



Safety Information (incl. vaccine) report and research in Japan

Current Update of Pharmacovigilance regulations

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Regulations from R&D to Post-approval

- New drug development hurdles continue to rise internationally, considering the current global pharmaceutical R&D situation:
 - Difficulties in exploring new drugs,
 - Soaring research and development costs, etc..
- It is a common global regulatory issue to secure early access and safety of patients in order to **maintain and improve public health continuously**,
- Accordingly, improving both **efficiency of innovative pharmaceuticals development and productivity** should be essential.



Benefit · Risk assessment and safety measures Throughout the pharmaceutical life cycle

- Regulation throughout the entire life cycle of pharmaceuticals, under which
 - **effective and sustainable post-approval benefit and risk assessment** will contribute to ensuring further safety of new pharmaceuticals and to enabling early patient access.
 - it is desirable to build **a risk management system** including promotion of optimum use, isn't it?



Issues concerning the balance between
cost of achieving patient's early access and their safety
and
the efficiency / sustainability of “R&D to post-marketing
“ activities of companies

- Improve efficiency R&D in terms of product life cycle by improving post-approval benefits and risk assessment
- Improve optimization and efficiency of post-marketing studies utilizing real world data
- Enhance provision of safety information



Pharmaceuticals and Medical Devices Act (PMD Act)

Revised and enacted on 25 November 2014

Article 1. (Purpose)

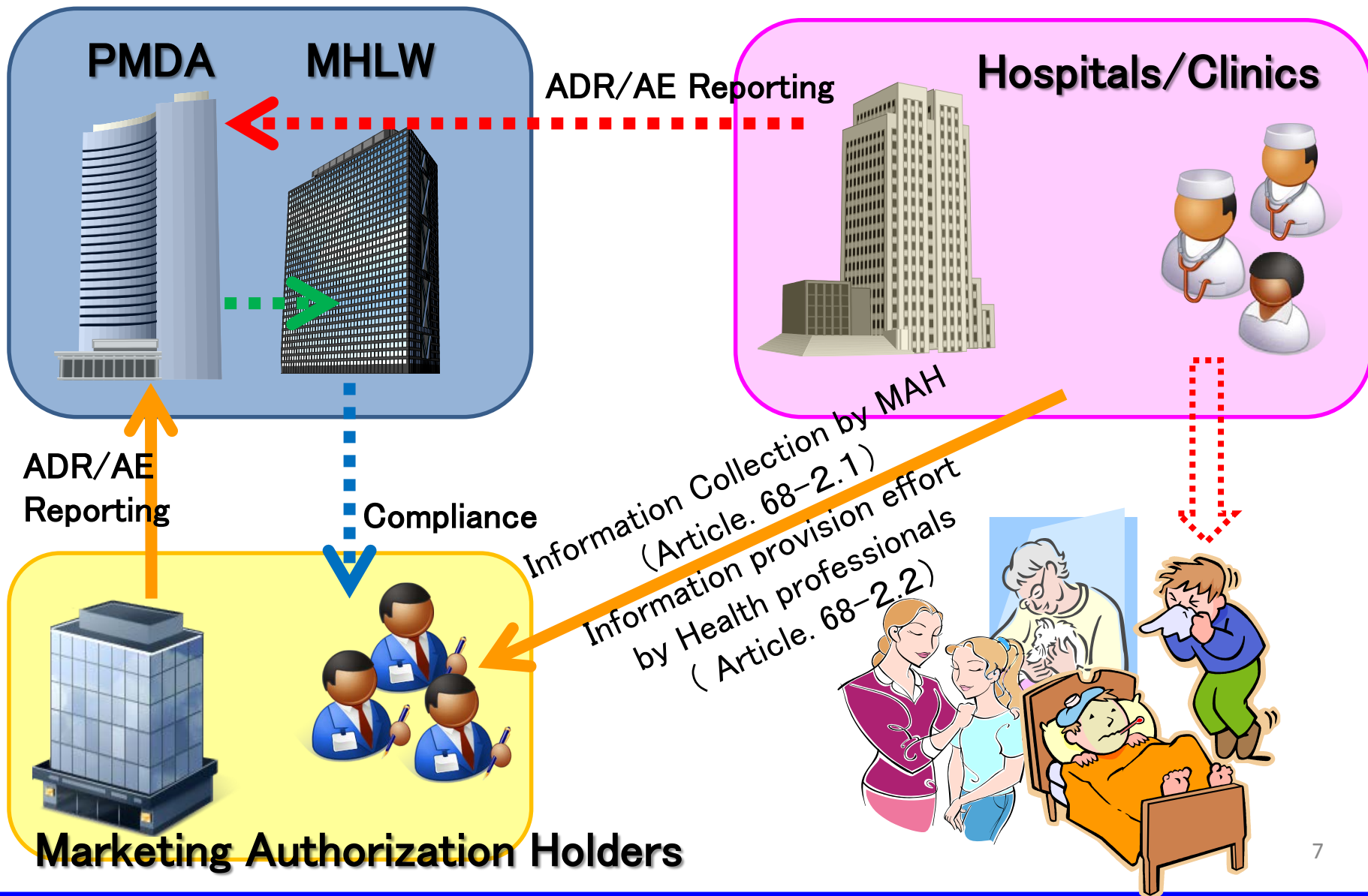
The purpose of this Act is to ensure the quality, efficacy and safety of products such as pharmaceuticals, quasi-drugs, cosmetics, medical devices and regenerative medical products (hereinafter referred to as "pharmaceuticals, etc.") and to take necessary regulatory measures to prevent occurrence and expansion of public health hazards associated with their use. In addition, it is purposed to improve public health by taking measures concerning the regulation of designated drugs, and by promoting the research and development of pharmaceuticals, medical devices, regenerative medical products, etc., which are of particularly high necessity for medical purposes.



