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

Current Update of Pharmacovigilance regulations

7 December 2016

厚生労働省 医薬・生活衛生局
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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)

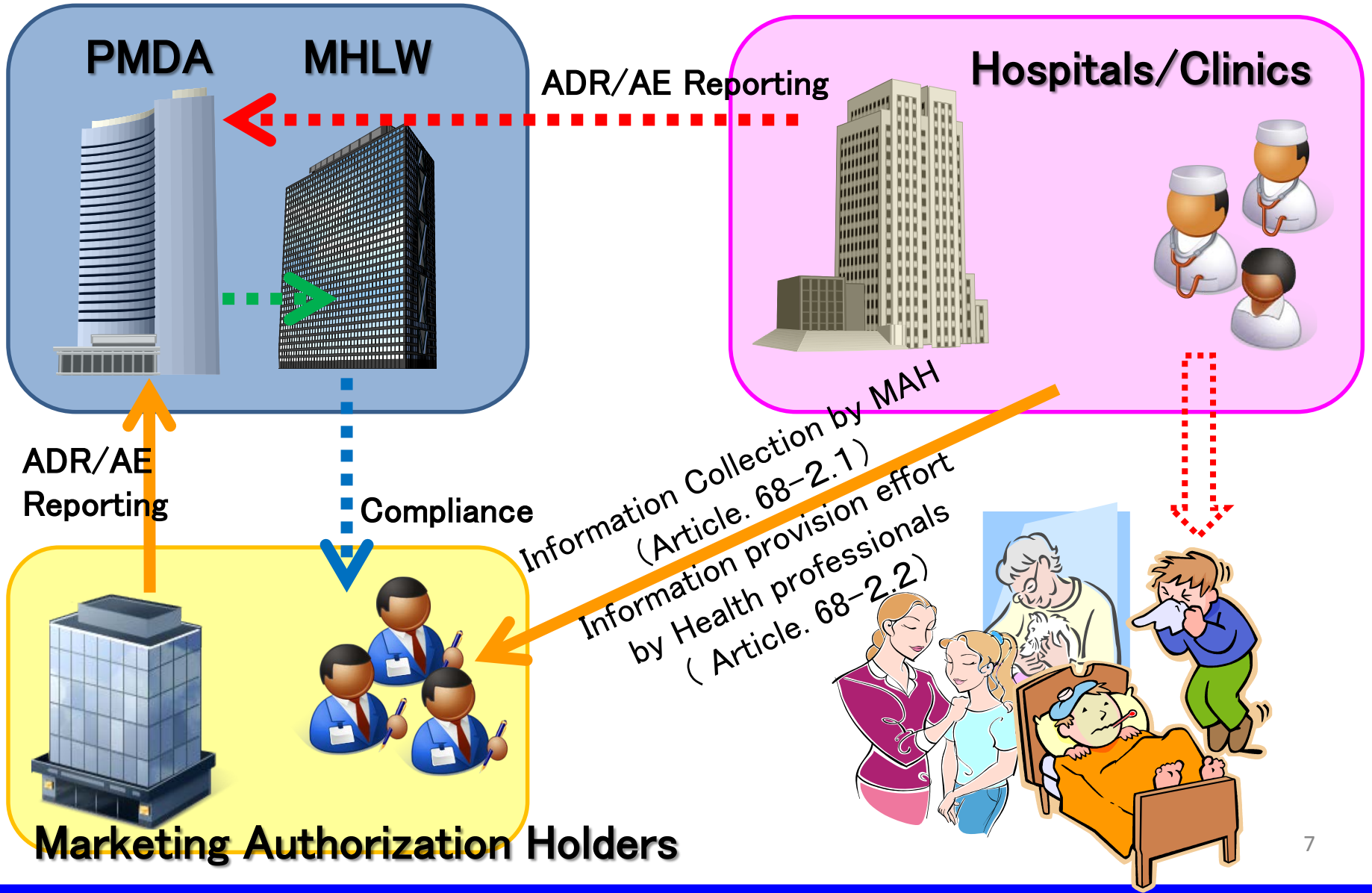
Revised and enacted on 25 November 2014

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

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

厚生労働省
Ministry of Health, Labour & Welfare

Pre-market review

PMDA

Review & Inspection Operation

(commissioned by MHLW)

Report

MHLW

Considering PMDA's review report

APPROVAL

External advisory

PFS Council

Pharmaco-vigilance

PMDA

Information clearing house, Review & analysis (commissioned by MHLW)

- Vigilance information collection, storage,
- review, analysis,
- Information provision, consultation

