Present and future of drug safety measures in Japan

日本における医薬品の安全対策の現状と今後について

Shoji TAKAMATSU, Ph.D.
Office of Safety Ⅱ

Agenda

1. Background

2. Recent PMDA
   drug safety measures

3. Safety measures in the future

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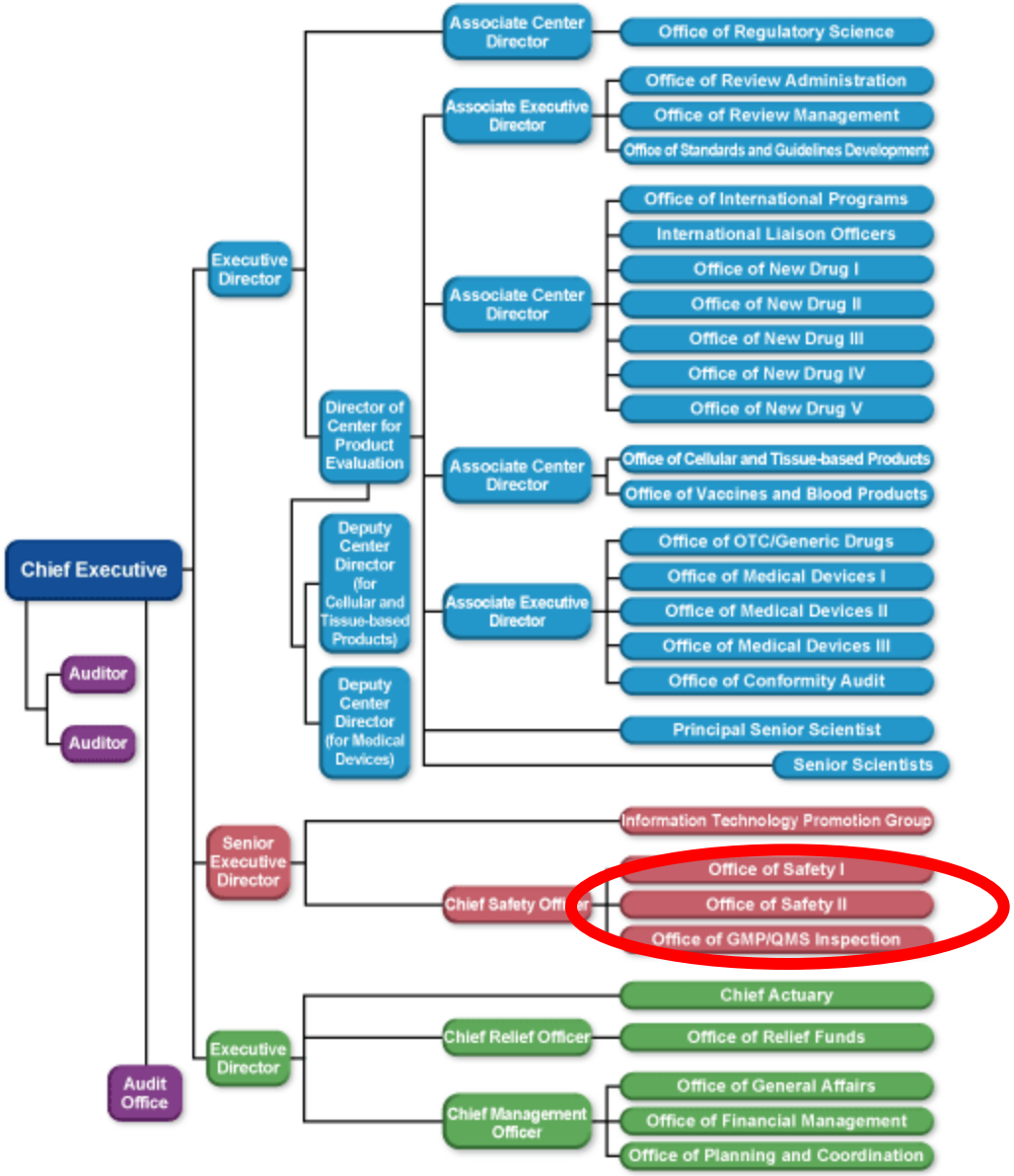
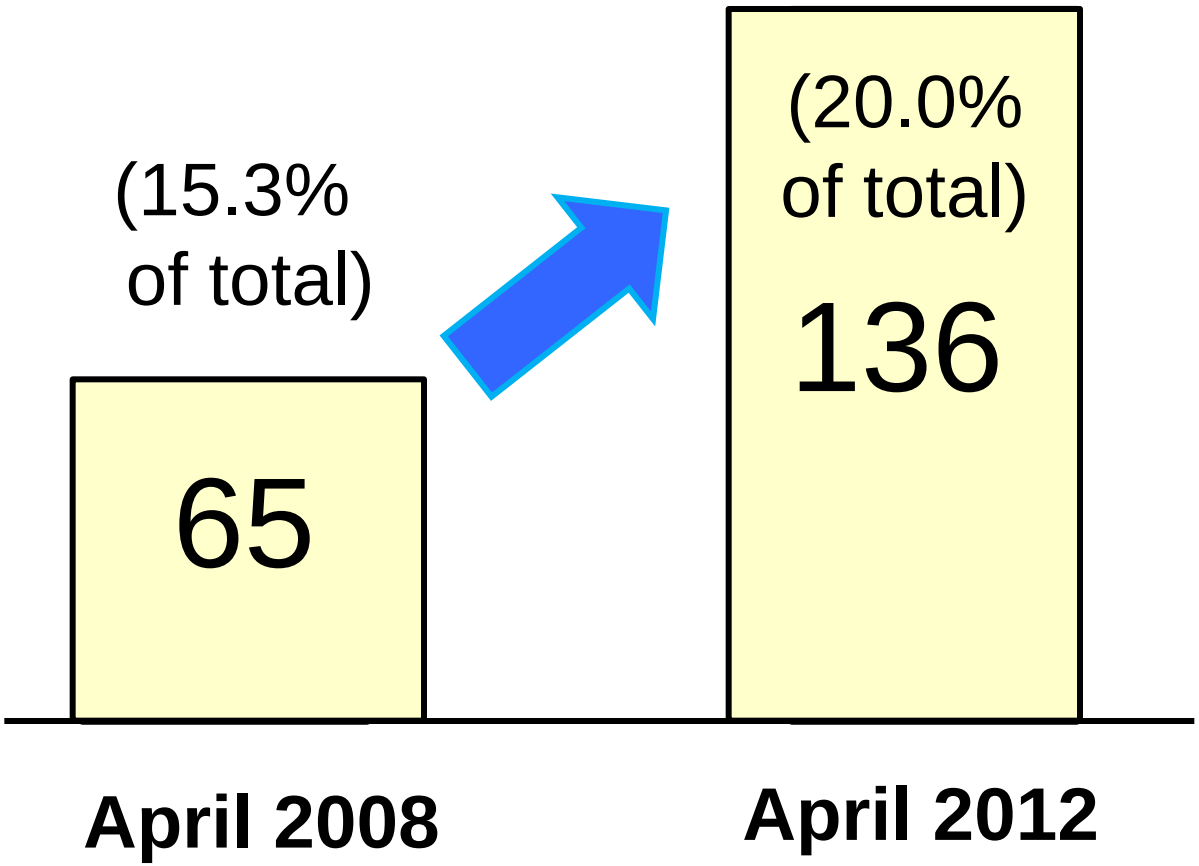
Organization Chart (As of October 1,2012)



The Number of Staff (Safety Division)



Major Post-Marketing Surveillance (PMS) Systems in Japan

1. Re-examination system
2. Re-evaluation system
3. Adverse reaction and infectious diseases reporting system

（Pharmaceutical Affairs Act : PAA）

4. Early Post-marketing Phase Vigilance (EPPV)

Purpose:

Ensuring
- **effectiveness**
- **safety**
- **quality**

of post-marketing

Post-approval ADR Reporting Rule by MAH

Serious-ness	Predict-ability	Time frame of report to PMDA
Serious	Not predictable	**15 days**
	Predictable	- Death etc.* **15 days** - Others **30 days**
Not serious	Not predictable	**Annually** **(Annual Cumulative Report)**
	Predictable	-

- Reporting time frame depends on seriousness and predictability of the case. (Article 253 of the Ministerial Ordinance on PAA)
- No timeframe defines for HCP reporting

*** - Death**
- ADR caused by new drug ingredient within 2 years after approval
- ADR detected by Early Post-marketing Phase Vigilance (EPPV)

ADR Report from Health Care Professionals (HCPs)

- Voluntary basis
  - since 1967: designated medical institutions
  - since 1984: designated pharmacies
  - since 1997: all medical institutions and pharmacies
- Stipulated in PAA
  - since 2003
- HCPs shall report to MHLW when they
  - detect occurrence of any disorders suspected to be caused by ADRs
  - confirm that it is necessary to prevent occurrence or spread of hazards
- No timeframe defines for HCPs reporting

Direct Investigation by PMDA (since 29th July, 2010)

(limited in the case of death or severe ADR)

HCPs

Electronic Reporting

FAX

MHLW

② (Paper and Electronic Reports)

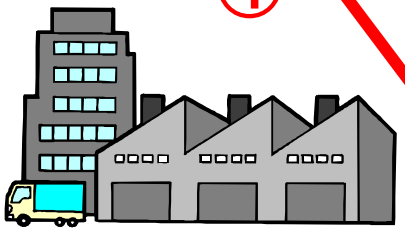
① Postal Mail

③

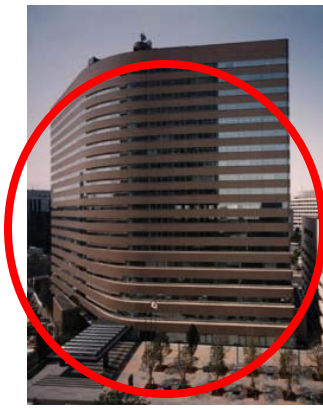
④

Investigation :Since July, 2010

⑤ Feedback



MAH



PMDA

ADR Report from HCPs

- Number of investigation by PMDA :

  Death : **83**cases, Serious : **1,090**cases

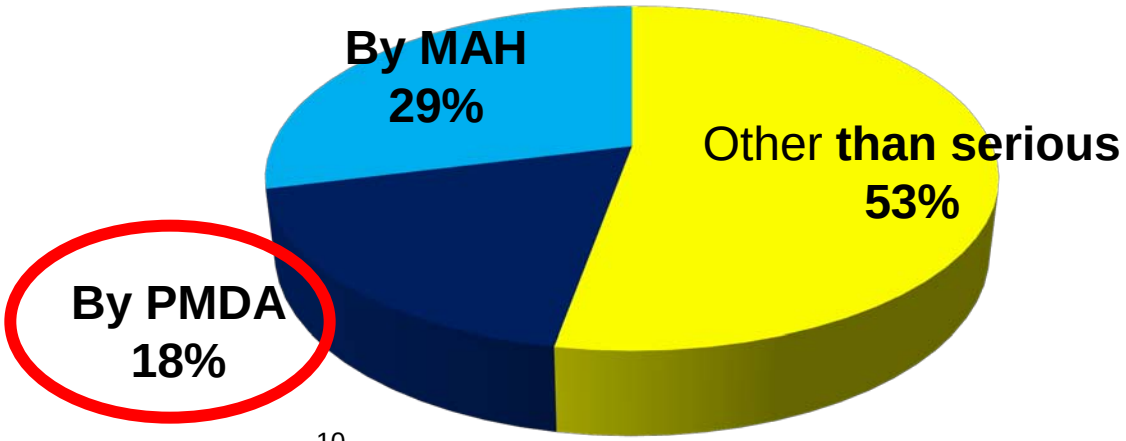
  (date of December 31,2012)

