:

  ✓Safety information in patient populations (e.g. elderly patients, patients with renal impairment or hepatic dysfunction, pregnant women, and pediatric patients) that are excluded from clinical studies but are expected to frequently use the drug in clinical settings

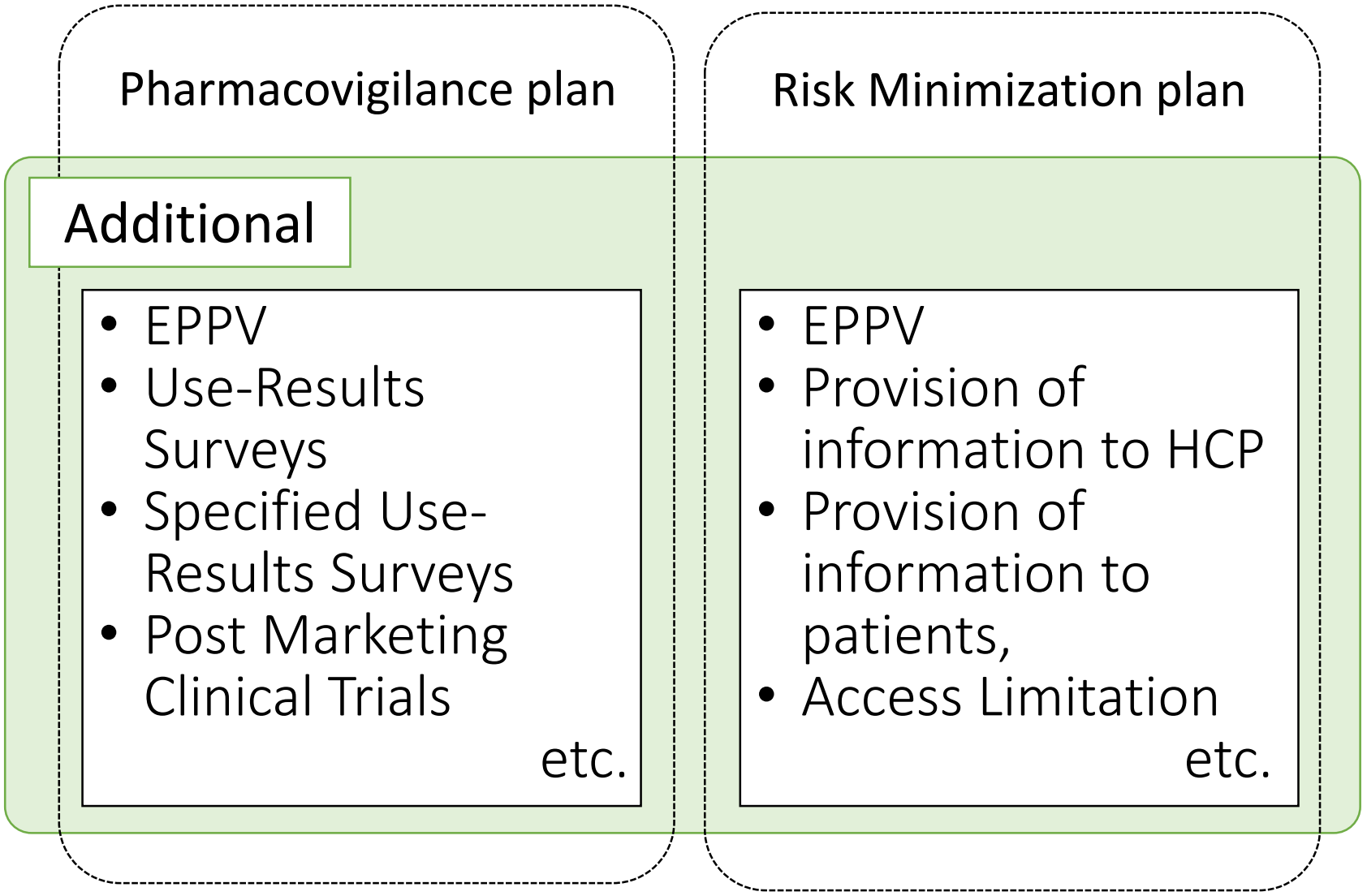
RMP Conceptual Diagram



RMP Conceptual Diagram



RMP Conceptual Diagram



Content of J-RMP

1. Summary of Risk management plan
    1.1 Safety specification
    1.2 Concerns for efficacy
2. Summary of pharmacovigilance plan
3. Summary of plans for surveillance and studies for efficacy
4. Summary of risk minimization plan
5. Lists
    5.1 A list of pharamacovigilance plan
    5.2 A list of plans on surveillance and studies for efficacy
    5.3 A list of risk minimization plane