RISK monitoring ICT Strategy

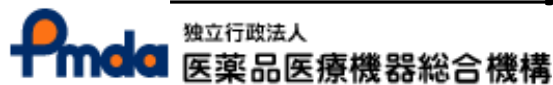


Safety Information Collection

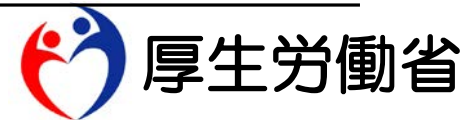




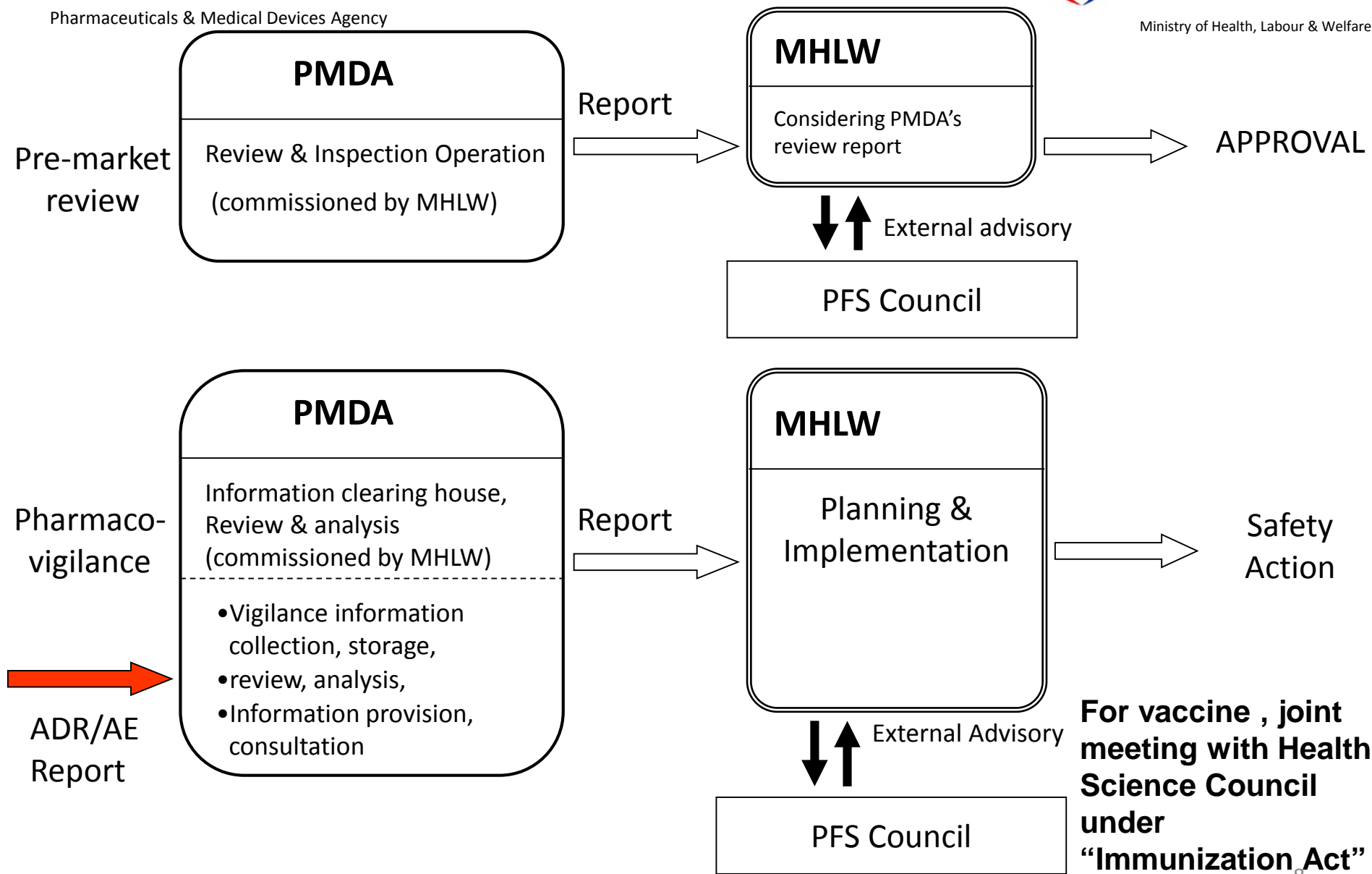
Pre-market & post-market review scheme of MHLW & PMDA