- Number of feedback to MAH : **1,101**cases

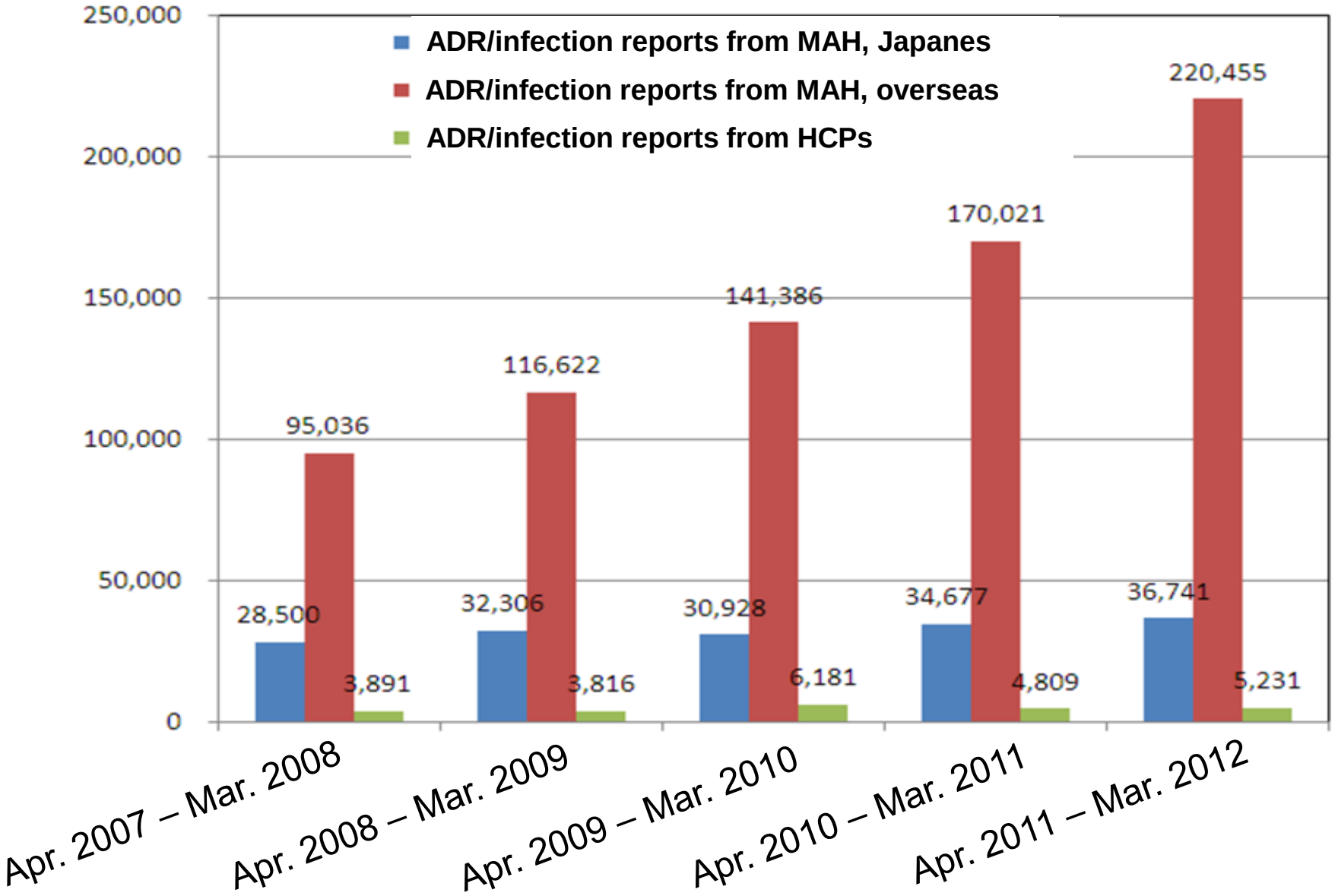
  (date of December 31,2012)

- Proportion of investigation by PMDA :

1st Apr. 2012 – 31th Aug. 2012



The Number of ADR/infection Reports



Early Post-marketing Phase Vigilance (EPPV)

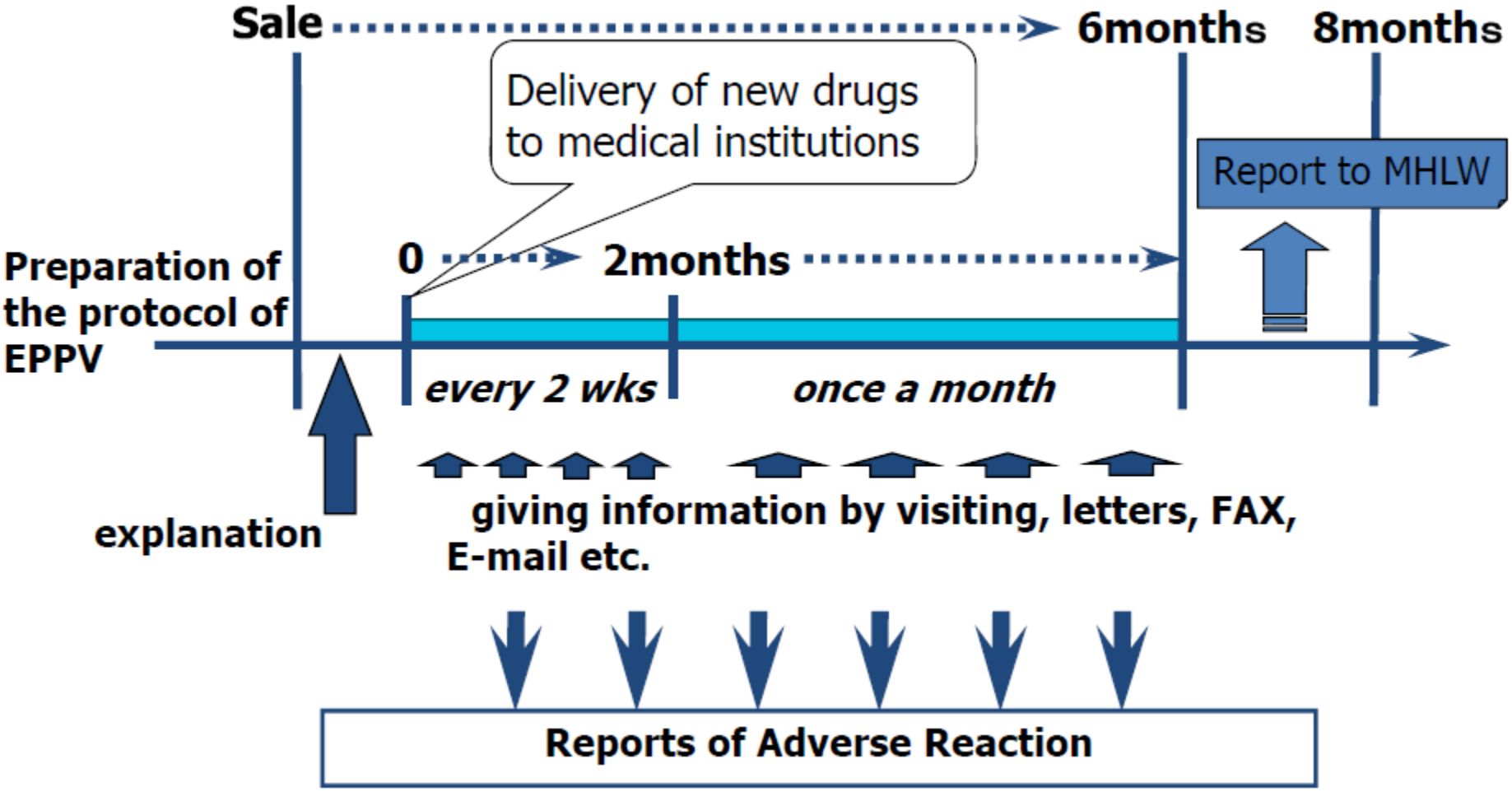
Enforced on Oct 1, 2001

1. To ensure necessary information for appropriate use (contraindication, careful administration etc) is explained to the medical institutions 2 weeks before delivery.

2. To request medical institutions to use the drugs carefully and report serious ADRs, if occurred, immediately to pharmaceutical companies

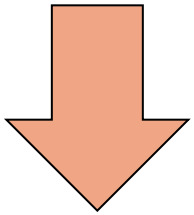
3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.

Scheme of Early Post-marketing Phase Vigilance (EPPV)