Post-marketing Safety Measures

- Outline
- Scientific Research and Analyses
- Information Services
  - Drugs
    - Risk Manegement Plan
    - The Yellow Letter / Bule Letter
    - Safety Information announced by MHLW
    - PMDA Risk Communications
    - Revisions of PRECAUTIONS
    - **MHLW Pharmaceuticals and Medical Devices Safety Information**
    - PMDA Alert for Proper Use of Drugs
  - Medical Devices

MHLW Pharmaceuticals and Medical Devices Safety Information (FY2015)

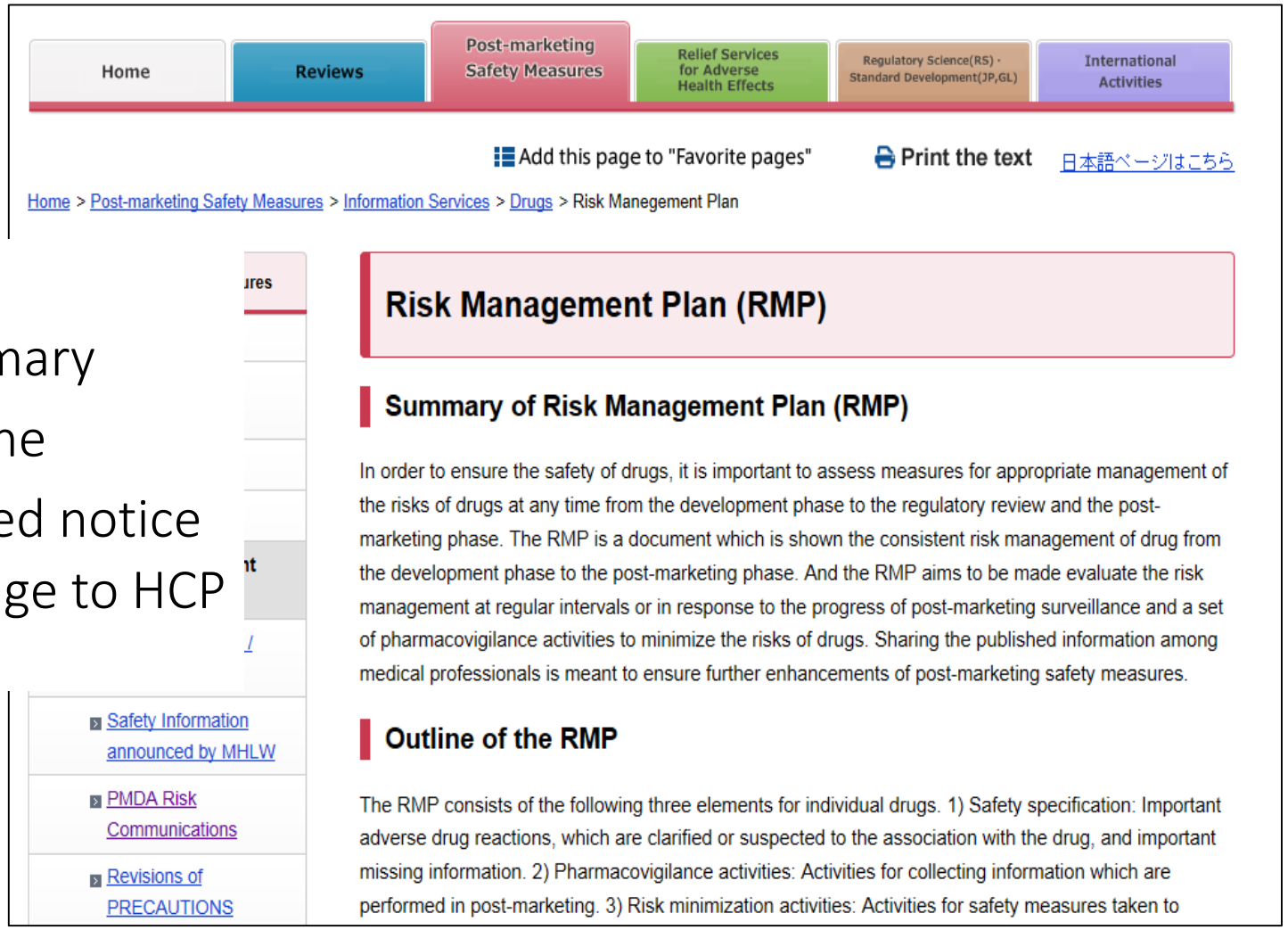
FY 2015 (No.322-)