ADR/AE Report

Report

MHLW

Planning & Implementation

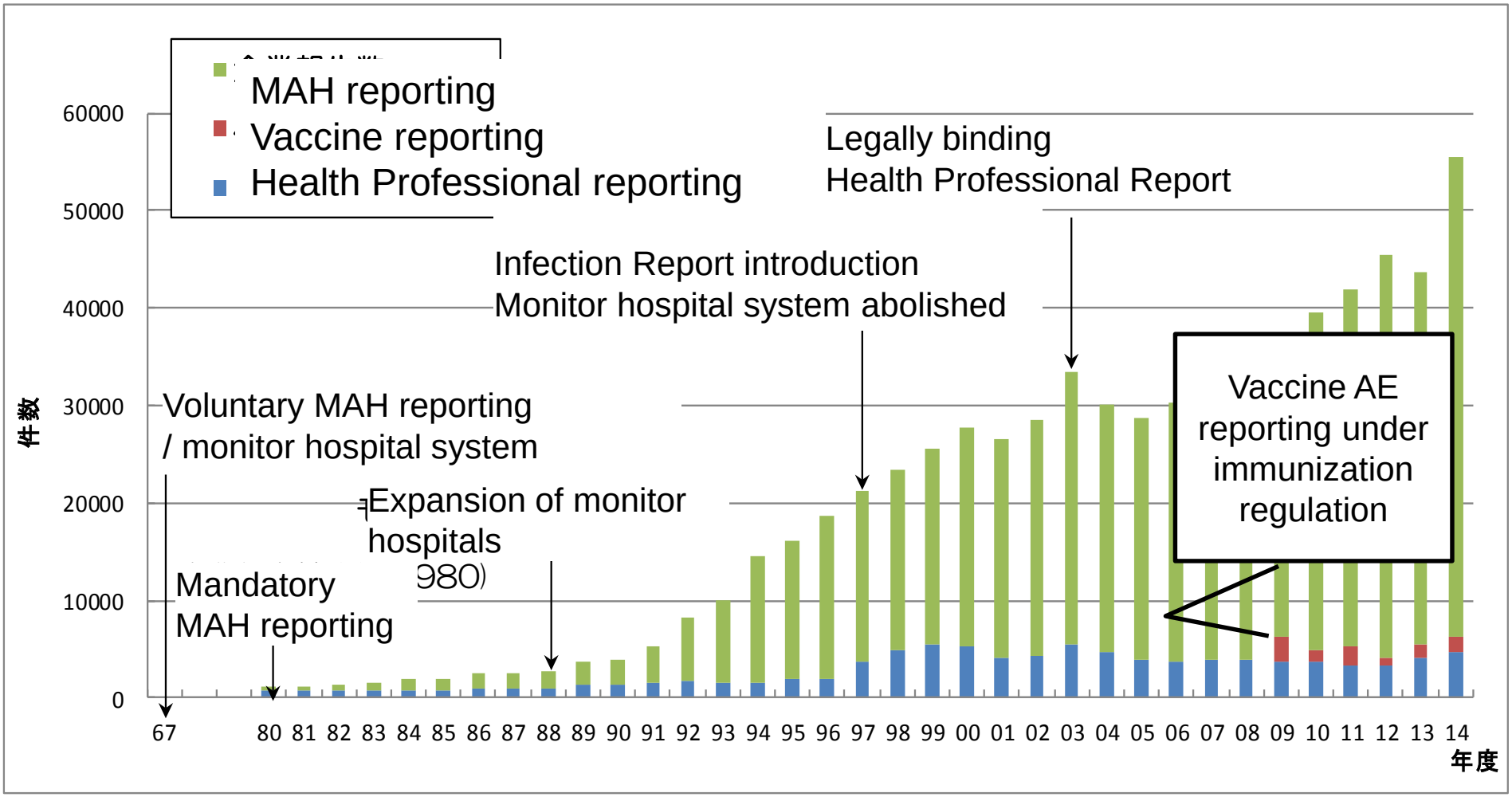
Safety Action

External Advisory

PFS Council

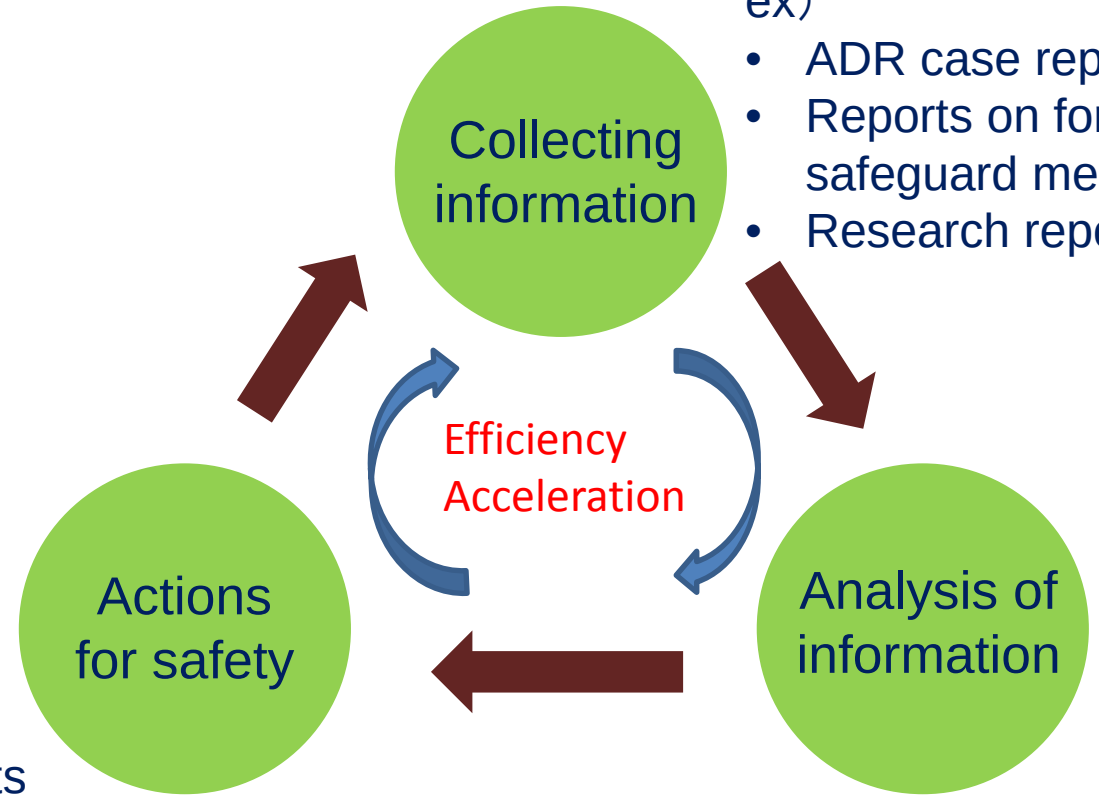
For vaccine , joint meeting with Health Science Council under "Immunization Act"

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

Current environment of drug development and drug safety

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”