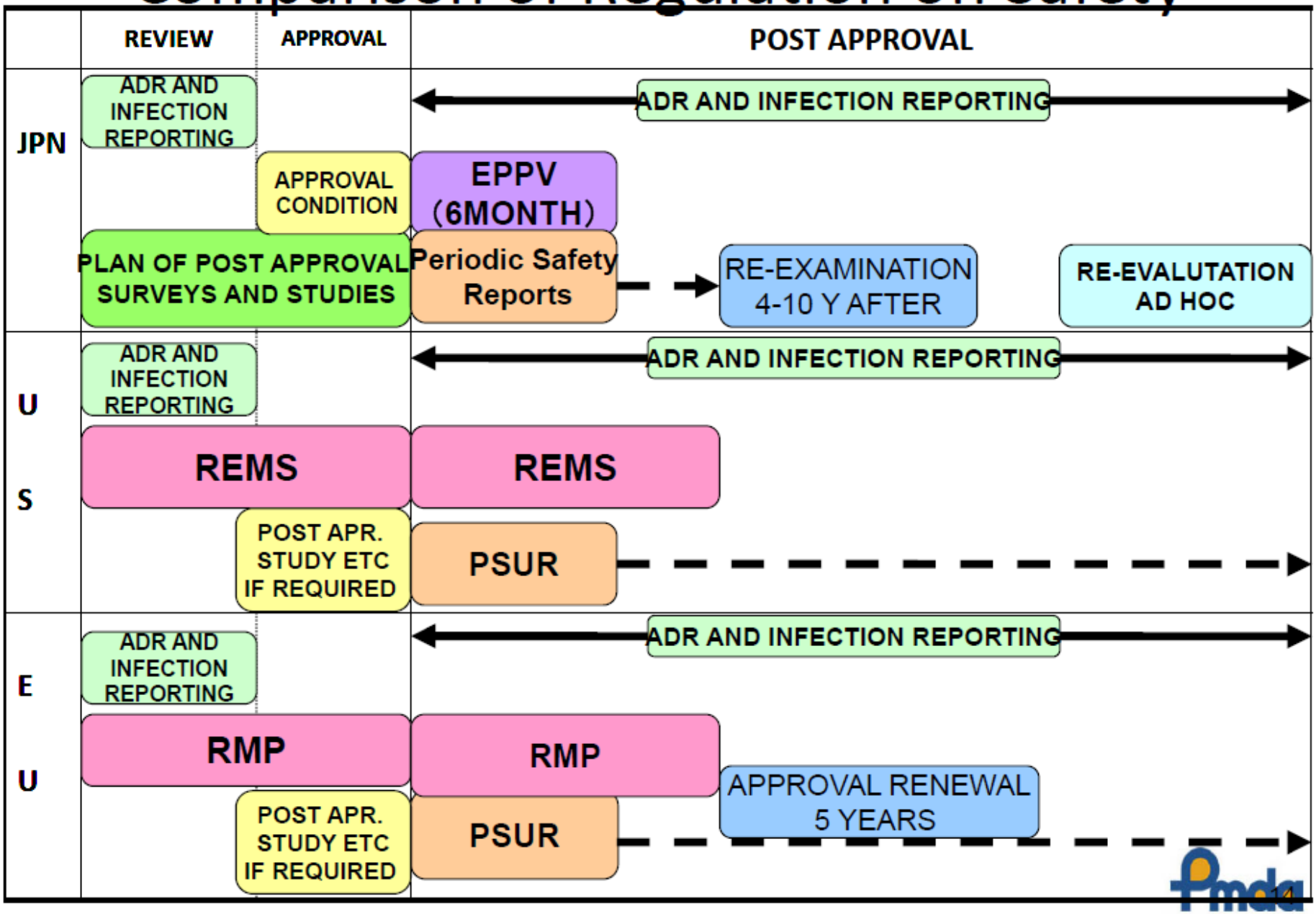
Purpose and Meaning of EPPV

- Promote proper use of new drugs
- Detect serious ADRs earlier
- Take safety measures quickly



- Protect patients from known/unknown ADRs
- Secure patients to access new drugs
- EPPV for quick and effective action to early stage safety problems

Comparison of Regulation on Safety



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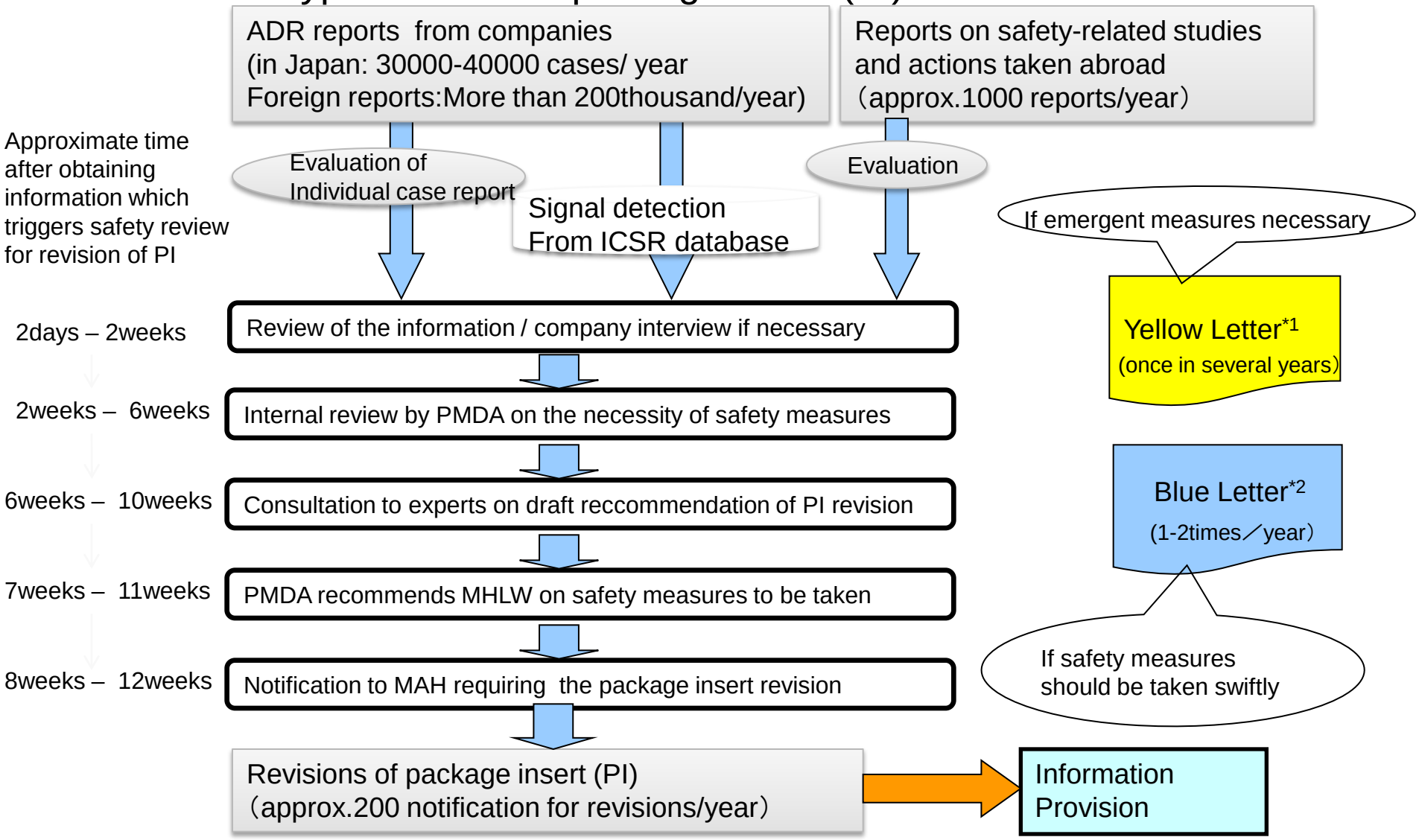
Time course of review for safety measures

in typical cases of package insert (PI) revisions



Note:

＊1：Yellow Letter is “Dear Healthcare Professional Letter of Emergent Safety Communications”

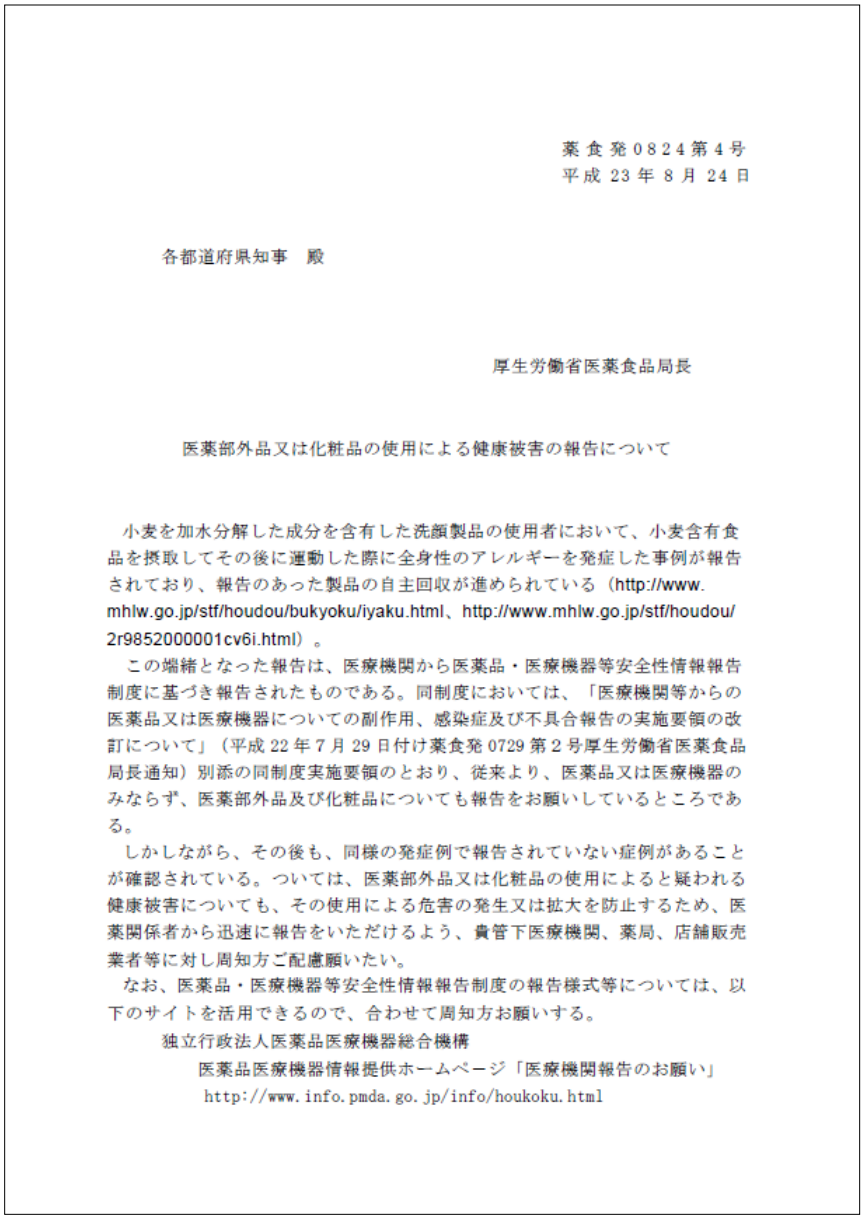
＊2：Blue Letter is “Dear Healthcare Professional Letter of Rapid Safety Communications”

Information on safety measures

- Spontaneous ADRs/infections reports
- Research reports/reports of measures taken overseas
- Periodic safety reports and periodic safety update reports
- Reports for unexpected/non-serious ADRs
- Periodic reporting system for infections

etc.