Japanese version issued on	No.	Table of contents	Posted on	PDF
July 7, 2015	324	1. Risk Management Plan 2. Important Safety Information (1)crizotinib (2)technetium (^{99m}Tc) hydroxymethylenediphosphonate injection, kit for the preparation of technetium (^{99m}Tc) hydroxymethylenediphosphonate injection 3. List of Products Subject to Early Post-marketing Phase Vigilance (as of May 31, 2015)	July 7, 2015	(Summary)
			coming soon	-
		1. Utilization of New Bar Code Labeling and Termination of		

Information about the J-RMP (in English)

Content

- Summary
- Outline
  - -Related notice
- Message to HCP



http://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html

Publication of RMP (informed via e-mail)

【ＰＭＤＡメディナビ】

医薬品リスク管理計画の掲載のお知らせ
(2014/1/8 配信)

本日、「医薬品リスク管理計画（RMP）について」のページを更新しましたのでお知らせします。
http://www.info.pmda.go.jp/rmp/rmp_index.html#select0

RMP提出品目一覧に、以下の医薬品のRMPを掲載しました。

■販売名：ケアラム錠25 mg
一般名：イグラチモド
製販業者：エーザイ株式会社

■販売名：ニ　　ト錠25mg
一般名：イ
製販業者

RMPの　　情報No.300にも
解説さ

【医薬
http:　　page=3

医療従事者の
市販後の安全対策への

Translation:
RMP website has been updated to include RMPs for following products

Agenda

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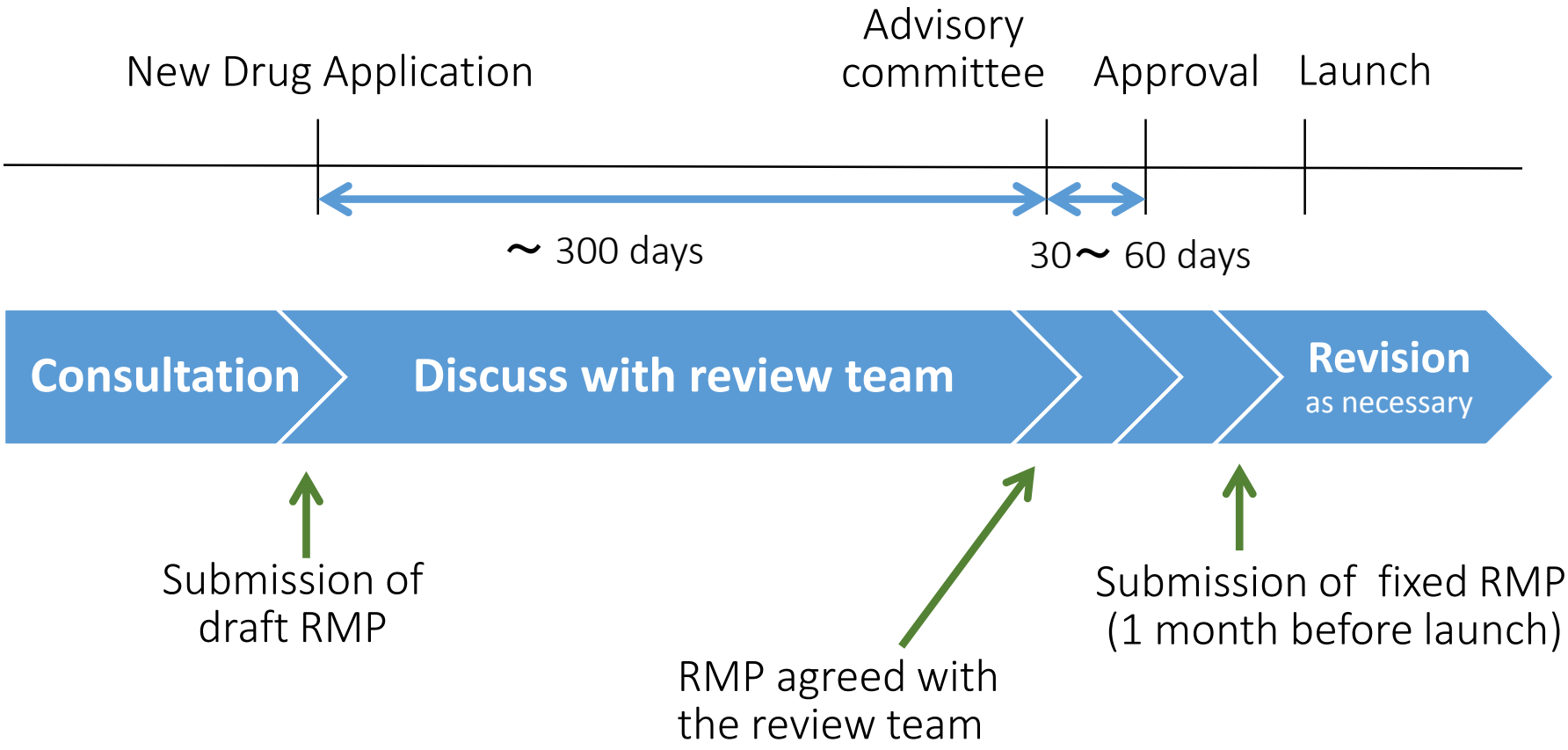
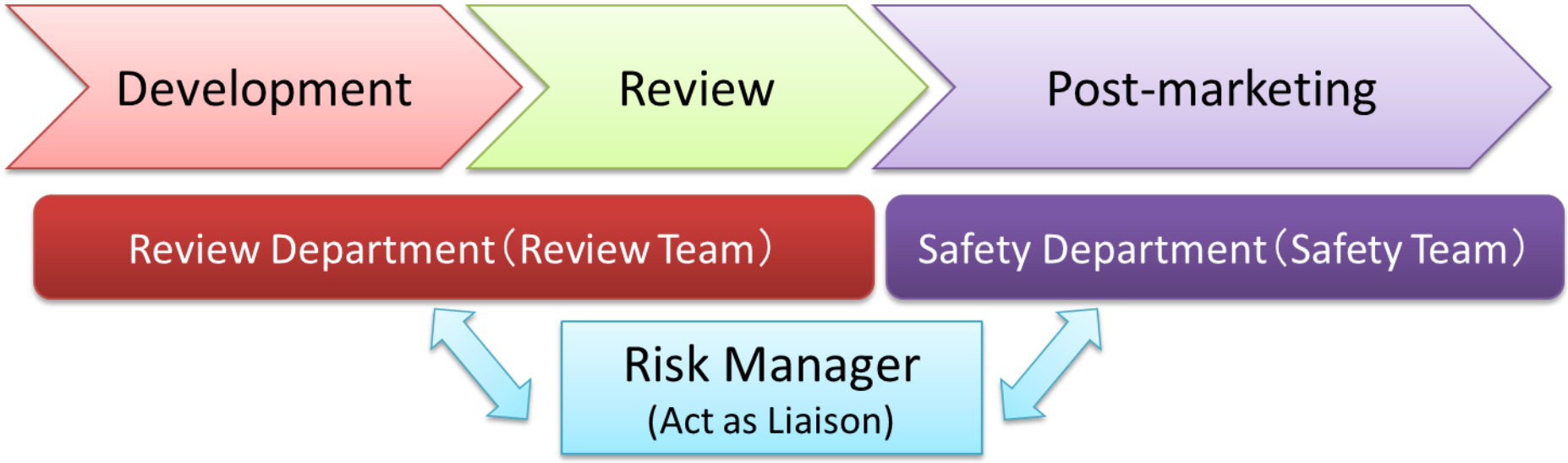
Development and revision of RMP