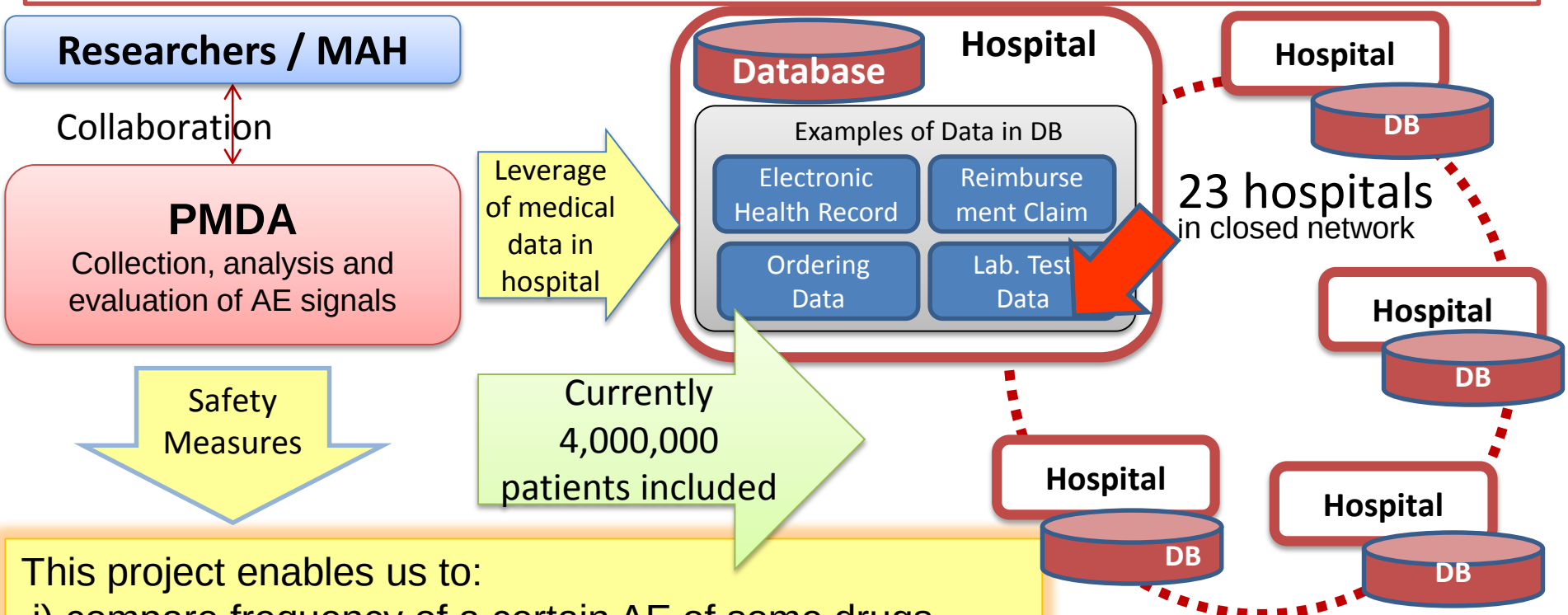
- Minister’s round-table conference for medical ICT
- Personal Information Protection Law

  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.



This project enables us to:

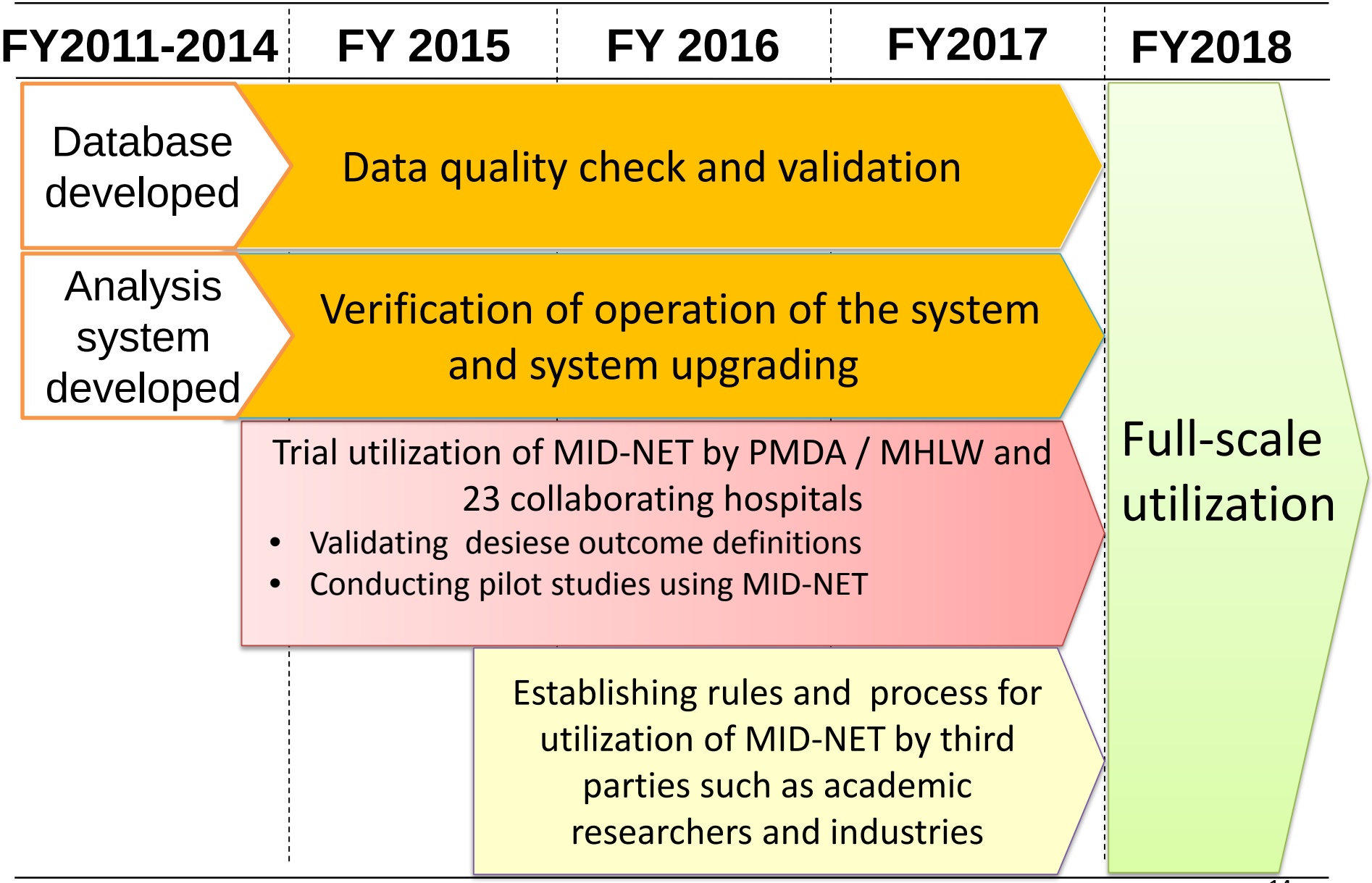
i) compare frequency of a certain AE of some drugs.