Pharmaceuticals & Medical Devices Agency

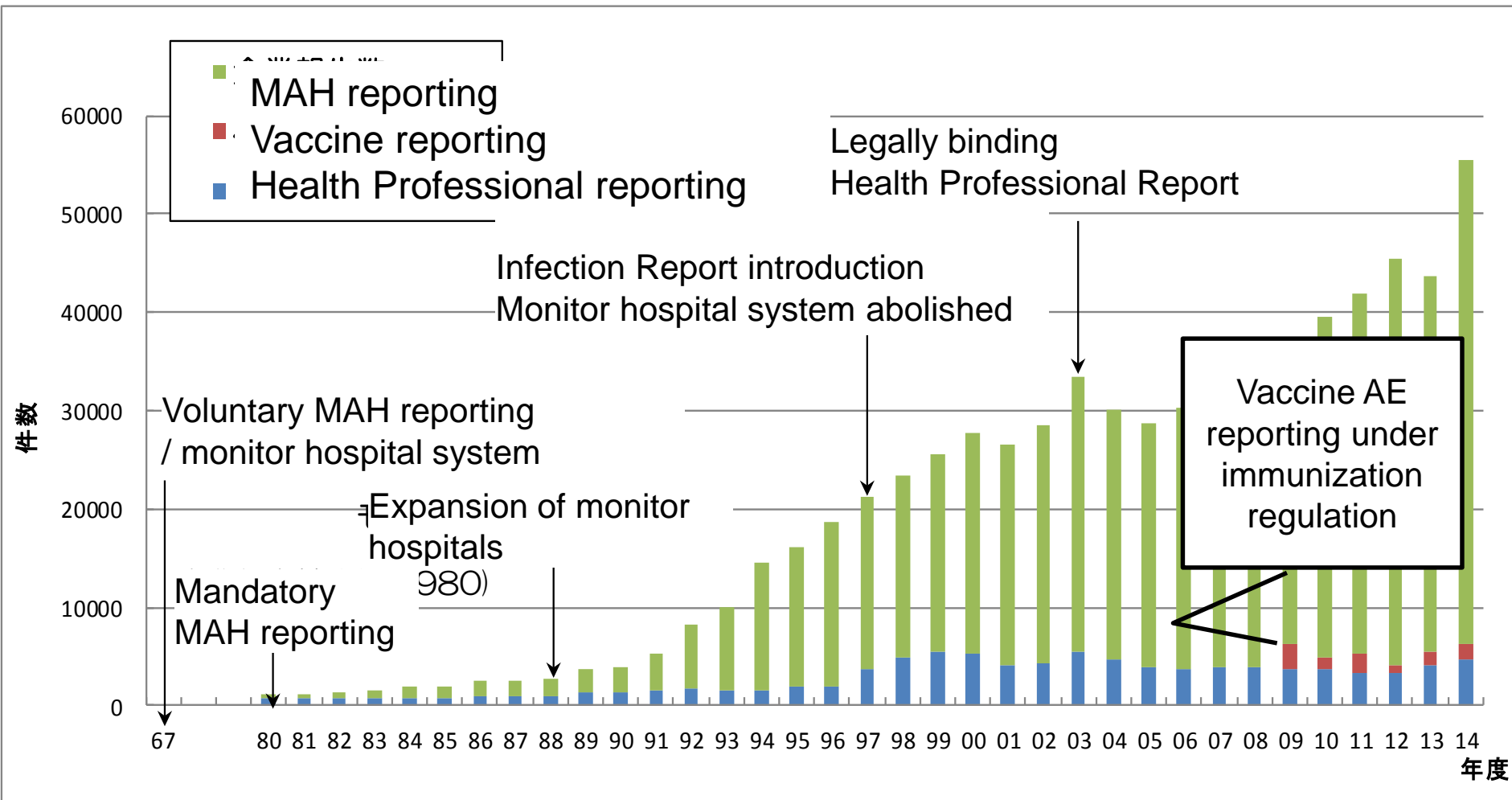


Ministry of Health, Labour & Welfare

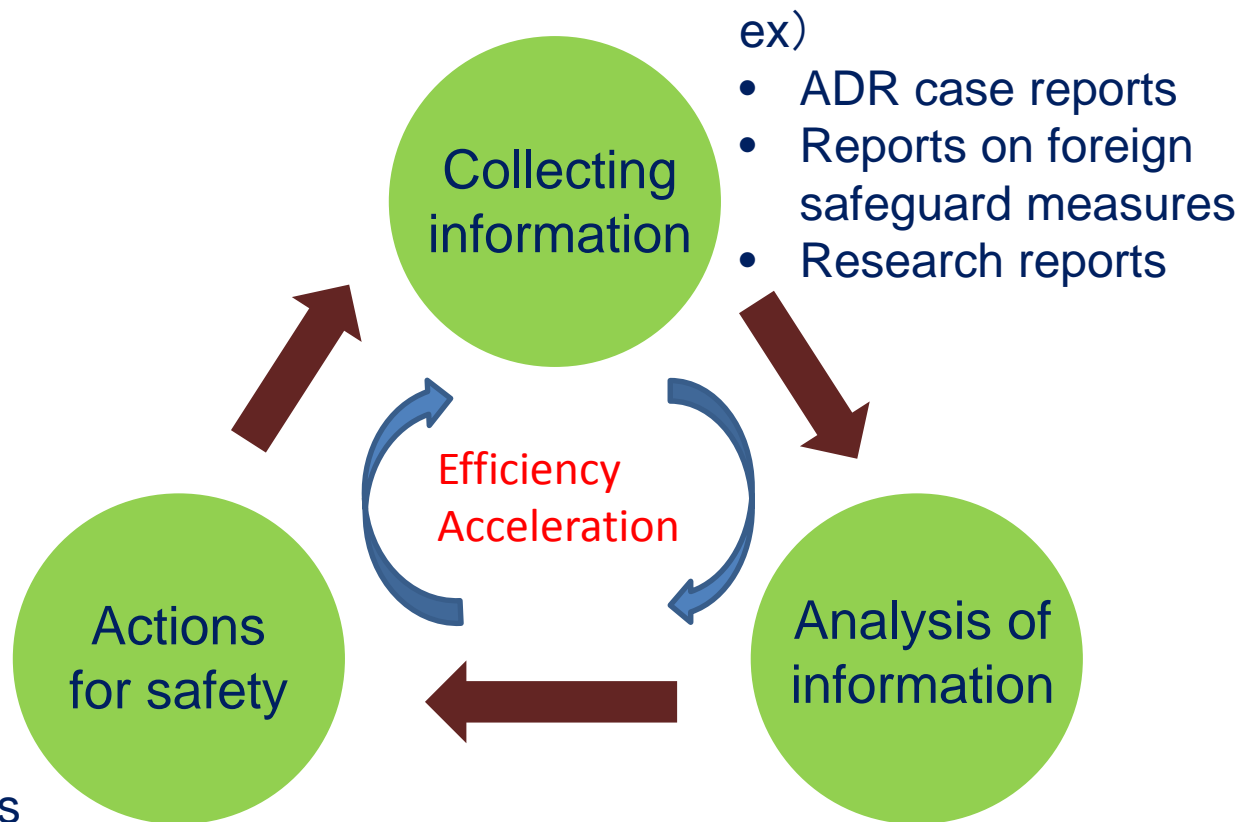




Spontaneous ADR and Infection Reports



Basic concept of pharmacovigilance measures



ex)

- ADR case reports
- Reports on foreign safeguard measures
- Research reports

ex)

- Recall of products
- Release of “Yellow Letter” or “Blue Letter”
- Revision of precautions of package inserts
- Distribution of notification documents

Global concern on safety of drugs

Limitation of spontaneous ADR reporting

International harmonization

- Implementation of E2E

New technologies for drug safety evaluation (ICT)

- Data mining
- Pharmacoepidemiology using electronic medical Records
Claim Database (ex. NDB, JMDC, MDV, etc.),
DRG(DPC) database, etc.)
HIS (hospital information system of individual hospital)



**NEED TO MODERNIZE RISK MANAGEMENT PROGRAM :
USE OF ELECTRONIC MEDICAL DATABASE**



Recent trend of medical ICT in Japan

- Japan Revitalisation Strategy 2016
Chapter2 (2) iii) BD utilization in promoting innovation, the medical field and developing policy
“Collaboration among MID-NET and pediatric DB, etc. and the expansion of private utilization”
- Minister’s round-table conference for medical ICT
- Personal Information Protection Law
Prior agreement of utilization of personal medical record
- Establishment of the organization to collect medical information and provide the processed data

Electronic Medical Information Database Network(MID-NET)

- MHLW/PMDA joint project (FY2011 to FY2017)
- Epidemiological approach with medical data from target 10,000,000 patients allows us to take necessary safety measures.(ex. Adverse event signal detection)
- 23 hospitals install DBs.
- Data analysis system is developed and utilized in PMDA.

Researchers / MAH

Collaboration

PMDA

Collection, analysis and evaluation of AE signals

Safety Measures

Leverage of medical data in hospital

Currently 4,000,000 patients included

Database

Hospital

Examples of Data in DB

Electronic Health Record

Reimbursement Claim

Ordering Data

Lab. Test Data

Hospital

DB

23 hospitals in closed network

Hospital

DB

Hospital

DB

Hospital

DB

Scattered relational data network keeping personal information within each hospital

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.

In the Japanese population

Plan for full-scale utilization of MID-NET

FY2011-2014

FY 2015

FY 2016

FY2017

FY2018

Database developed

Data quality check and validation

Analysis system developed

Verification of operation of the system and system upgrading

- Trial utilization of MID-NET by PMDA / MHLW and 23 collaborating hospitals
- Validating disease outcome definitions
 - Conducting pilot studies using MID-NET

Establishing rules and process for utilization of MID-NET by third parties such as academic researchers and industries

Full-scale utilization



Example of Pilot Use of MID-NET

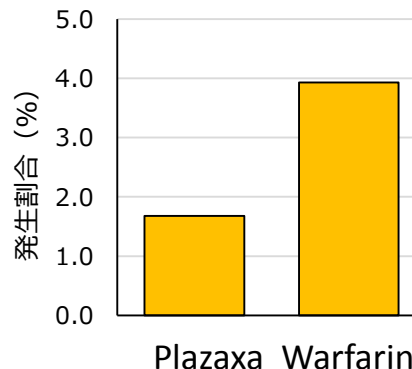
< Risk of bleeding associated with Plazaxa >

Real time safety monitoring is available for drug safety evaluation

Comparison of gastrointestinal bleeding risk between Warfarin and Plazaxa

協力医療機関A (2015年4月-2016年7月)

	Prescription	Patient No.	Bleeding	
			n	rate
Plazaxa	795	119	2	1.7%
Warfarin	10,739	891	35	3.9%



The risk of bleeding by dabigatran is not higher than that of warfarin in Japan

Stratification by Creatinine value at the first administration

協力医療機関A (2015年4月-2016年7月)

	Patient No.	Normal -0.9mg/dL		Mild 0.9-1.35mg/dL		Moderate 1.35-2.7mg/dL		Severe 2.7-mg/dL		NT	
		n	rate	n	rate	n	rate	n	rate	n	rate
		Plazaxa	119	60	50.4%	28	23.5%	5	4.2%	0	0%
Warfarin	891	326	36.6%	239	26.8%	96	10.8%	36	4.0%	194	21.8%

Plazaxa(dabigatran) is carefully prescribed for patients with impaired renal function.