Risk Manager System

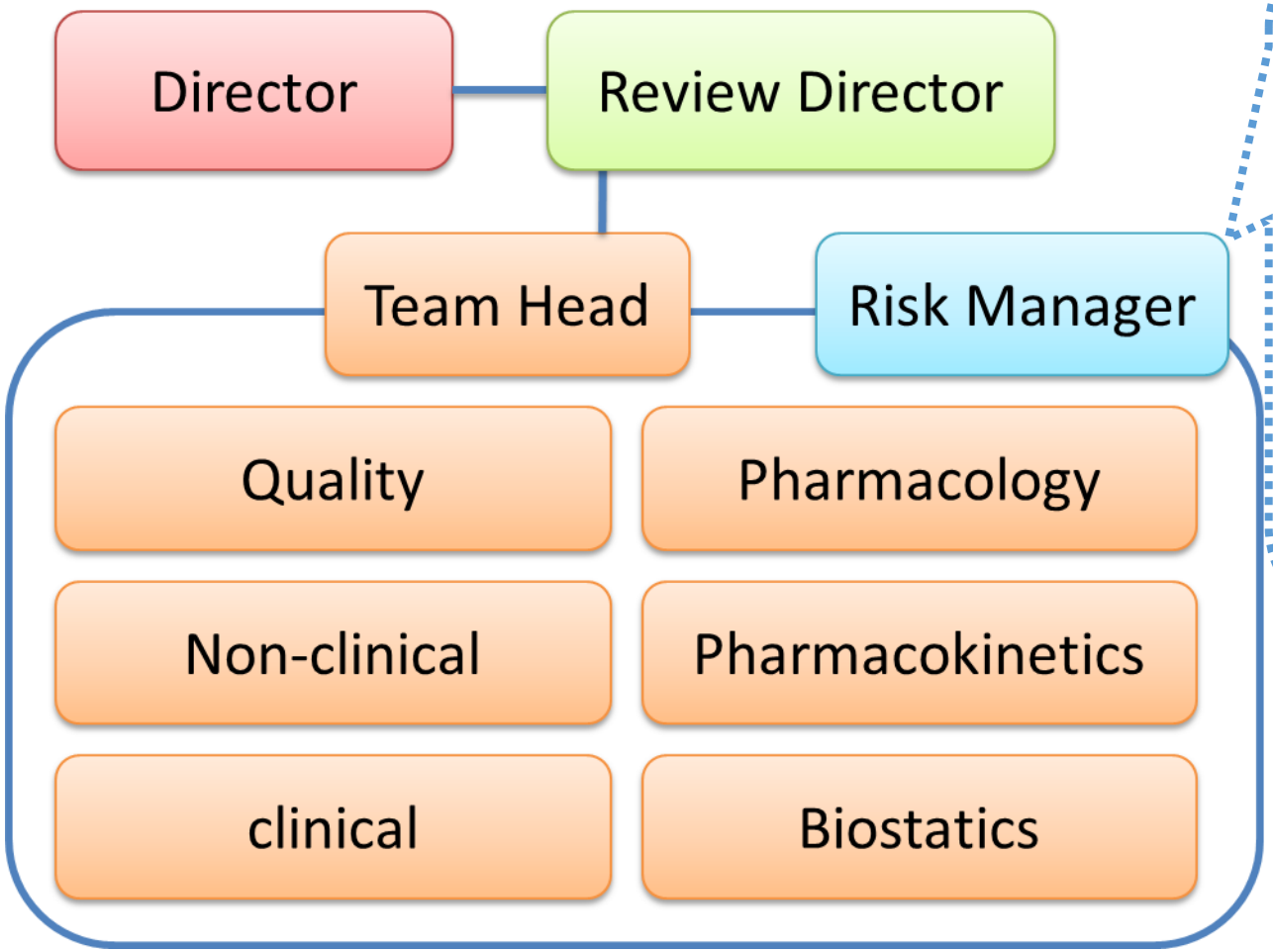


- PMDA consistently monitor the safety of drugs from the clinical stage to post-marketing stage with cooperation between Review team and Safety team
- In PMDA, Risk manager system has been started since April 2010.

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**

Composition of review team



RMs・・・

- are on the member of Safety Team.
- spend much time as a member of a Review Team.
- involve consultations of new drug development, safety evaluations of new drugs and considerations of package inserts and RMP.