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



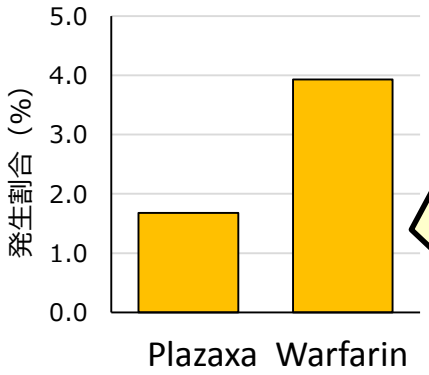
Example of Pilot Use of MID-NET
< Risk of bleeding associated with Plazaxa >

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%	26	21.8%
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

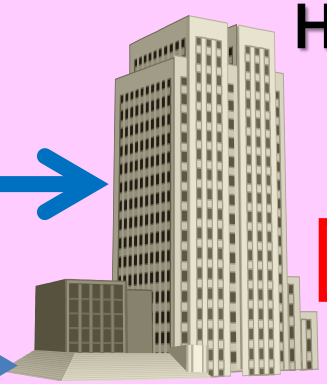
Safety Communication

MHLW

PMDA

PMDA
Medi-Navi

Health Professionals



WEB site

Guidance

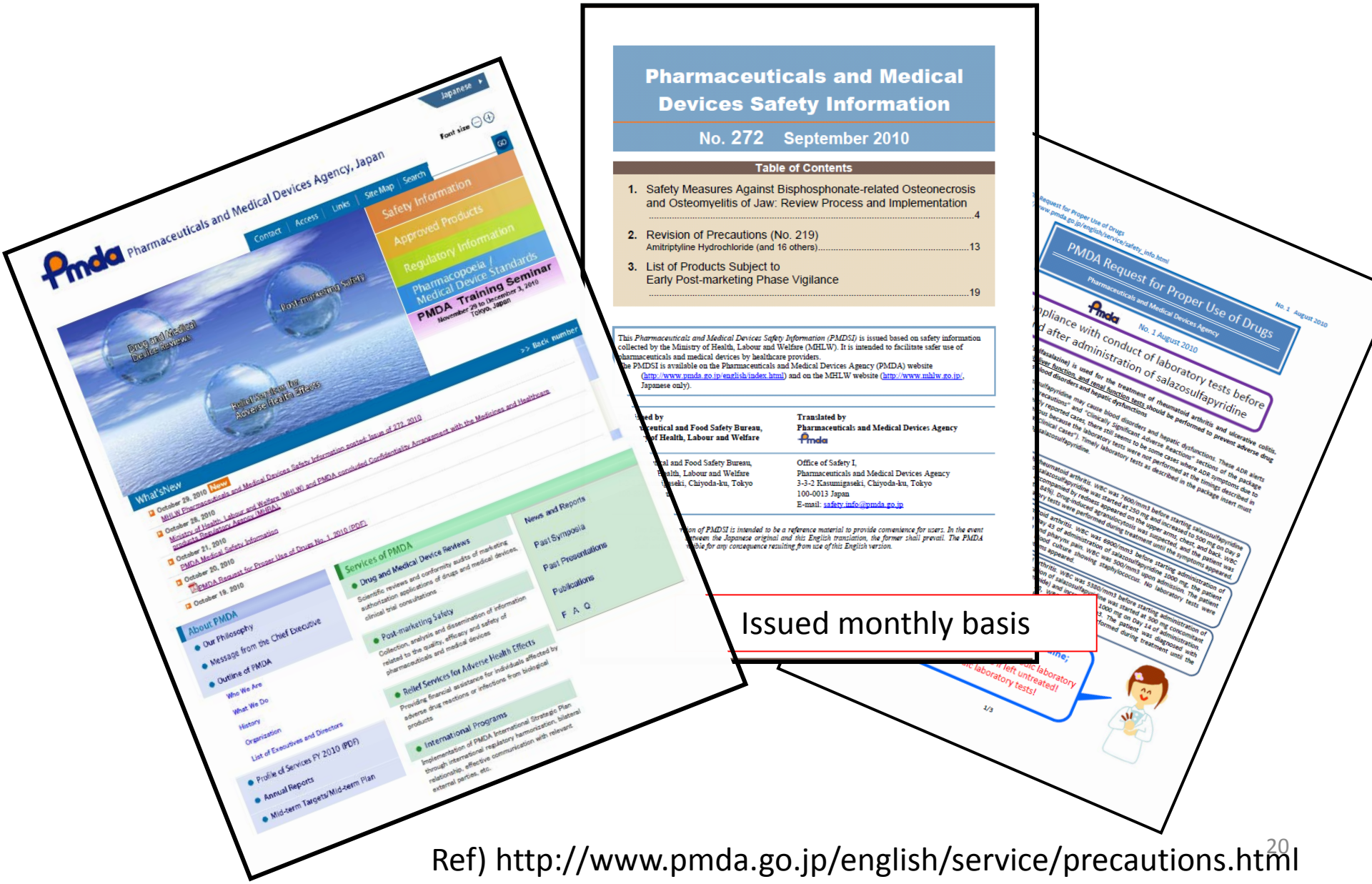
Information by
Medical Representatives

Compliance
guidance

MAH

How to deliver information to patients?