Planned pilot studies of MID-NET in FY2016

Prescription survey, Risk & Benefit balance evaluation

Study Topic

- 1 Actual situation of codeine prescriptions in pediatric patients
- 2 Risks of cardiovascular events associated with type II anti-diabetic drugs (risk comparisons between different classes)
- 3 Changes on laboratory test results such as AST, BUN, CK, albumin and leukocytes after first administration of drugs which was newly approved in Japan.
- 4 Hyperglycemia associated with atypical antipsychotic drugs
- 5 Impacts of the safety measure for serious hypocalcemia induced by denosumab (anticancer drug)
- 6 Anaphylaxis associated with injectable antibacterial drugs
- 7 Actual situation of prescription drugs in pregnant women



Measures to use ICTs for risk management

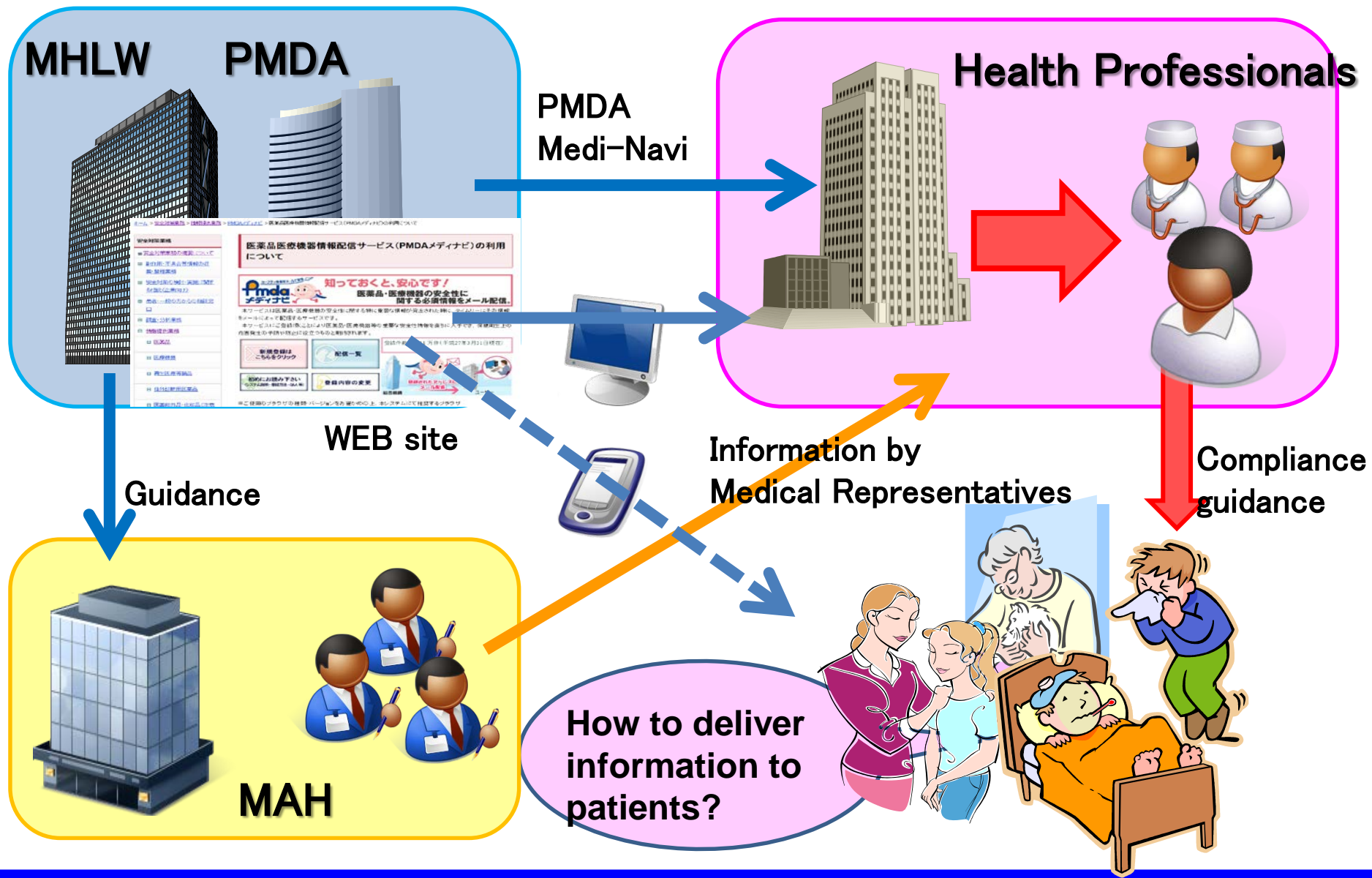
- GPSP(Good Postmarketing Surveillance Practice) regulation revision and the clinical data reliability standard guidance revision (planned in 2017) to accommodate electronic medical records(EMRs) for securing data integrity
- For MID-NET full scale utilization (target 2018) :
 - Institutional Review Committee and its operational rule setting for MID-NET
 - User fee setting for MID-NET



RISK communications



Safety Communication



Communications through PMDA

The screenshot shows the PMDA website interface. At the top, it says 'Pmda Pharmaceuticals and Medical Devices Agency, Japan'. There are navigation links for 'Contact', 'Access', 'Links', 'Site Map', and 'Search'. A main menu includes 'Safety Information', 'Approved Products', 'Regulatory Information', 'Pharmacopoeia / Medical Device Standards', and 'PMDA Training Seminar'. A 'What's New' section lists recent updates, including 'MHLW Pharmaceuticals and Medical Devices Safety Information noted issue of 271_2010' and 'PMDA Medical Safety Information'. A 'Services of PMDA' section lists 'Drug and Medical Device Reviews', 'Post-marketing Safety', and 'Relief Services for Adverse Health Effects'. There is also a 'News and Reports' section with links to 'Past Symposia', 'Past Presentations', and 'Publications'.

Pharmaceuticals and Medical Devices Safety Information

No. 272 September 2010

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) website (<http://www.pmda.go.jp/english/index.html>) and on the MHLW website (<http://www.mhlw.go.jp/>, Japanese only).

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Version of PMDSI is intended to be a reference material to provide convenience for users. In the event of a discrepancy between the Japanese original and this English translation, the former shall prevail. The PMDA is not liable for any consequence resulting from use of this English version.