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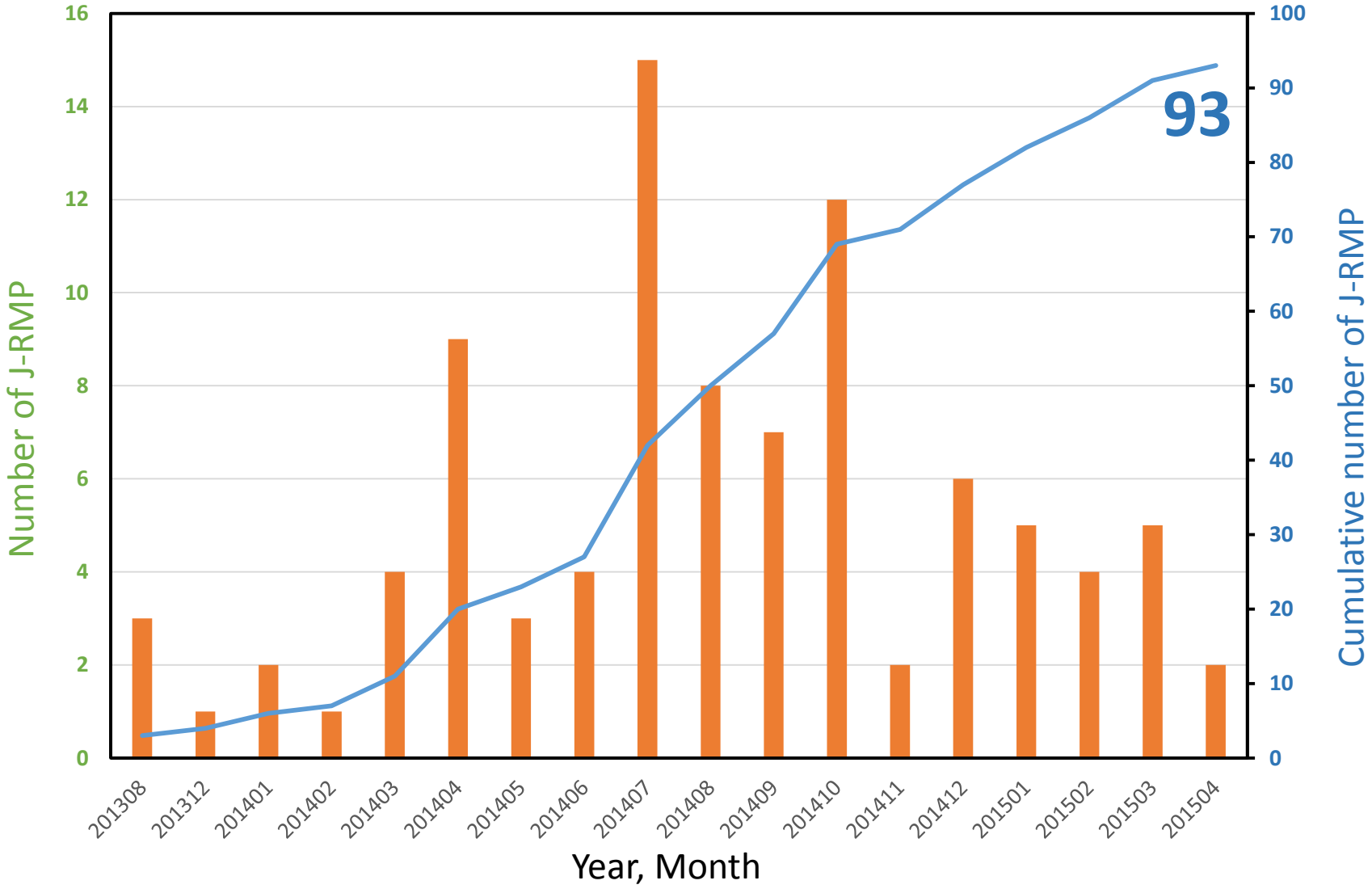