Communications through PMDA



Ref) http://www.pmda.go.jp/english/service/precautions.html

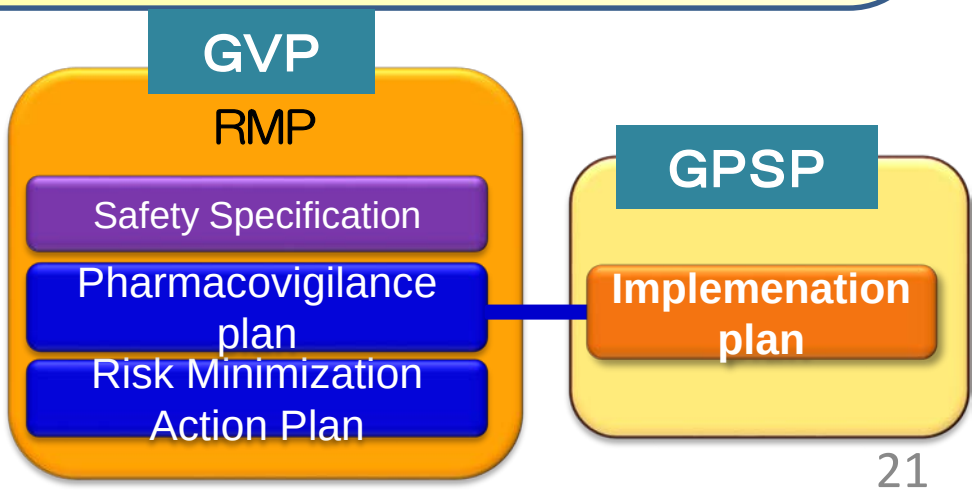
Risk Management Plan

■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

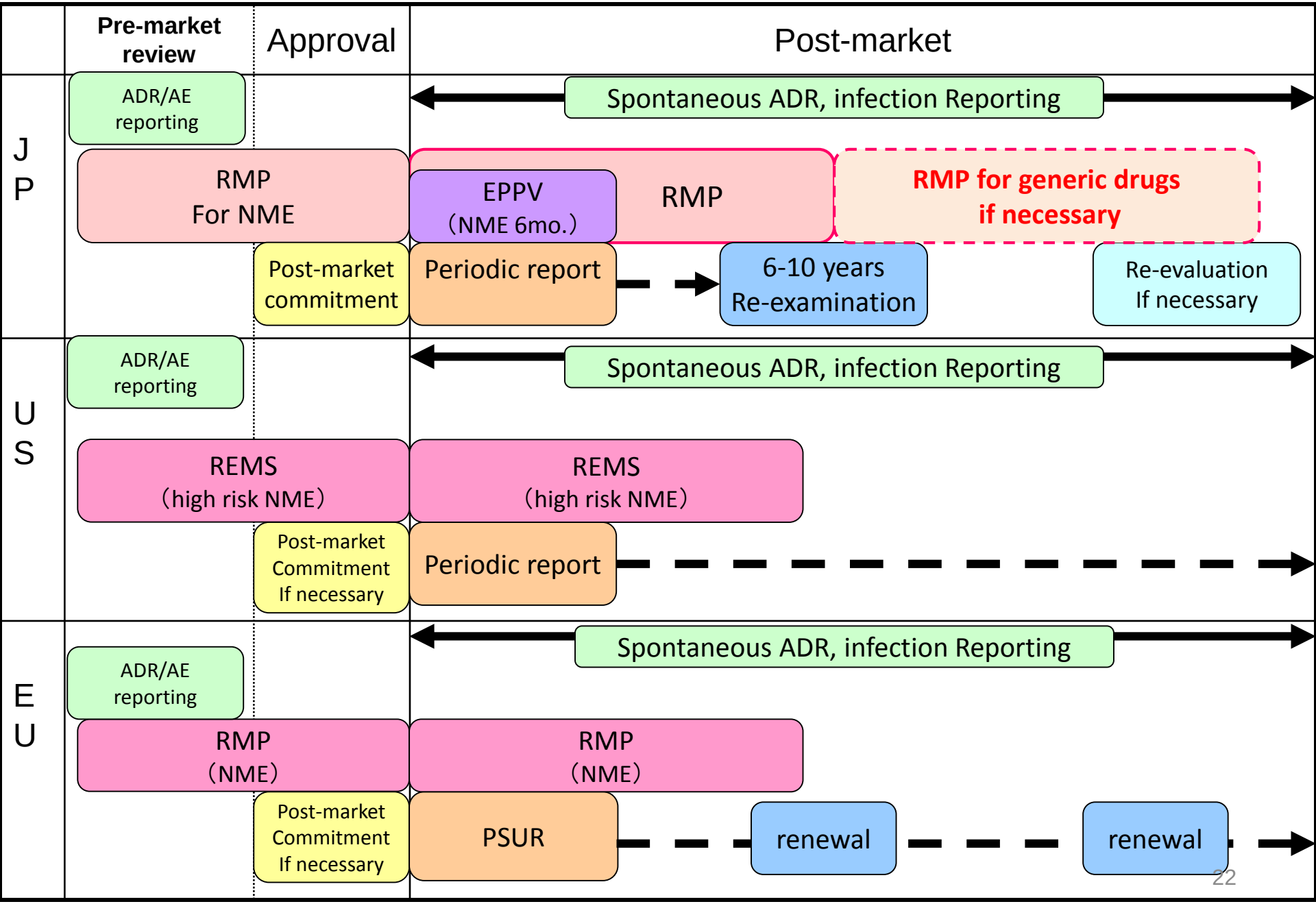
are to be addressed in "Risk Management Plan" (RMP) so as to carry out constant risk management throughout R&D and post-approval phases and to improve post-approval safety.

■RMP guideline
NMEs and biologics ⇒ 2012 April
⇒ 2013 April NDA implementation
Generic Drugs ⇒ 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