Safety Measures Triggered by ADR Reports from HCPs



薬食発0824第4号
平成23年8月24日

各都道府県知事　殿

厚生労働省医薬食品局長

医薬部外品又は化粧品の使用による健康被害の報告について

小麦を加水分解した成分を含有した洗顔製品の使用者において、小麦含有食品を摂取してその後に運動した際に全身性のアレルギーを発症した事例が報告されており、報告のあった製品の自主回収が進められている（http://www.mhlw.go.jp/stf/houdou/bukyoku/iyaku.html、http://www.mhlw.go.jp/stf/houdou/2r9852000001cv6i.html）。

この端緒となった報告は、医療機関から医薬品・医療機器等安全性情報報告制度に基づき報告されたものである。同制度においては、「医療機関等からの医薬品又は医療機器についての副作用、感染症及び不具合報告の実施要領の改訂について」（平成22年7月29日付け薬食発0729第2号厚生労働省医薬食品局長通知）別添の同制度実施要領のとおり、従来より、医薬品又は医療機器のみならず、医薬部外品及び化粧品についても報告をお願いしているところである。

しかしながら、その後も、同様の発症例で報告されていない症例があることが確認されている。ついては、医薬部外品又は化粧品の使用によると疑われる健康被害についても、その使用による危害の発生又は拡大を防止するため、医薬関係者から迅速に報告をいただけるよう、貴管下医療機関、薬局、店舗販売業者等に対し周知方ご配慮願いたい。

なお、医薬品・医療機器等安全性情報報告制度の報告様式等については、以下のサイトを活用できるので、合わせて周知方お願いする。

独立行政法人医薬品医療機器総合機構
医薬品医療機器情報提供ホームページ「医療機関報告のお願い」
http://www.info.pmda.go.jp/info/houkoku.html

- Systemic allergies occurred with people who use the face wash containing hydrolyzed wheat

Pilot Program of
“Direct Patient Reporting System for Adverse Drug Reactions”

（since 26th Mar. 2012）

ADR Reports by Patients

(26th Mar. 2012 – 31th Dec. 2012)

1. **Number of reports** : 164 reports
2. **Number of drugs** : 213 drugs（201 prescription drugs , 12 OTC drugs）
3. **Status of reporters** : 129 reports from patients or consumers, 35 reports from families
4. **Fatal cases** : 7 reports

PMDA English website

http://www.pmda.go.jp/english/index.html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e.g <Q and A> Resuming vaccination with the pediatric pneumococcal conjugate vaccine and the Hib vaccine (dated March 29 2011)
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Home > Services of PMDA > Post-marketing Safety > Safety Information > PMDA Risk Communications

PMDA Risk Communications

Drug Risk Information of Ongoing Evaluation Updated

(Download this page for PDF version (PDF))

This webpage was developed to provide drug risk information which has come under review by the PMDA/MHLW. Information provided here is as follows:

1. Risk Information was suggested by a certain amount of accumulated information on Adverse Drug Reactions (ADR) reports or Early Postmarketing Phase Vigilance (EPPV). Certain safety measures such as revision of Precautions section in the labeling of the product might be taken after the ongoing review.

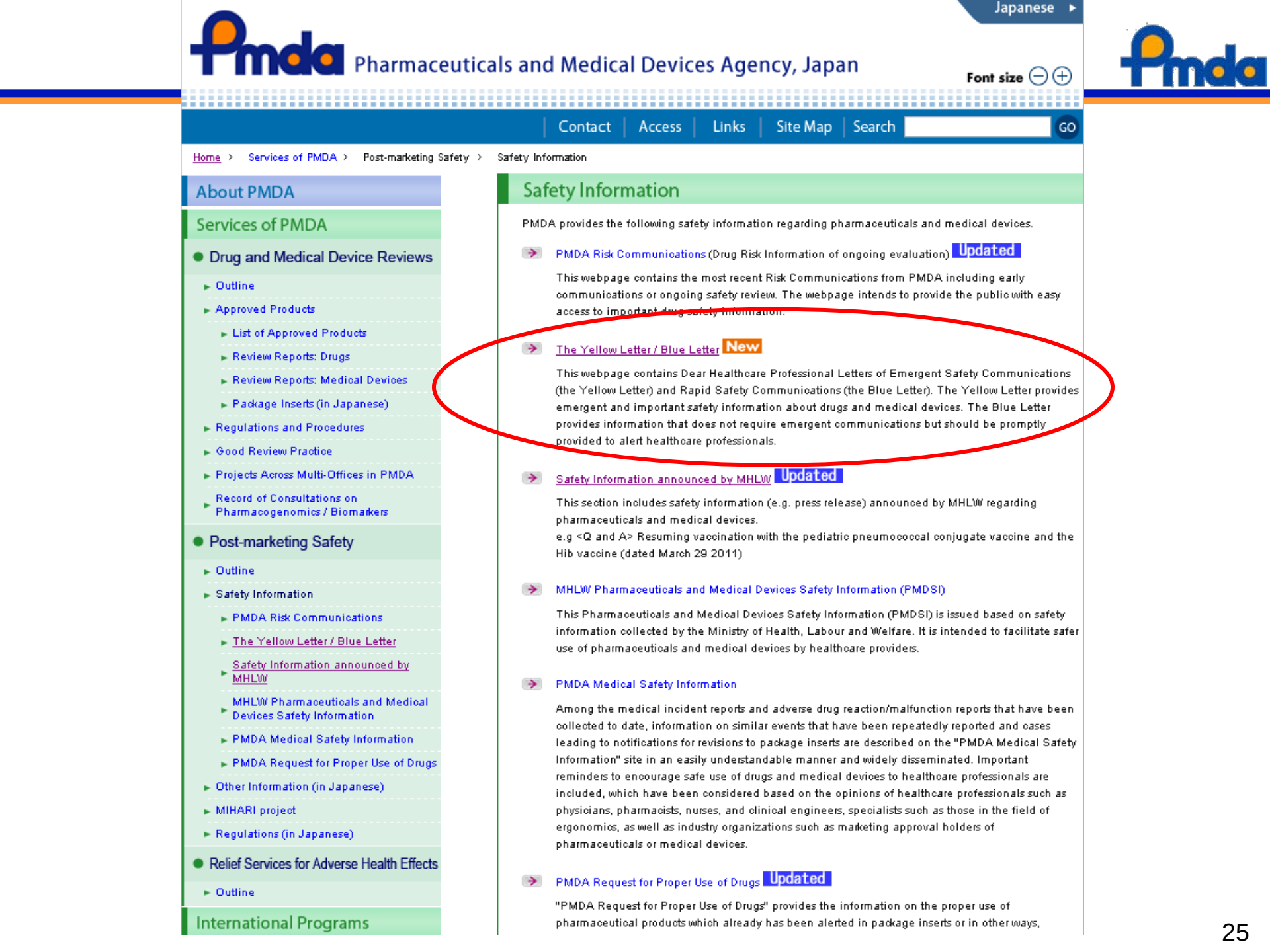
2. Risk Information which has attracted attention in foreign drug regulatory agencies or academic societies and PMDA/MHLW has started its evaluation. Information provided here is still under review. If you are taking the following medicines, you should NOT stop taking them or reduce the dosage only on your own judgment. Consult your healthcare professional if you have any questions or concerns about these medications.

1. Risk Information which some safety measures might be taken.

Posted Date	Nonproprietary Name (Click on each drug name for more information on Package inserts (Japanese text only))	Risk Information Ongoing Evaluation	Related Information	Evaluation Result (Japanese Text Only)
New January 25, 2013	Propafenone Hydrochloride	Hepatic dysfunction, Jaundice	-	-
	4. Human Chorionic Gonadotrophin	Alert for the use of these drugs to patients with endometrial hyperplasia		

2. Risk Information which has attracted attention in foreign drug regulatory agencies or academic societies and PMDA/MHLW has started its evaluation.

Posted Date	Nonproprietary Name (Click on each drug name for more information on Package inserts (Japanese text only))	Risk Information Ongoing Evaluation	Related Information	Evaluation Result
December 28, 2011	Aliskiren Fumarate	MHLW/PMDA starts review of Rasilez (Aliskiren Fumarate) Communication on combination therapy of Rasilez with an ACE inhibitor or ARB to hypertension patients with complication of diabetes (PDF)	EMA: European Medicines Agency starts review of aliskiren-containing medicines following termination of ALTITUDE study (PDF)	Package insert revision (PDF)
November 30, 2011	Avastin (bevacizumab)	Japan's view on Avastin (bevacizumab) for breast cancer indication (PDF)	Press Announcement from the FDA Review report of AVASTIN® 100mg/4mL Intravenous Infusion and AVASTIN® 400mg/16mL Intravenous Infusion on July 14, 2011 (Japanese text only) (PDF)	-
July 29, 2011	Somatropin (genetical recombination)	Update on Ongoing PMDA/MHLW Review the Safety of	For patients treated (are treating) with the recombinant growth	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The Yellow Letter / Blue Letter

To prevent health hazards associated with the use of drugs and medical devices, it is important that post-marketing reports of adverse reactions and defects be collected and reviewed in order to promptly provide feedback about necessary information to medical institutions.

According to Article 77-4 of the Pharmaceutical Affairs Law (Law No. 145, 1960), when MAHs of drugs or medical devices learn that the use of drugs or medical devices that they have marketed might cause onset or spread of hazards to public health or hygiene, necessary measures shall be taken, including recall, suspension of sales, and information provision to prevent such hazards.

Based on the above provision, various types of safety information have been provided. Particularly important safety information which requires immediate communication is provided through the Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter) or Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter). The Yellow Letter contains emergent and important safety information about drugs and medical devices. The Blue Letter contains information that does not require emergent communications as Yellow Letter but should be promptly provided to alert healthcare professionals.

Copies of letters sent to healthcare professionals

Date sent	Dear Healthcare Professional Letters	Relevant case reports
New September 11, 2012	RANMARK (denosumab) - Risk of severe hypocalcaemia, including fatal cases (PDF)	Severe hypocalcaemia fatal cases where the causal relationship to RANMARK (denosumab) cannot be ruled out (PDF)

Dear Healthcare Professional Letter of Rapid Safety Communication

September 2012

RANMARK SUBCUTANEOUS INJECTION 120mg (denosumab)

-Risk of severe hypocalcaemia, including fatal cases

11 September 2012

Dear Healthcare Professional,

DAIICHI SANKYO COMPANY, LIMITED would like to inform you of new important safety information related to hypocalcaemia associated with RANMARK (denosumab). There have been reported 32 cases of severe hypocalcaemia from 17 April 2012 to 31August 2012. Of them, there were 2 fatal cases for which the causality to the drug could not be ruled out. (The number of patients using this drug after launching the drug estimated by MAHs: approximately 7,300) In the light of this situation, package inserts of RANMARK has been revised to include WARNINGS to the section of Precautions.

Serum calcium should be measured before administration of RANMARK

Serum electrolyte levels such as serum calcium should be measured before administration of the drug. Corrected serum calcium levels* should be checked, and if hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. Hypocalcaemia can occur at any time from within a few days after initiating the administration of this drug. Serum electrolyte levels such as serum calcium should be monitored frequently and patients should be carefully monitored after the start of the treatment.

Oral Supplementation of Calcium and vitamin D is required.

To reduce the risk of onset of hypocalcaemia, supplementation of calcium (at least 500mg/day) and natural vitamin D (at least 400 IU/day) is required in all patients every day unless corrected serum calcium levels are high. For Patients with renal impairment, activated vitamin D should be used depending on the degree of renal impairment, due to the impaired activation of vitamin D. Calcium supplementation should be determined as needed and dosage of calcium should be adjusted appropriately.

Patients with severe renal impairment are at a greater risk of developing hypocalcaemia and therefore use the drug cautiously.

If hypocalcaemia is observed, calcium and vitamin D should be administered orally and when requiring emergency treatment, appropriate measures such as concomitant use of I.V. administration of calcium should be taken.