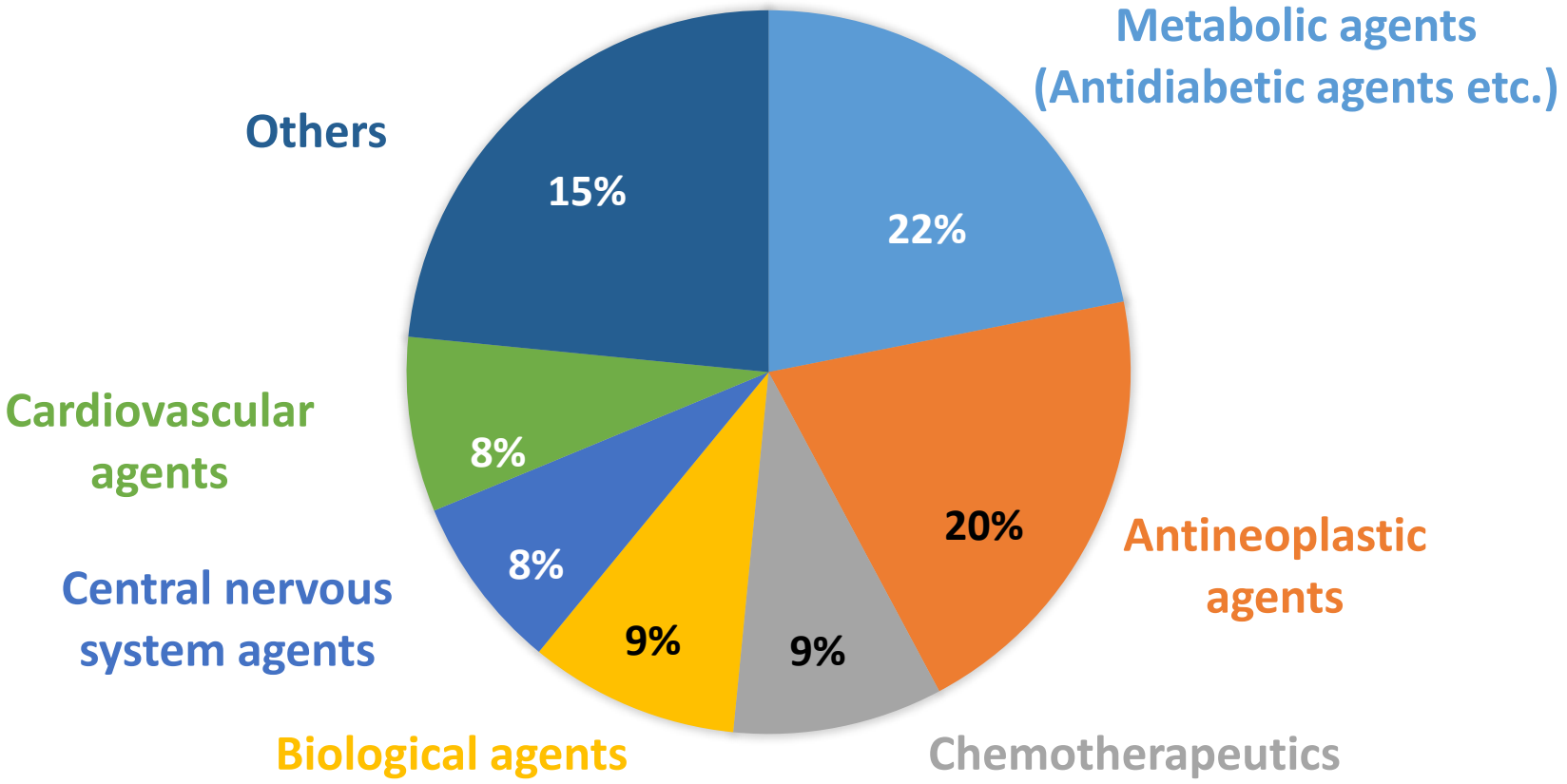
Number of J-RMP