Issued monthly basis

The screenshot shows a document titled 'PMDA Request for Proper Use of Drugs' for 'salazosulfapyridine'. It includes a table of contents and a detailed section on 'Compliance with conduct of laboratory tests before and after administration of salazosulfapyridine'. The text describes the use of laboratory tests to monitor for adverse effects like blood disorders and hepatic dysfunction. It mentions that WBC counts should be performed before and after treatment, and that patients should be monitored for symptoms like joint pain and fever. A cartoon character of a doctor is shown at the bottom right, with a speech bubble saying 'Laboratory tests are important! If left untreated, it can lead to serious complications!'

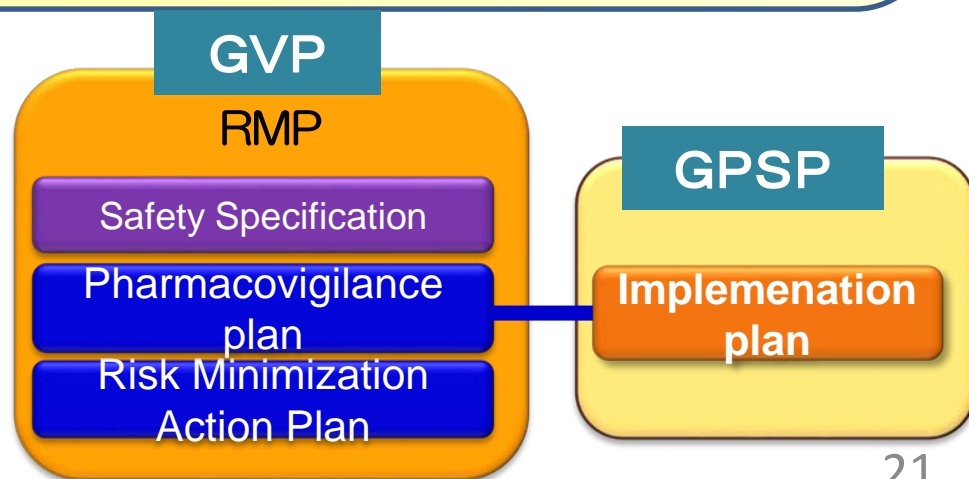
Risk Management Plan

- Risk mitigation and minimization of pharmaceuticals
 - **Safety Specification** : safety concerns based on available findings
 - **Pharmacovigilance Plan** : post-marketing reporting, study, survey
 - **Risk Minimization Action Plan** : Measures to minimize risk are to be addressed in “Risk Management Plan” (RMP) so as to carry out constant risk management throughout R&D and post-approval phases and to improve post-approval safety.

- RMP guideline
 - NMEs and biologics → 2012 April
 - Generic Drugs → 2013 April NDA implementation
 - 2014 August ANDA implementation

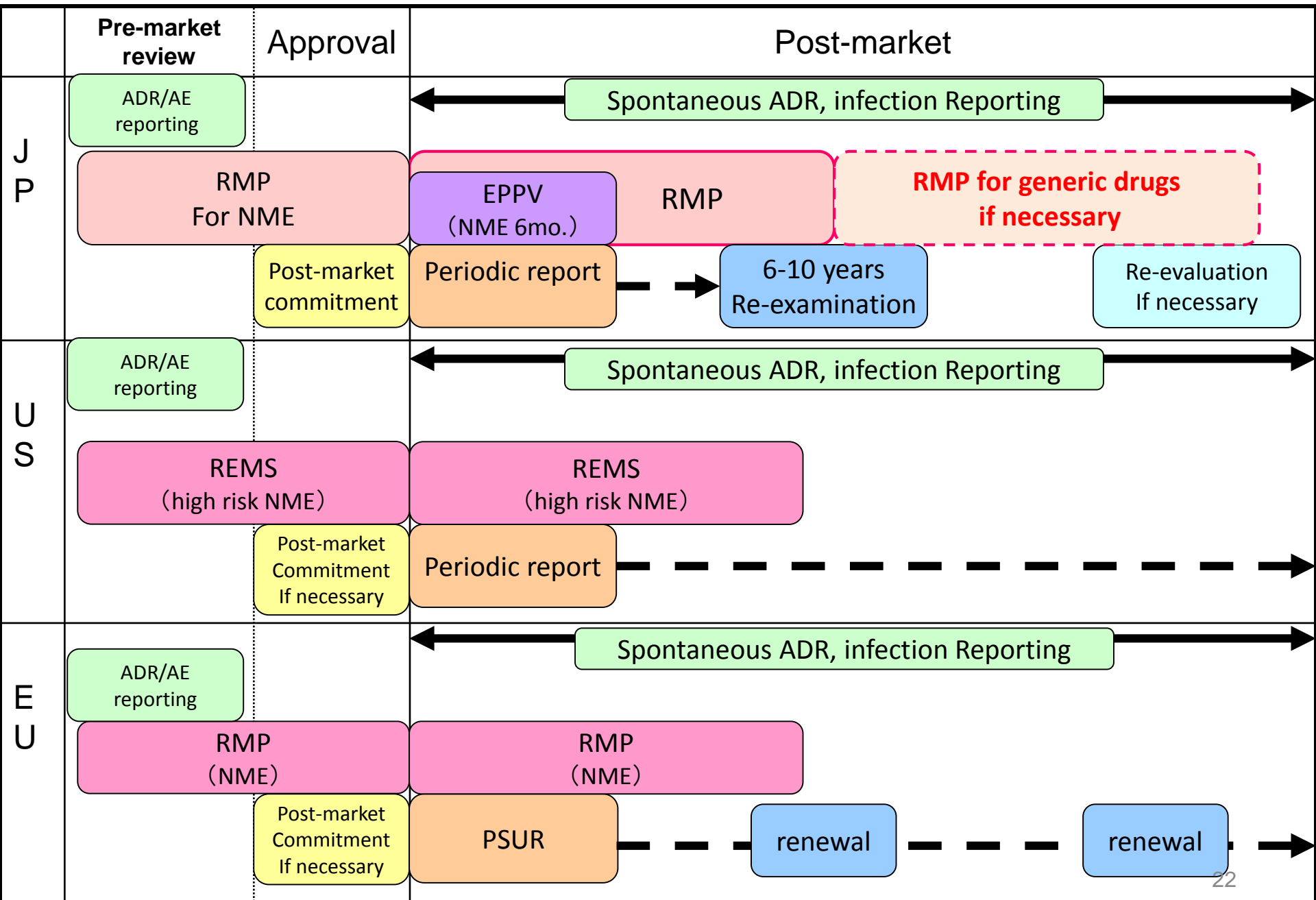


- GVP • GPSP Ordinance was revised (11 March 2013)
 - RMP became a part of GVP operations (RMP is requested as an approval condition)
 - **Implemented in October 2014**