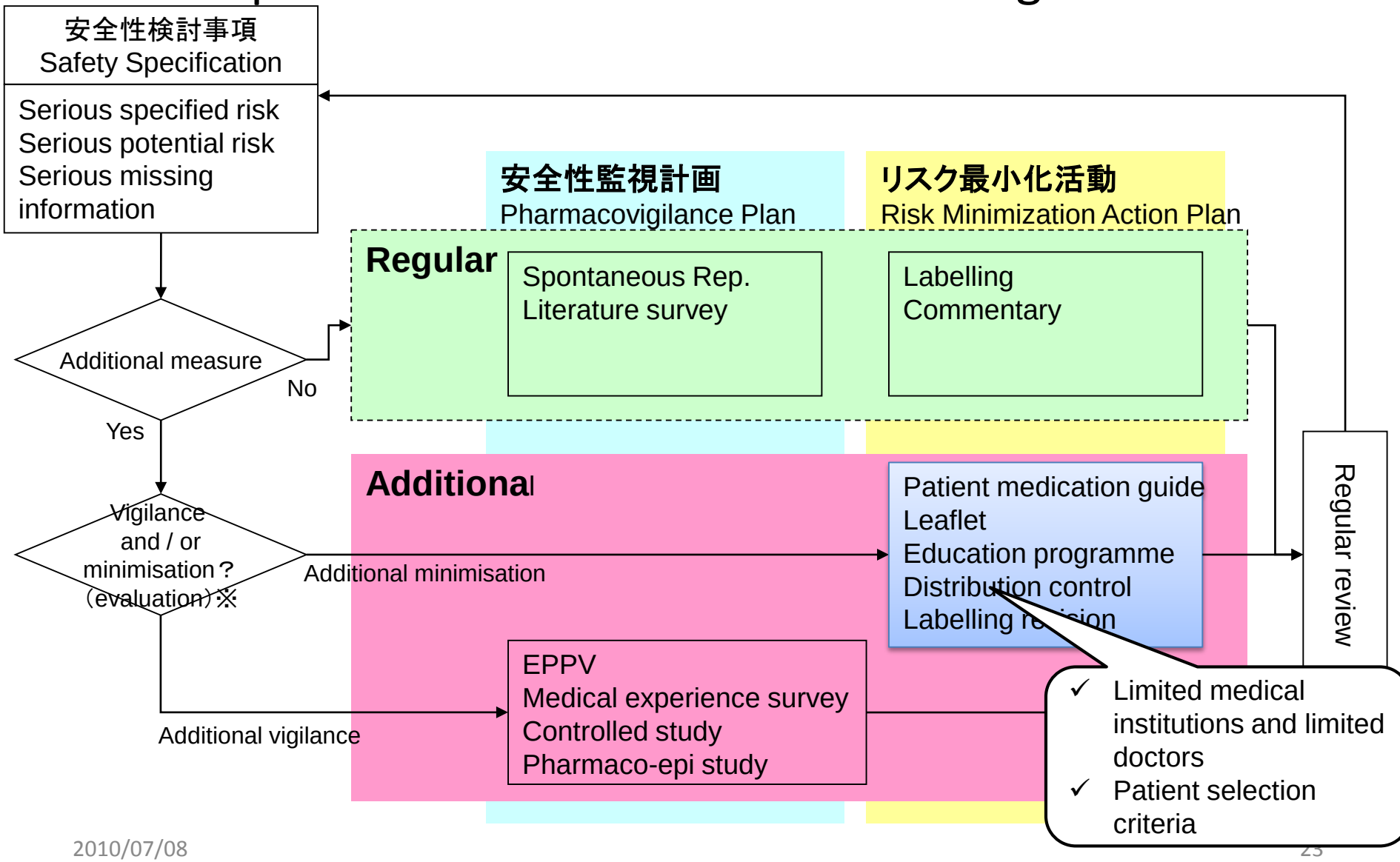


Post-approval Risk management measures JP, US, EU



Concept of structured RMP

implementation in line with ICH-E2E guideline

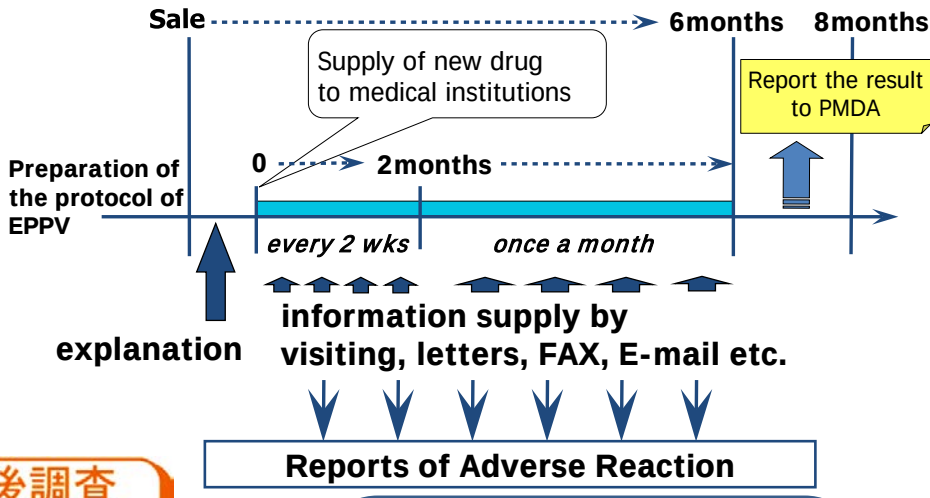


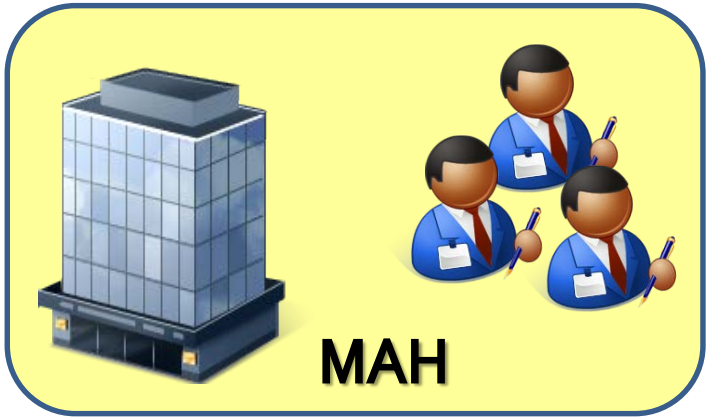
EPPV as a risk management tool