Types of drugs requiring J-RMP



N = 64 (As of Nov 2014)

Additional Risk minimisation measures

Additional Risk minimization measures		N=82
Communication to HCPs	Early Post-marketing Phase Vigilance	79%
	Educational material	60%
	Rapid release of information	12%
Communication to Patients	Educational material	38%
Restricted access		6%
Others		10%

As of Mar 2015

Additional Pharmacovigilace activities

Additional Pharmacovigilace activities	N=82
Early Post-marketing Phase Vigilance	76%
Use-results survey	56%
Specified use-results survey	52%
Post-marketing clinical study	39%
Others*	4%

*PK/PD studies, Patient Registry etc.

As of Mar 2015

Discussion point about Safety Specification

Examples:

- What is the difference between identified risks and potential risks ?
- What is “important” ?
- Are all patient population excluded from clinical study defined in “Important Missing Information” ?

Case study

- Drug X is an oral glucose-lowering agent.
- Pregnant women were excluded from clinical trials.

✓ Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013（published by the Japan Diabetes Society）

" Insulin therapy should be given in pregnant women in whom the glycemic goals cannot be achieved with diet therapy alone. As the use of glucose-lowering agents is not recommended, they should be switched to insulin therapy. (grade A; consensus) "

✓ "Drug X" Package insert in Japan

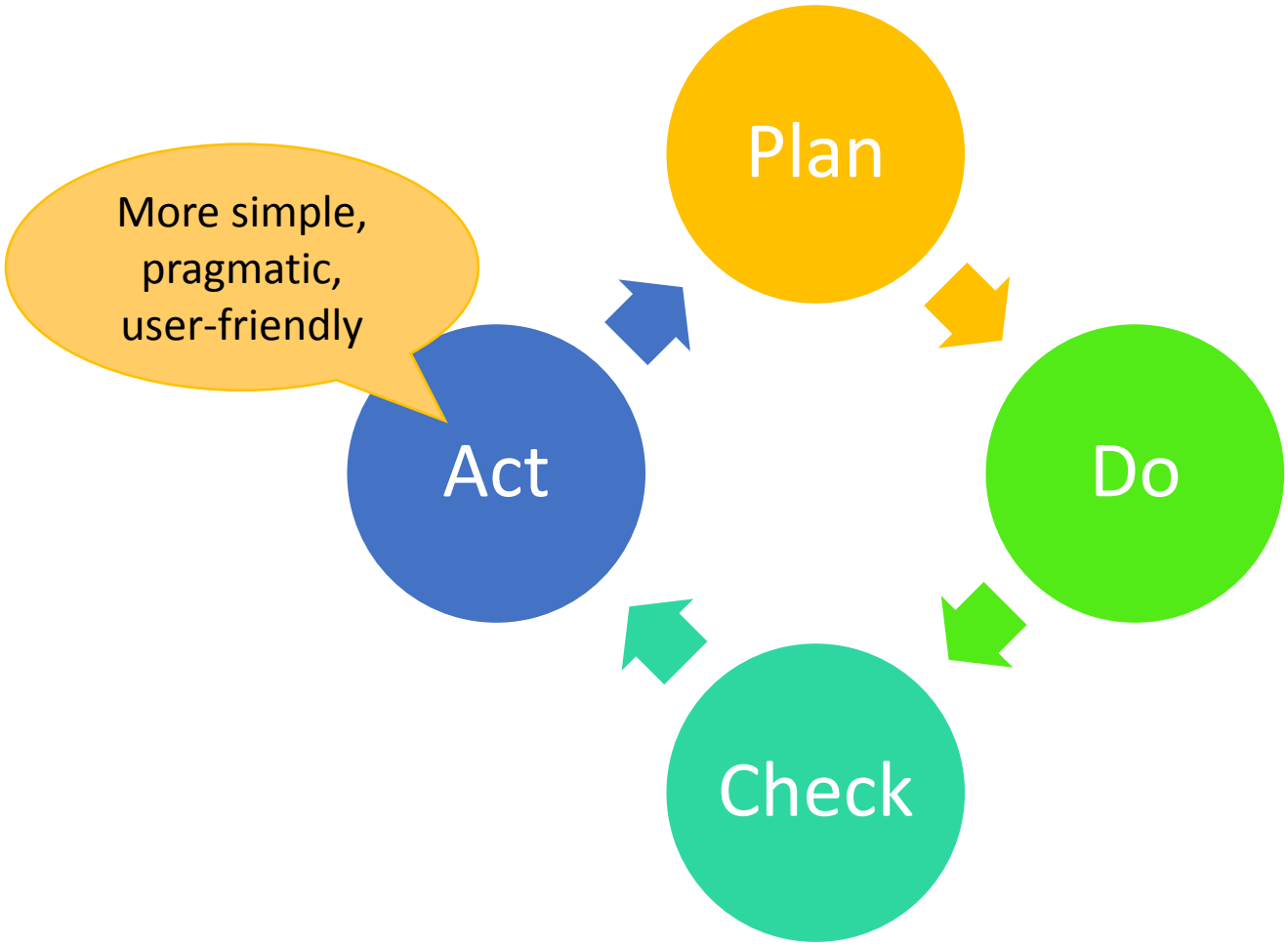
" Pregnancy : As the use of "Drug X" is not recommended in pregnant or possibly pregnant women, Insulin therapy should be given to them. "

Future Challenges in Pharmacovigilace activities

Additional Pharmacovigilace activities	N=82
Early Post-marketing Phase Vigilance	76%
Use-results survey	56%
Specified use-results survey	52%
Post-marketing clinical study	39%
Others	4%

We need to look for more efficient and meaningful Pharmacovigilance activities !

Future Challenges in Risk minimisation measures



We need to develop methodologies to evaluate effectiveness of risk minimization!

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Characteristics of J-RMP