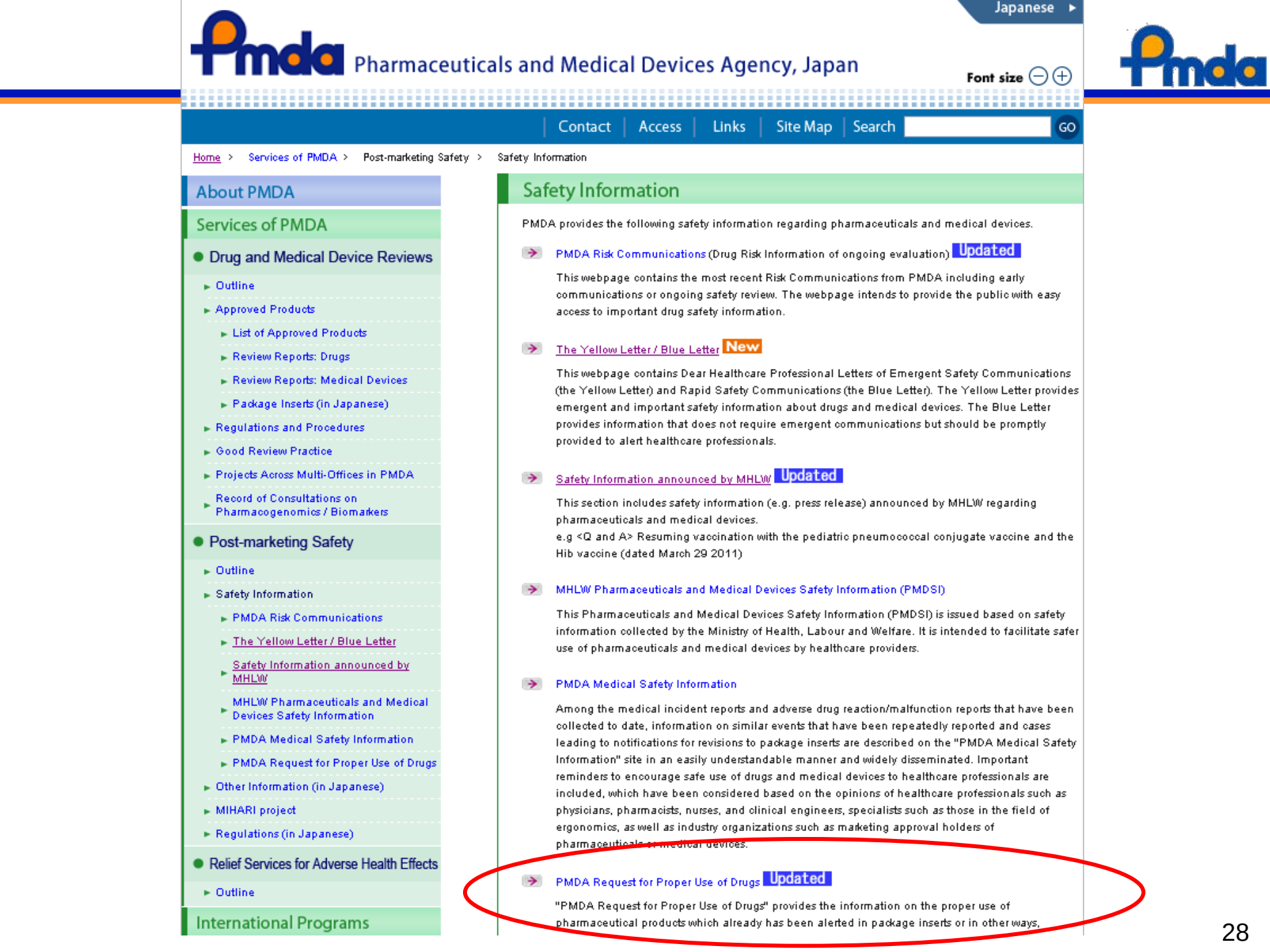
*In patients with hypoalbuminaemia, corrected serum calcium levels applying the following formula should be used due to false low calcium levels, when patients have serum albumin levels ＜4.0g/dL.
Corrected serum calcium levels (mg/dL) = serum calcium levels (mg/dL)＋4－serum albumin levels (g/dL)

Annex: revised copy of the RANMARK of package inserts

DAIICHI SANKYO COMPANY, LIMITED

Pharmaceuticals and Medical Devices Agency

Translated by Office of Safety Ⅰ,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp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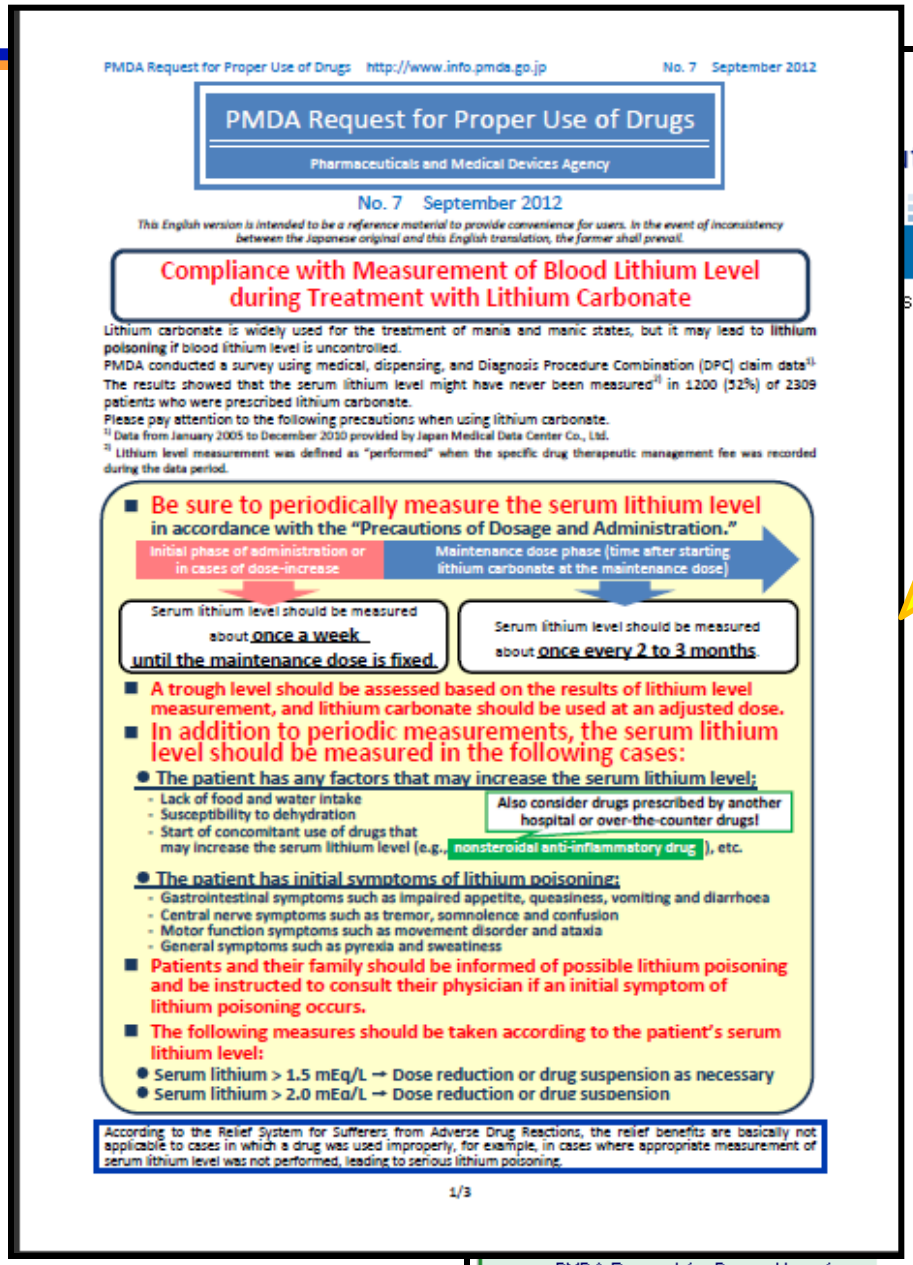

PMDA Request for Proper Use of Drugs http://www.info.pmda.go.jp No. 7 September 2012

PMDA Request for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 7 September 2012

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.

Compliance with Measurement of Blood Lithium Level during Treatment with Lithium Carbonate

Lithium carbonate is widely used for the treatment of mania and manic states, but it may lead to lithium poisoning if blood lithium level is uncontrolled.
PMDA conducted a survey using medical, dispensing, and Diagnosis Procedure Combination (DPC) claim data[1]. The results showed that the serum lithium level might have never been measured[2] in 1200 (52%) of 2309 patients who were prescribed lithium carbonate.
Please pay attention to the following precautions when using lithium carbonate.

[1] Data from January 2005 to December 2010 provided by Japan Medical Data Center Co., Ltd.
[2] Lithium level measurement was defined as "performed" when the specific drug therapeutic management fee was recorded during the data period.

- **Be sure to periodically measure the serum lithium level in accordance with the "Precautions of Dosage and Administration."**

Initial phase of administration or in cases of dose-increase	Maintenance dose phase (time after starting lithium carbonate at the maintenance dose)
Serum lithium level should be measured about **once a week until the maintenance dose is fixed.**	Serum lithium level should be measured about **once every 2 to 3 months.**

- **A trough level should be assessed based on the results of lithium level measurement, and lithium carbonate should be used at an adjusted dose.**
- **In addition to periodic measurements, the serum lithium level should be measured in the following cases:**
  - **The patient has any factors that may increase the serum lithium level;**
    - Lack of food and water intake
    - Susceptibility to dehydration
    - Start of concomitant use of drugs that may increase the serum lithium level (e.g., nonsteroidal anti-inflammatory drug), etc.

    Also consider drugs prescribed by another hospital or over-the-counter drugs!
  - **The patient has initial symptoms of lithium poisoning;**
    - Gastrointestinal symptoms such as impaired appetite, queasiness, vomiting and diarrhoea
    - Central nerve symptoms such as tremor, somnolence and confusion
    - Motor function symptoms such as movement disorder and ataxia
    - General symptoms such as pyrexia and sweatiness
- **Patients and their family should be informed of possible lithium poisoning and be instructed to consult their physician if an initial symptom of lithium poisoning occurs.**
- **The following measures should be taken according to the patient's serum lithium level:**
  - Serum lithium > 1.5 mEq/L → Dose reduction or drug suspension as necessary
  - Serum lithium > 2.0 mEq/L → Dose reduction or drug suspension

According to the Relief System for Sufferers from Adverse Drug Reactions, the relief benefits are basically not applicable to cases in which a drug was used improperly, for example, in cases where appropriate measurement of serum lithium level was not performed, leading to serious lithium poisoning.