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





市販直後調査
平成○年○月～平成○年○月

Visit for information provision

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

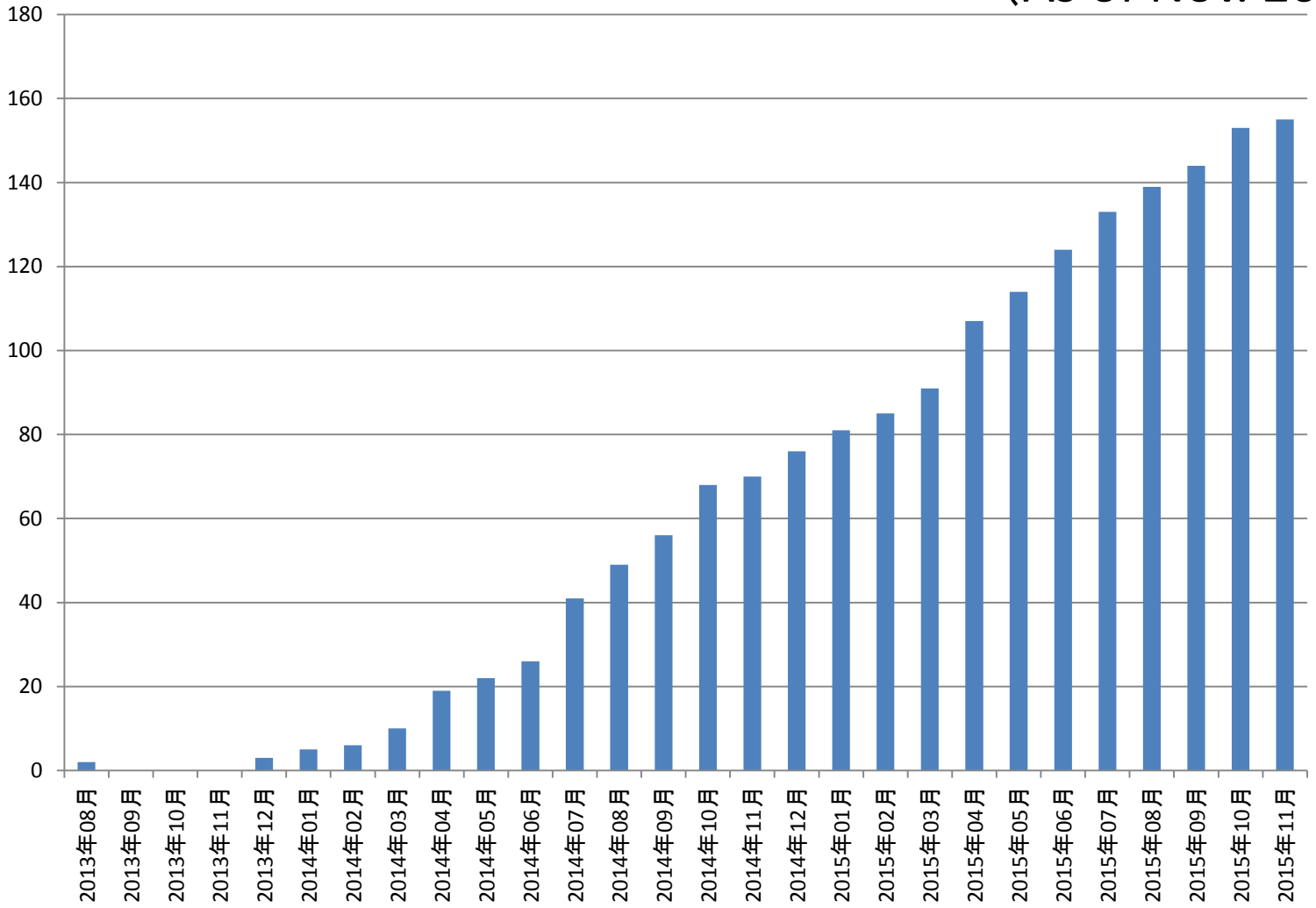
Visit for information collection（request survey and collect CRF）