- Optimal risk management and data collection
- Start to discuss at the submission of NDA
- Set up milestones
  - Obvious goal of surveillance
  - Revision of RMP by new information, if necessary
- Transparency among stakeholders
  - Overview of each RMP is published on PMDA website
- Information about the product is summarized briefly

Expected effects by RMP

- Regular evaluation of RMP
- Revision of contents of risk management
  - Comprehensive risk management through life-cycle of the product

  → Effective safety operations are expected!

- Sharing contents of risk management among the relative parties
  - MHLW/PMDA, MAHs ,Healthcare professionals and patients

  → Effective risk communications are expected!

PMDA Website on safety information

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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⚠ Safety Aleart & Recalls/ Review Reports/ Package Inserts

The informations,such as Package Inserts(in Japanese),Review Reports etc,are av
Please click the following links and search button.
Search system is provided in Japanese only.

Prescription Drugs — Search

- The Yellow Letter / Blue Letter
- Recalls(in Japanese)
- PMDA Alert for Proper Use of Drugs
- Revisions of PRECAUTIONS
- Safety information announced by MHLW
- PMDA Risk Communications

⊞ Open

Medical Devices — Search

- The Yellow Letter / Blue Letter(in Japanese)
- Recalls(in Japanese)
- Revisions of PRECAUTIONS(in Japanese)
- Notification on Self-Check(in Japanese)
- Safety information announced by MHLW(in Japanese)
- MHLW Pharmaceuticals and Medical Devices Safty Information

⊞ Open

Over The Counter/ Behinde The Counter — Search

- The Yellow Letter / Blue Letter
- Review Reports(in Japanese)

Regenerative Medical Products(Cell and Tisue based Products)

- Package Inserts(in Japanese)
- Review Reports

In vitro diagnostics — Search

- The Yellow Letter / Blue Letter(in Japanese)

PMDA English Website

http://www.pmda.go.jp/english/index.html

Thank you !

E-mail : sato-junko@pmda.go.jp

For additional questions please click on “Contact us” on our English website