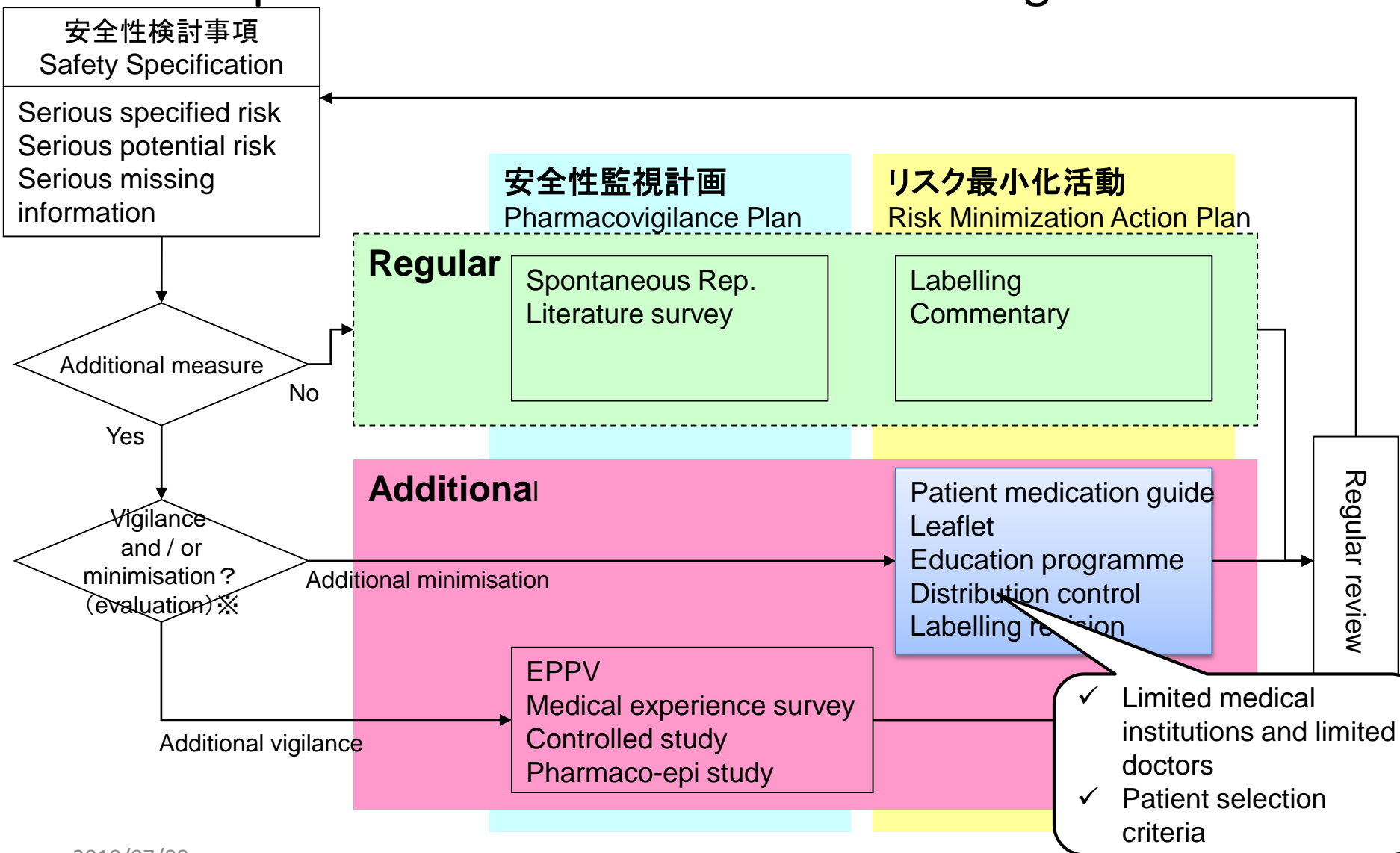
Post-approval Risk management measures JP, US, EU





Concept of structured RMP

implementation in line with ICH-E2E guideline

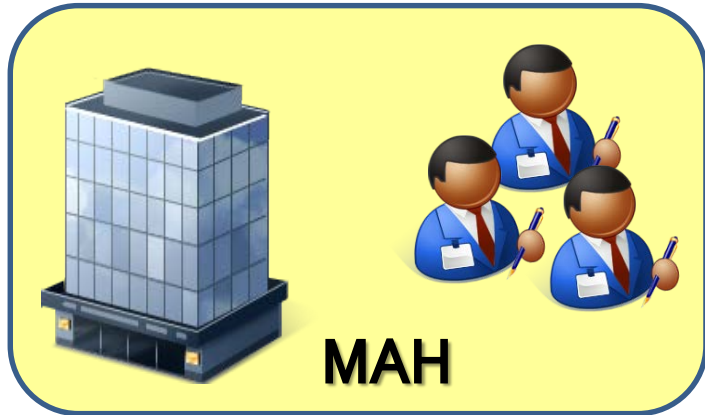
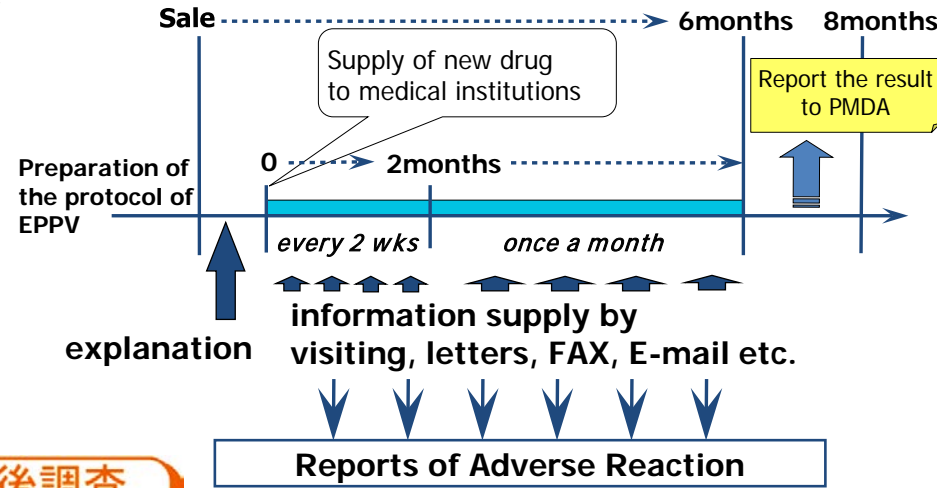


EPPV as a risk management tool

New pharmaceuticals are subject to **Early Post-marketing phase Vigilance (EPPV) for 6 months after launch**

MR's frequent visit to hospitals

- Provision of precaution information to hospitals
- Reminding hospitals to report ADRs



Visit for information provision

- Emergent safety information (Yellow letter)
- Safety alert (Blue letter)
- Labeling precaution and its revision



Visit for information collection (request survey and collect CRF)