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...ticals and Medical Devices Agency, Japan

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Safety > Safety Information > PMDA Request for Proper Use of Drugs

PMDA Request for Proper Use of Drugs

"PMDA Request for Proper Use of Drugs" provides the information on the proper use of pharmaceutical products which already has been alerted in package inserts or in other ways, however on which cases which were applied as relief benefits or were reported as adverse reactions have been still repeated. This page is intended to make easy-to-understand explanations ...phic illustrations on such safety matters that medical professionals should pay attention to ... and to ask them to maintain the proper use of drugs thoroughly.

Posted on	No.	Title
June 2012	9	Early D...ction of Drug-induced Serious Skin Disorders (PDF)
May 2012	8	Serious ...ocarnitinemia and hypoglycaemia in children treated with antibacteria...ith a pivoxil group (PDF)
Updated October 16, 2012 May 2012	7	Lithium Carbonate-induced Serious Lithium Poisoning and Compliance with Measurement of Blood Lithium Level (PDF)
February 2012	6	Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotorigine)-induced Serious Skin Disorders.(PDF)
December 2011	5	Periodic blood tests and symptom checks should be performed for prevention and early detection of agranulocytosis associated with the antithyroid drug thiamazole.(PDF)
November 2011	4	Recommendation of periodic liver function tests and monitoring of signs/symptoms for patients treated with the gout/hyperuricaemia treatment benzbromarone (PDF)
October 2011	3	Hepatitis B viral growth associated with the use of drugs with immunosupressive effects (PDF)
October 2011	2	Automobile accidents associated with the use of smoking cessation aid CHAMPIX (varenicline tartrate) (PDF)

PMDA Request for Proper Use of Drugs

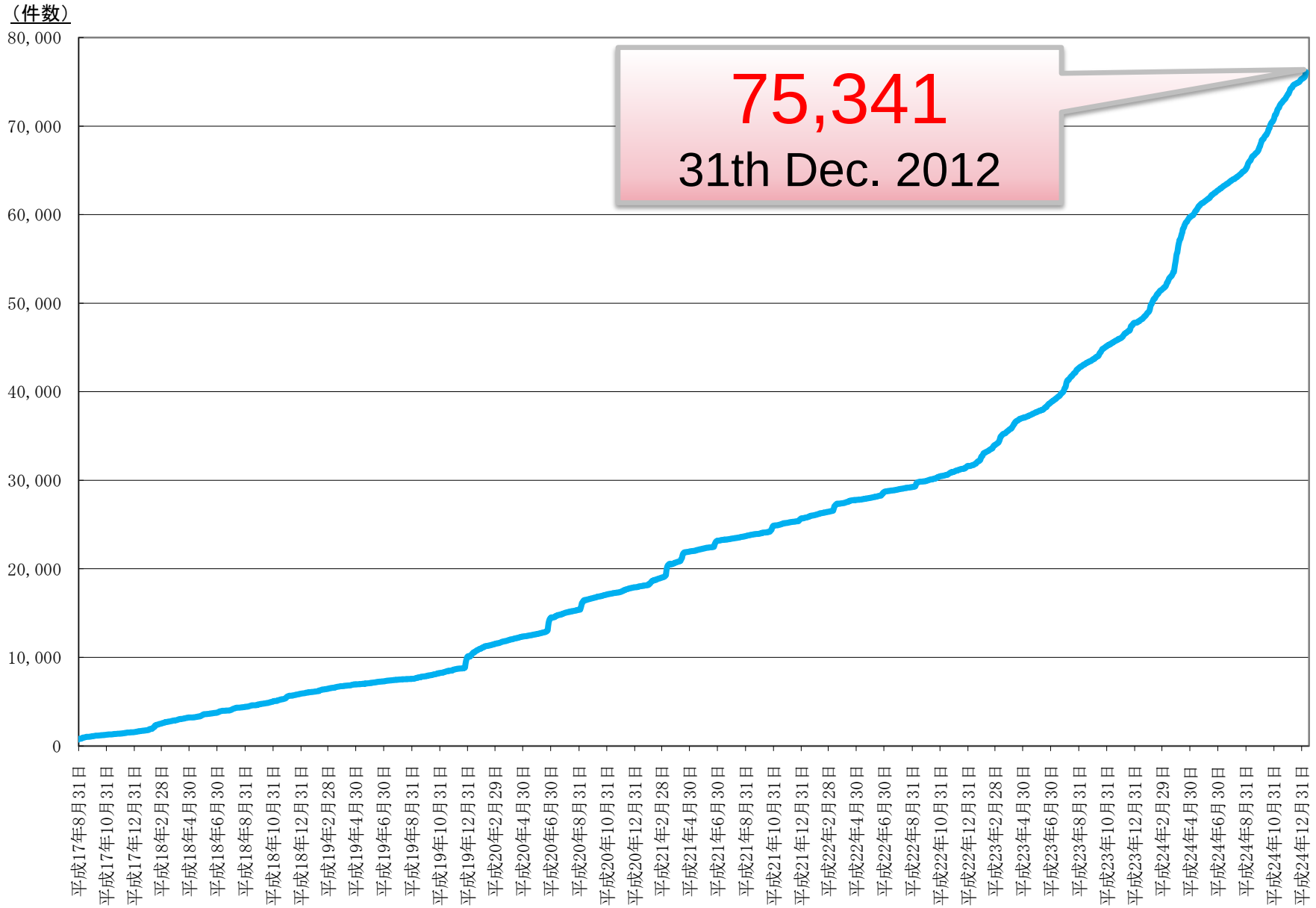
Pharmaceuticals and Medical Devices Information E-mail Service (PMDA medi-navi)

Information delivered by “PMDA medi-navi”

- **Yellow Letter , Blue Letter**
- **Recall Information**
- **Approval Information**
- **Notice Revision of PRECAUTIONS**
- **Pharmaceuticals and Medical Devices Safety Information**
- **PMDA Medical Safety Information**

etc.

The Number of Subscription to the PMDA medi-navi



Agenda

1. Background

2. Recent PMDA drug safety measures

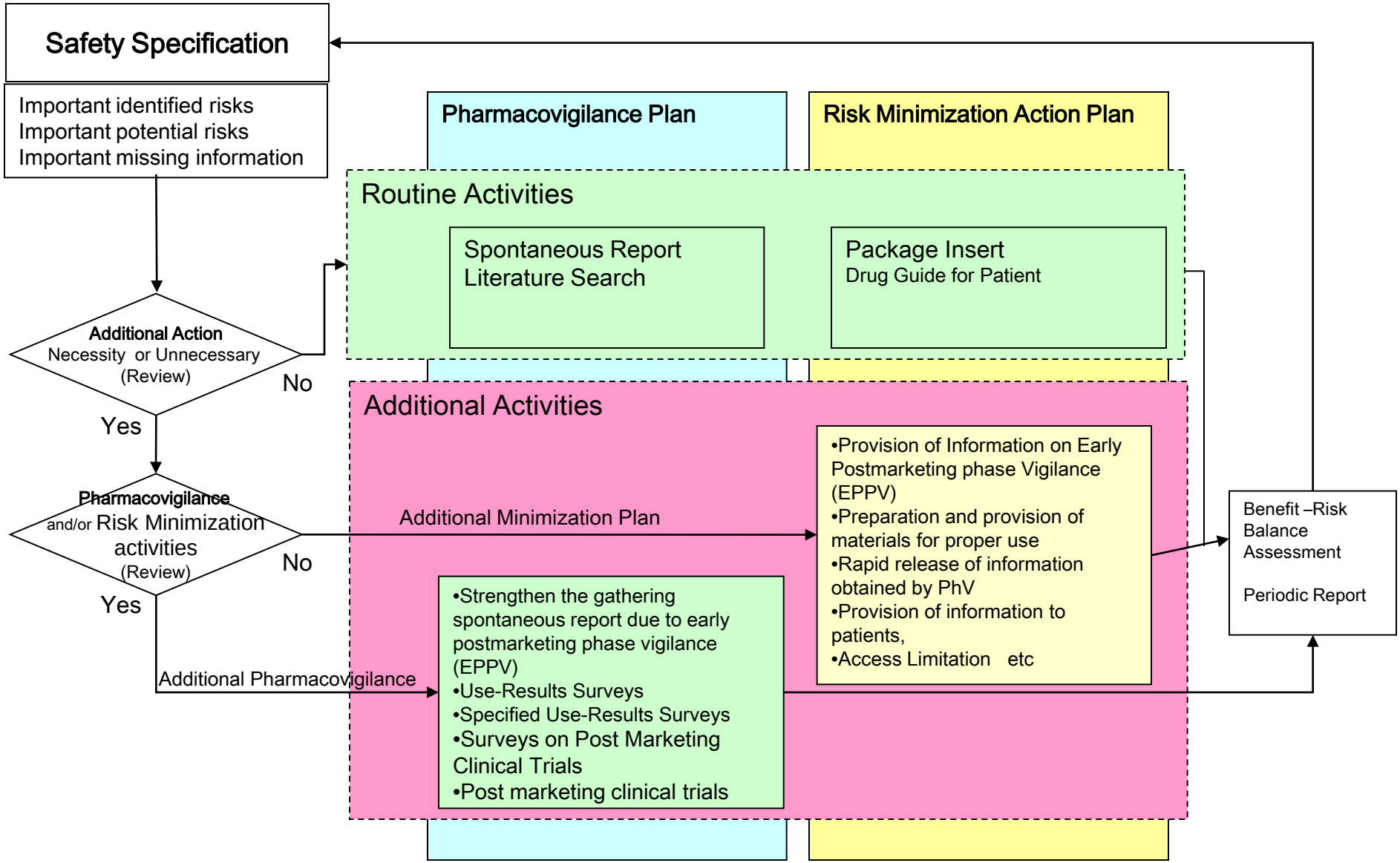
3. Safety measures in the future

Risk management plan (RMP) in Japan

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

- **Notification**
  - April 11, 2012: Guidance of RMP
  - April 26, 2012: Format of RMP
  - September 7, 2012: Q&A of RMP was published
  - Some points are under discussion by industries, MHLW and PMDA
  - Additional Q&A of RMP will be published in the first quarter of 2013
  - The guidance will be applicable after April 1, 2013

RMP Conceptual Diagram



PMDA English website (http://www.pmda.go.jp/)

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Home > Services of PMDA > Post-marketing Safety > Safety Information > Safety Information announced by MHLW

About PMDA

Services of PMDA

- Drug and Medical Device Reviews
  - Outline
  - Approved Products
    - List of Approved Products

Safety Information announced by MHLW

Date	Title
New September 11, 2012	Alert for the risk of severe hypocalcemia in patients who take RANMARK® (denosumab) (PDF)
April 11, 2012	Risk Management Plan Guidance (PDF)
February 14, 2012	PFSB/SD Notification 0214-9 "Call attention to the Precautions of anti-influenza virus drugs" (PDF)
August 12, 2011	Press Release: Warnings and Alerting: Severe haemorrhages in patients treated with an anticoagulant "Prazaxa capsules(dabigatran etexilate)" (PDF)
August 2, 2011	Risk Management Plan (RMP) Guidance (Draft) (PDF) (This draft guidance was issued to invite public comment by MHLW) http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495110028&Mode=0 (Japanese text ONLY)
June. 23, 2011	Safety Measures for diabetes medication "pioglitazone-containing products" (PDF) Annex (PDF)
March. 29, 2011	< Q and A > (PDF) Resuming vaccination with the pediatric pneumococcal conjugate vaccine and the Hib vaccine (Issued by the Tuberculosis and Infectious Disease Control Division, Health Service Bureau and Safety Division, Pharmaceutical and Food safety Bureau)