- **ADR report detail**
- **Post-markting studies**

RMP status is updated and published by PMDA website

Number of NMEs

（As of Nov. 2015）

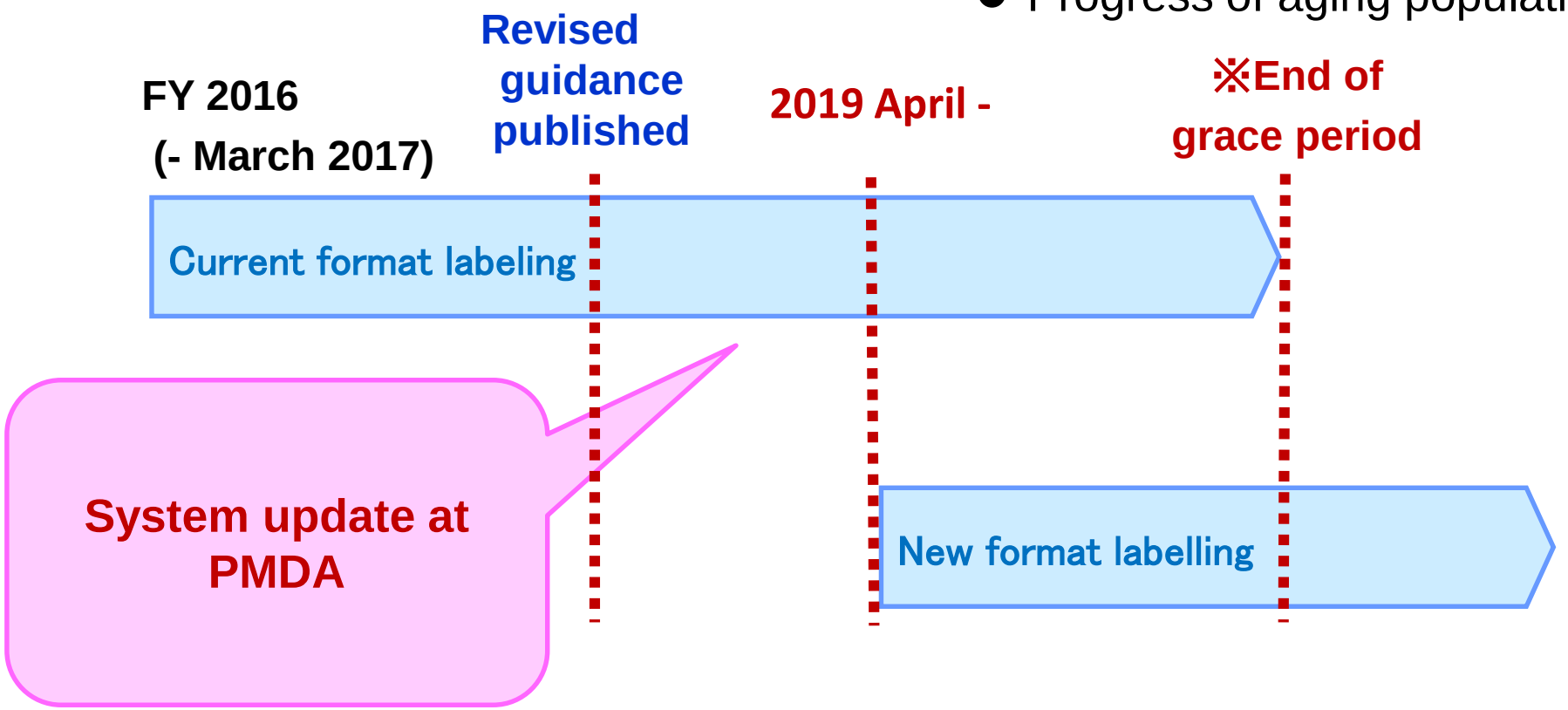


Labeling Format Guidance Revision

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

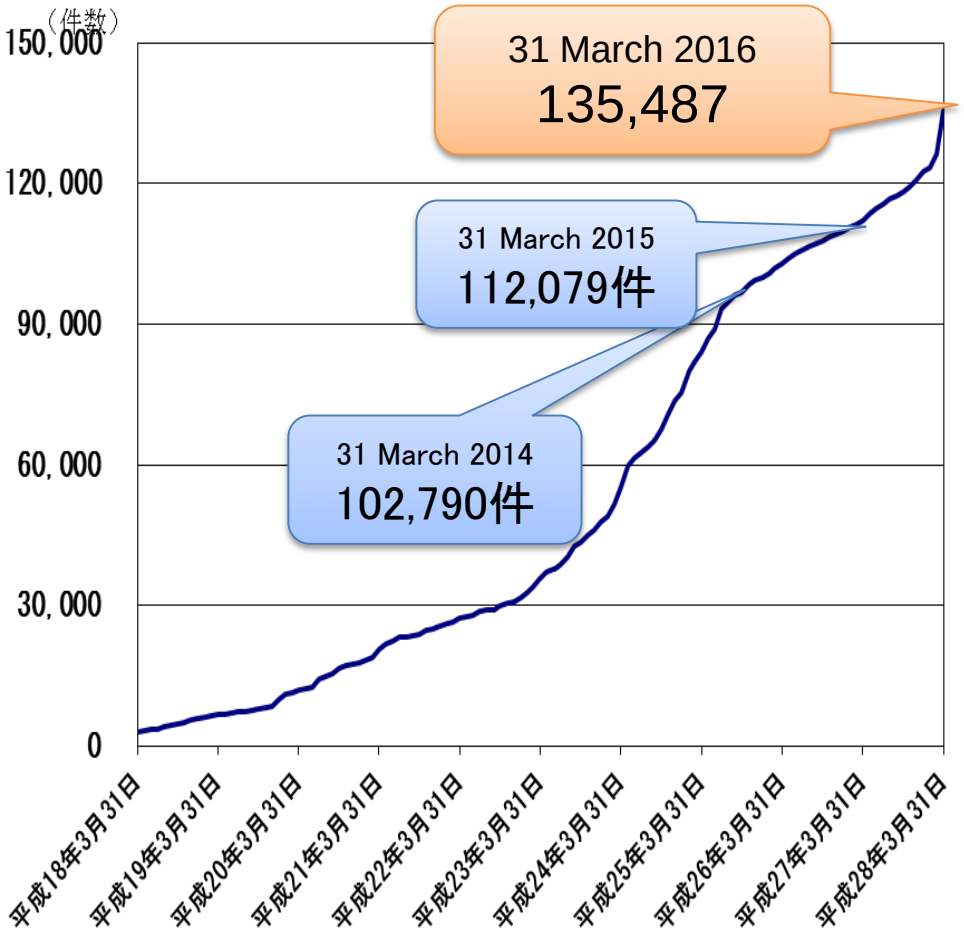
The current guidance was published in 1997. Since then :

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

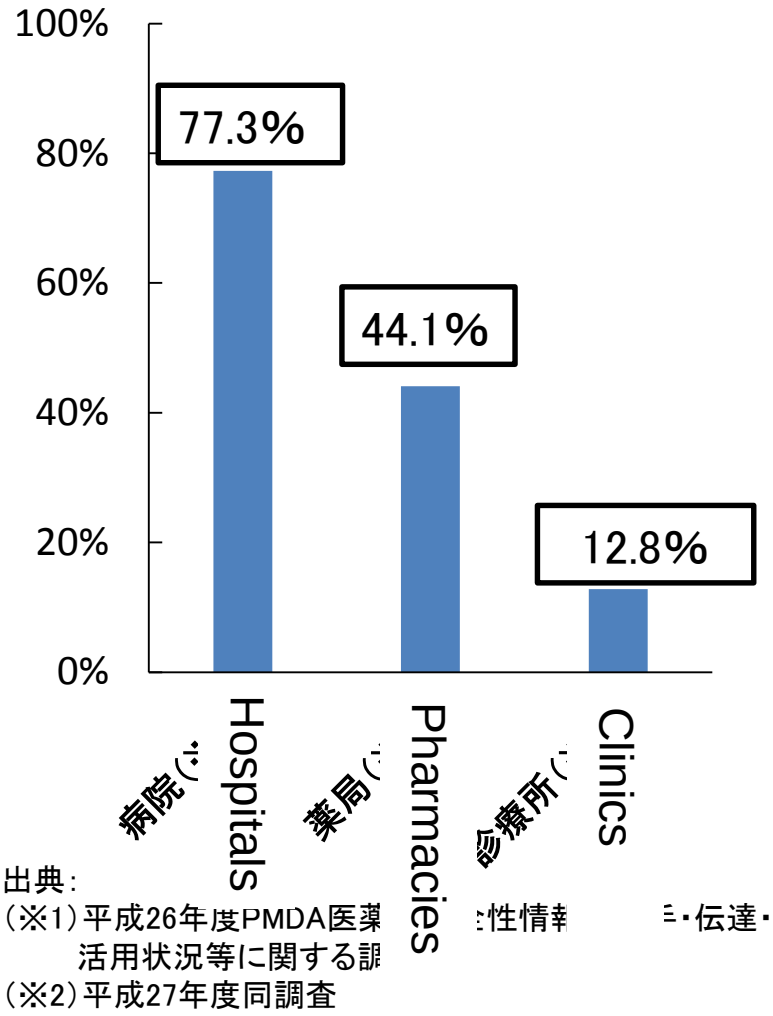


Registration of PMDA **Medi-Navi** (direct e-mailing list service to health professionals)

Registrants



Organizations of registrants



出典：
（※1）平成26年度PMDA医薬
活用状況等に関する調
（※2）平成27年度同調査

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