- ADR report detail
- Post-marketing studies

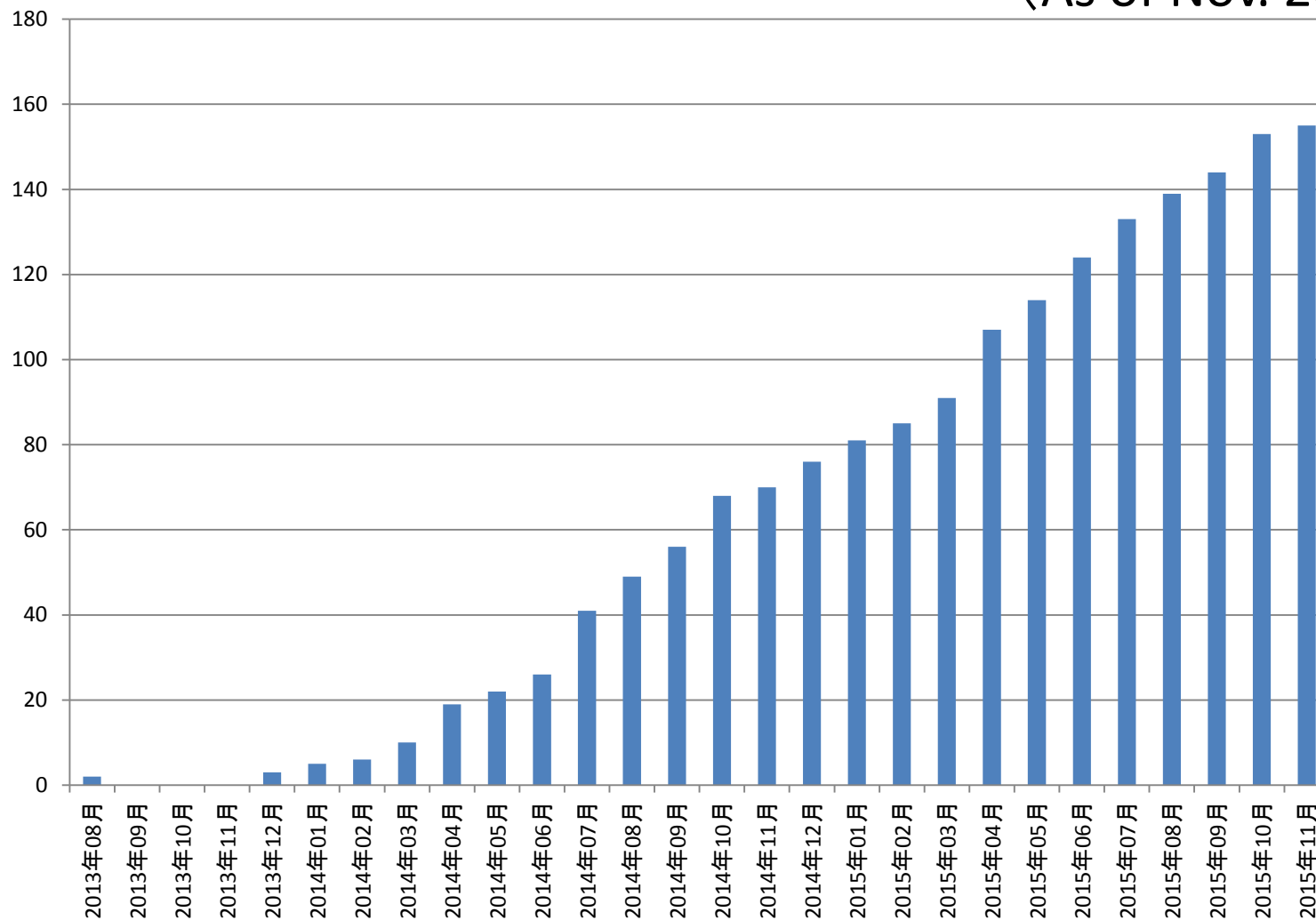




RMP status is updated and published by PMDA website

Number of NMEs

(As of Nov. 2015)





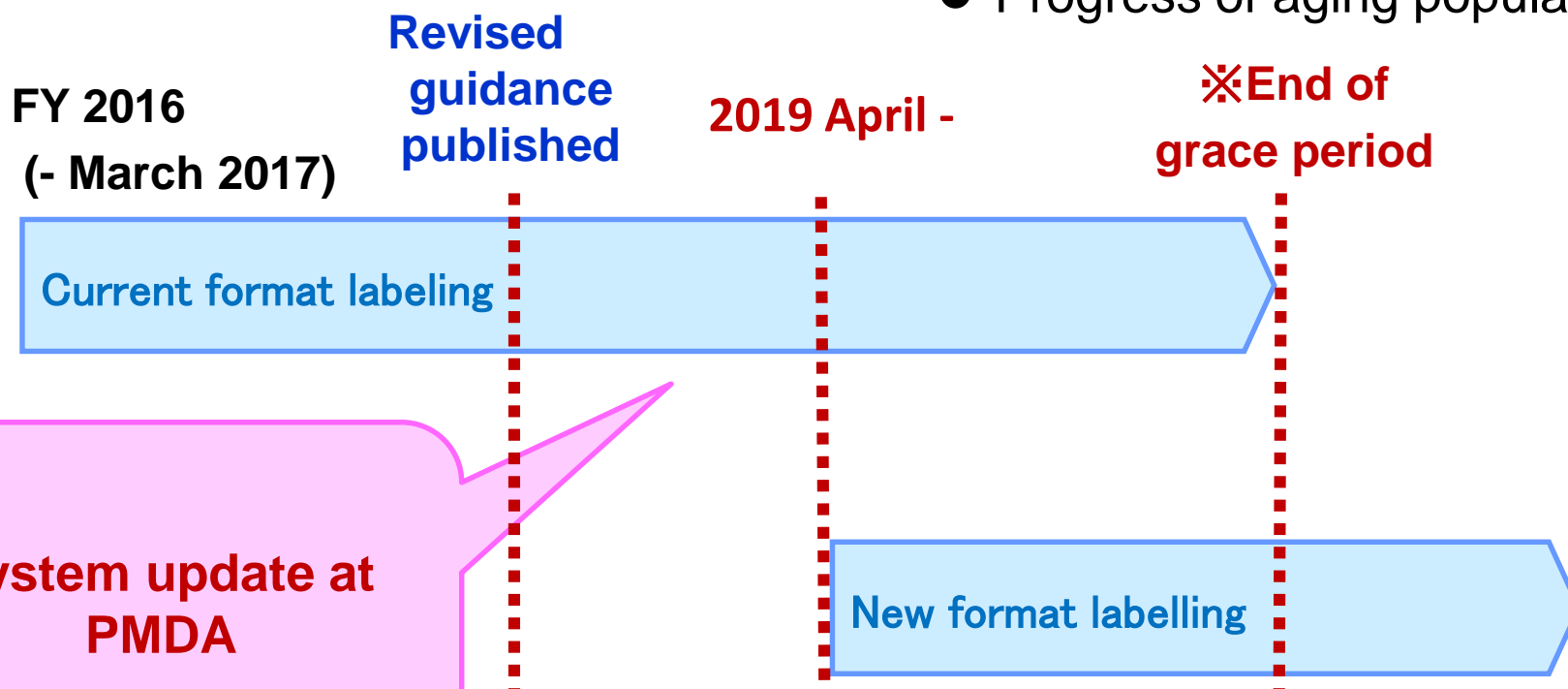
Labeling Format Guidance Revision

Public consultation

- From : 31 May 2016
- To : 15 July 2016 (comment closed)