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

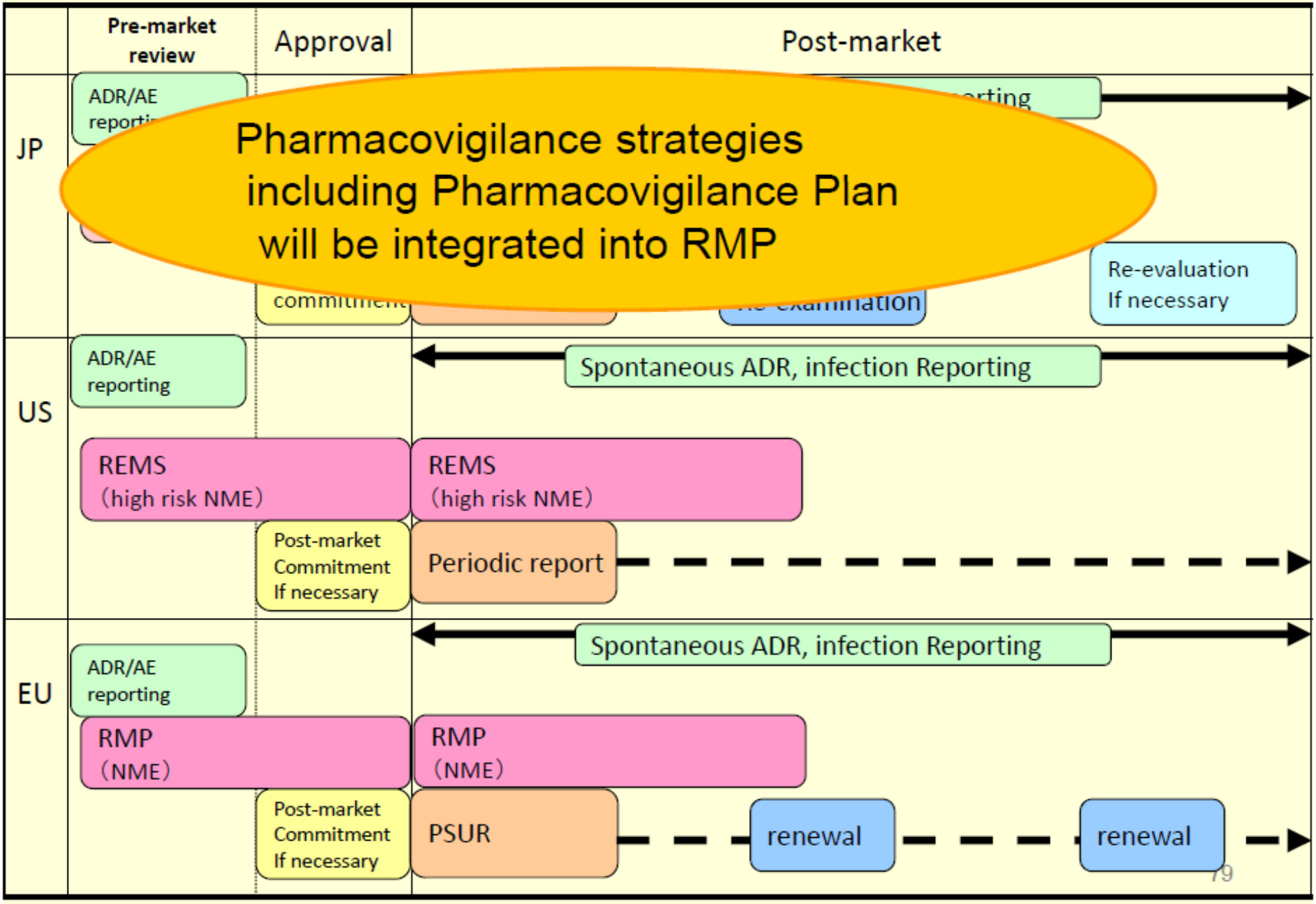
Contents of RMP

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 RMP in Japan

- 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

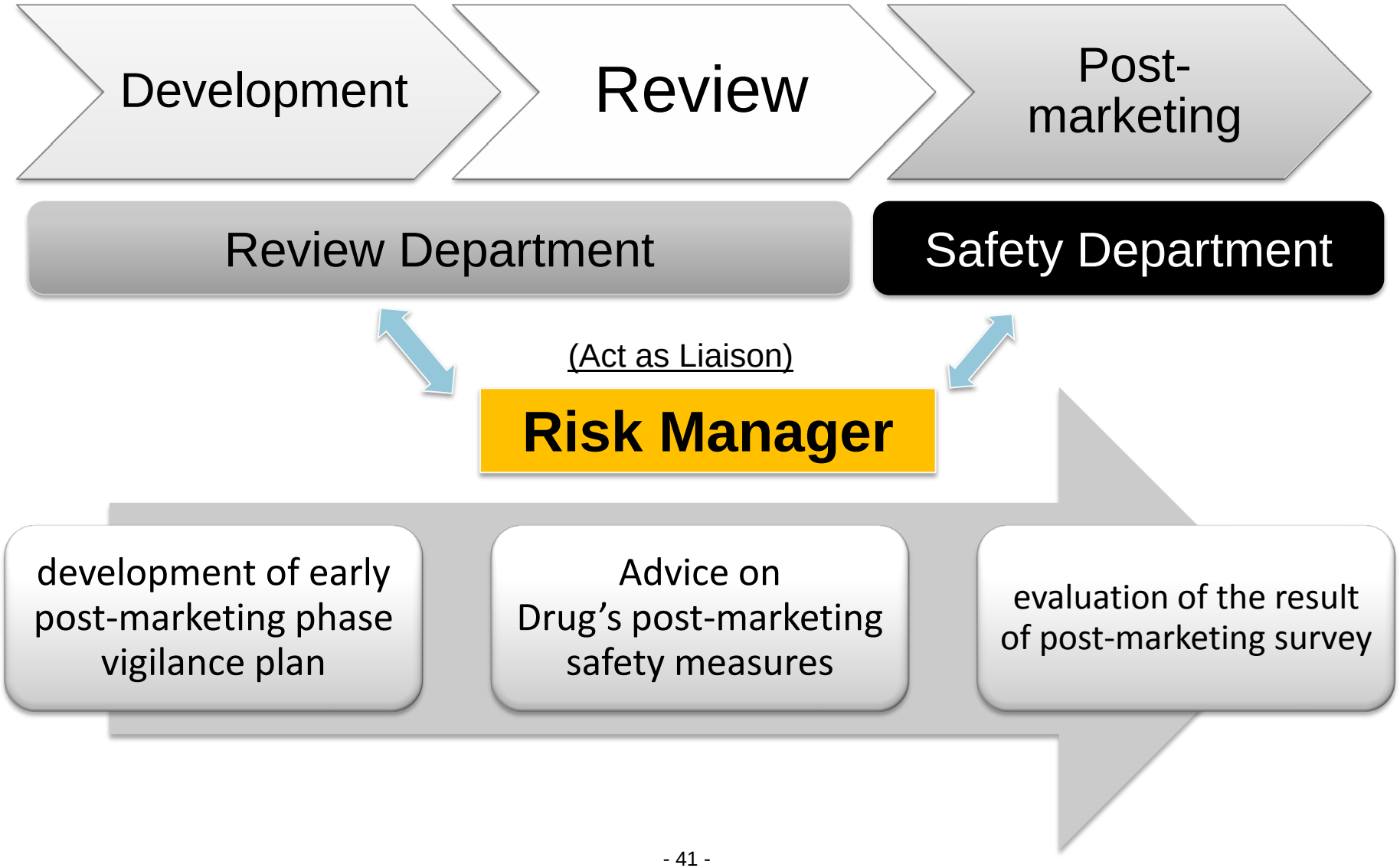
Phamacovigilance measures JP, US, EU



Risk Manager system

- 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**

Throughout Drug Life Cycle



MIHARI

Medical Information for Risk Assessment Initiative

This MIHARI's logo is made from crossed 4 arrows colored blue and green. Two blue arrows show two types of data sources (claim data and medical record data) and two green arrows show two types of analysis methods (pharmacopeidemiological analysis and data-mining analysis), respectively. These 4 arrows indicate that various kinds of data are analyzed from many directions in the MIHARI project.

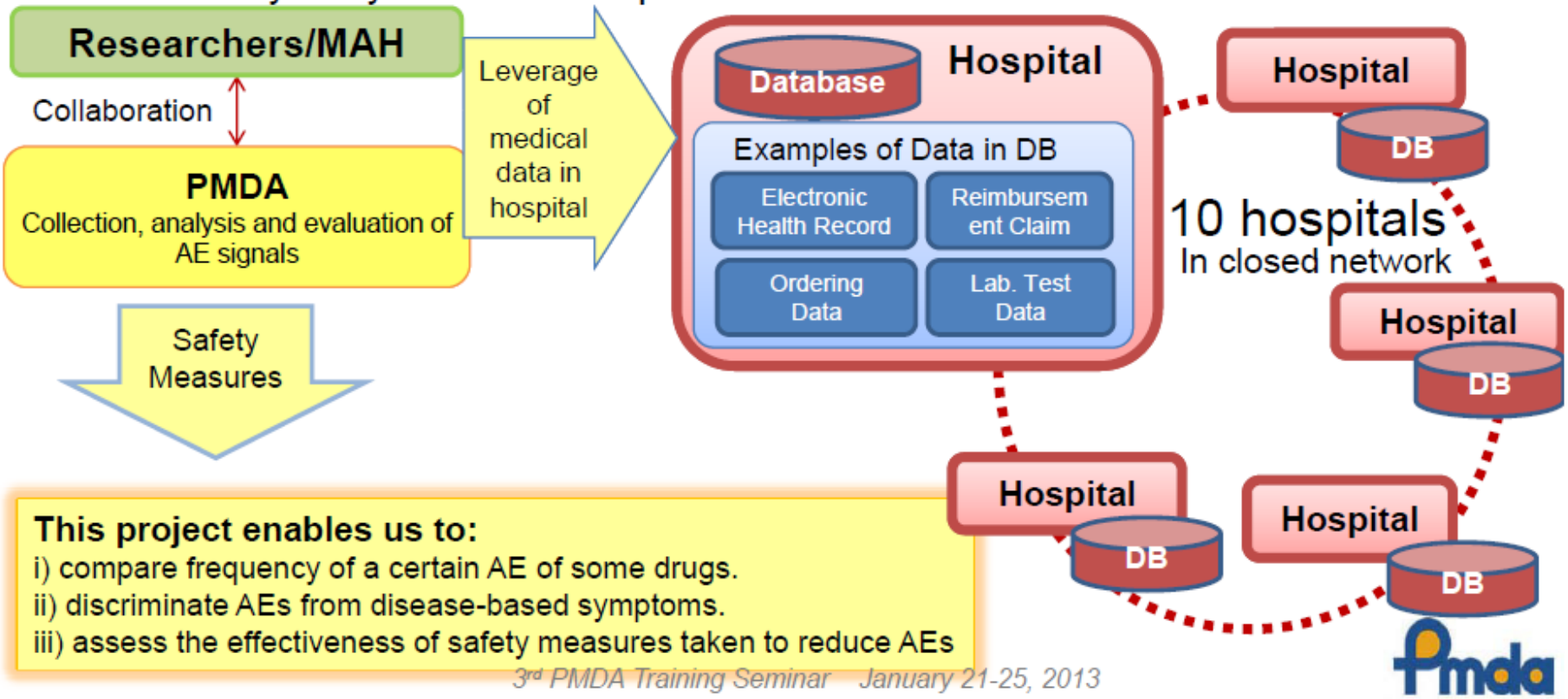
Utilization of Electronic Health Information for Post-Market Safety Measures

- Data/DB to be used
  - Electronic health records
  - Health insurance claim data
  - DPC
- Possible outcome/benefit
  - Comparison of AE incidence between new and existing drugs
  - Comparison of AE incidence between use and non-use of a drugs
  - Analysis of impact of safety measures

Development of EMR Network

(Budget: FY2011: approx. ¥370m*, FY2012: approx. ¥310m*)
*: Pharmaceutical industries burden the same amounts

- ■5 years MHLW/PMDA joint project (FY 2011 to FY 2015)
- ■Epidemiological approach with medical data from 10m patients allows us to take necessary safety measures. (ex. Adverse event signal detection)
- ■10 hospitals install DBs, one of which is under development in Hospital of Univ. of Tokyo.
- ■Data analysis system is developed and utilized in PMDA.



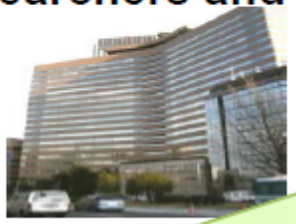
This project enables us to:
i) compare frequency of a certain AE of some drugs.
ii) discriminate AEs from disease-based symptoms.
iii) assess the effectiveness of safety measures taken to reduce AEs

EMR : Electronic Medical Record

Selected Collaborative Hospitals which install DBs

- Now first DB is under development in Hospital of Univ. of Tokyo
- Other 9 hospitals install DBs in FY 2012~2013

PMDA, researchers and MAH



Data utilization with 10 collaborative hospitals

7 hospitals

3 hospital groups

Tohoku Univ.

NTT hospital group

Tokushukai group

Kyushu Univ.

Saga Univ.

Kagawa Univ.

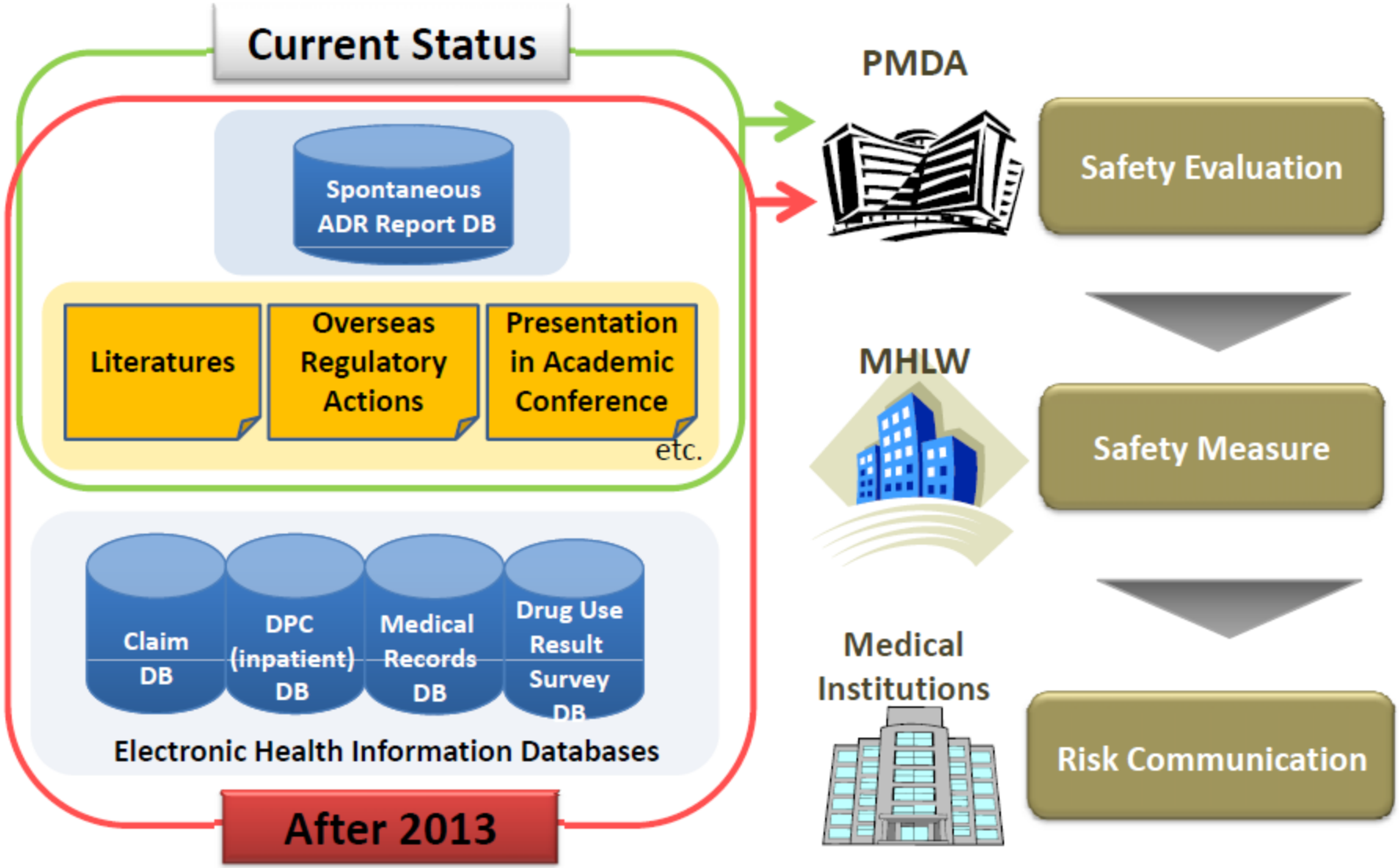
Univ. of Tokyo

Chiba Univ.

Hamamatsu Univ.

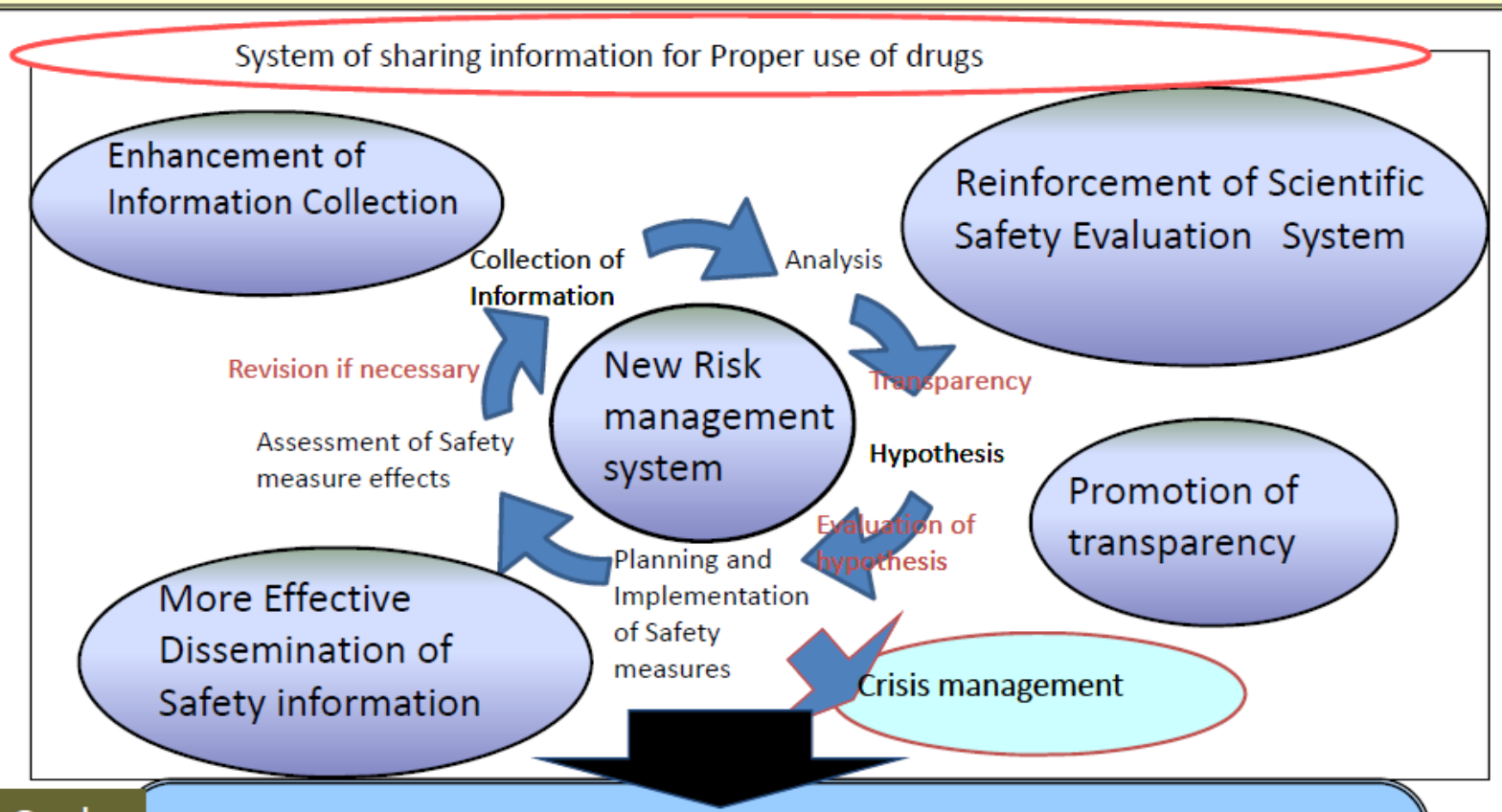
Kitasato Institute group

Goal of MIHARI project



What is our Goal?

PMDA/MHLW Policy to enhance safety measures



Goal

- Prevention of serious drug safety-related crisis from Japan
- Effective encouragement of proper drug use
- Ensuring completion of lifecycle of drugs
- Ensuring credibility to post-market safety management system.

Thank you for your attention.

http://www.info.pmda.go.jp/

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