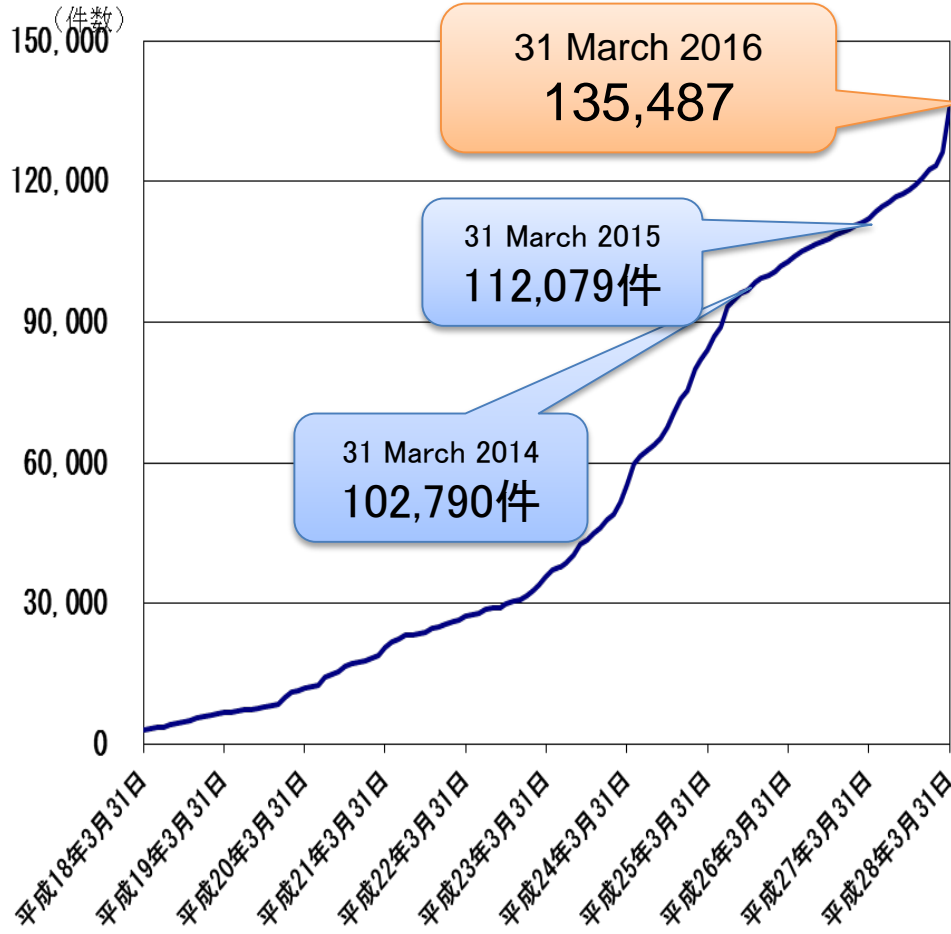
The current guidance was published in 1997. Since then :

- Progress of information technology
- Progress of medicine
- Progress of aging population

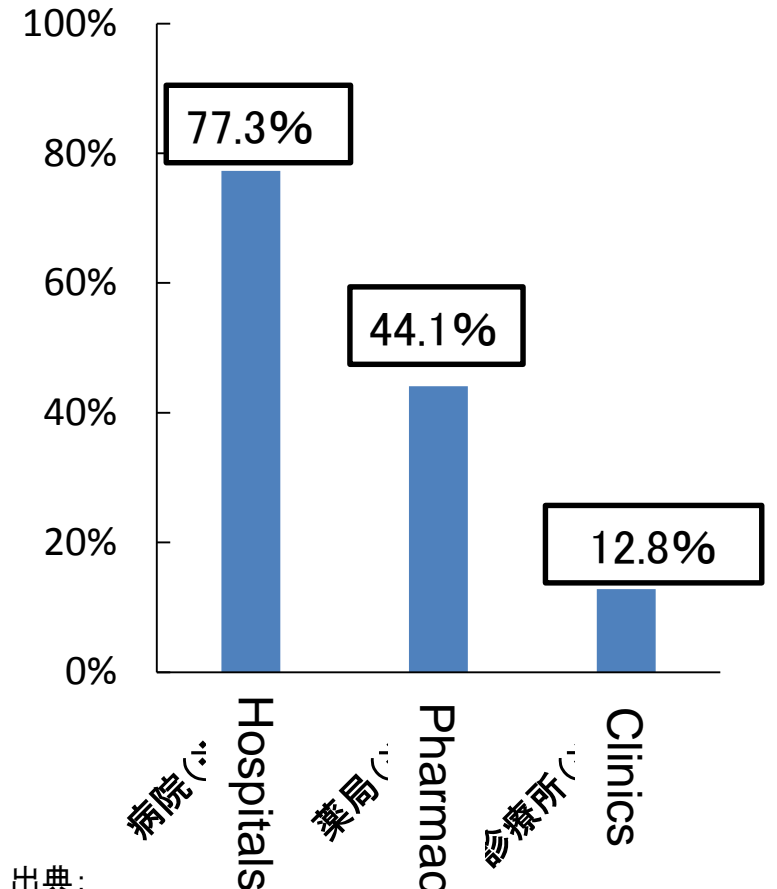


Registration of PMDA Medi-Navi (direct e-mailing list service to health professionals)

Registrants



Organizations of registrants



出典:

(※1) 平成26年度PMDA医薬活用状況に関する調査

(※2) 平成27年度同調査

性情事

伝達

Encourage and promote registrations from clinics in FY 2016



Challenges in summary (1)

- **Progress in Safety Monitoring Network**
 - Shifting from utilization survey **to real world data** study
 - Quantitative and qualitative improvement of **spontaneous reporting system including generics from health professionals**
 - **Effective collaboration** with various information sources (**academic society**, CIN, patient s)
 - Make full use of the useful **clinical experience of pediatric - pregnancy** administration for appropriate use (budgetary project)



Challenges in summary (2)

- **Improvement of quickness and convenience of information utilization and outreach**
 - Promote and penetrate the use of **PMDA Med-Navi**
 - Penetrate **RMP and optimize the use** of new drugs, while enhancing risk minimization tool and **cooperating with medical professionals, etc.**
 - Improve **risk communication** with health professionals and **patients** (provision of contents aimed at various level of users , incl. **labelling format revision**)
- **International Collaboration with foreign regulatory agencies**
 - Enhance exchange information **with Asian** and Western agencies
 - Enhance information provision in English for foreign users



Thank you for your attention
謝謝您的關注

Better today,
better tomorrow,
safer use of pharmaceuticals
for peace of mind of patients

