New Streams of Risk Management

Tomiko TAWARAGI
Chief Safety Officer
Pharmaceuticals and
Medical Devices Agency (PMDA)

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DIA DEVELOP INNOVATE ADVANCE

PMDA Third Mid-term Plan for Safety (ctd.)

- 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

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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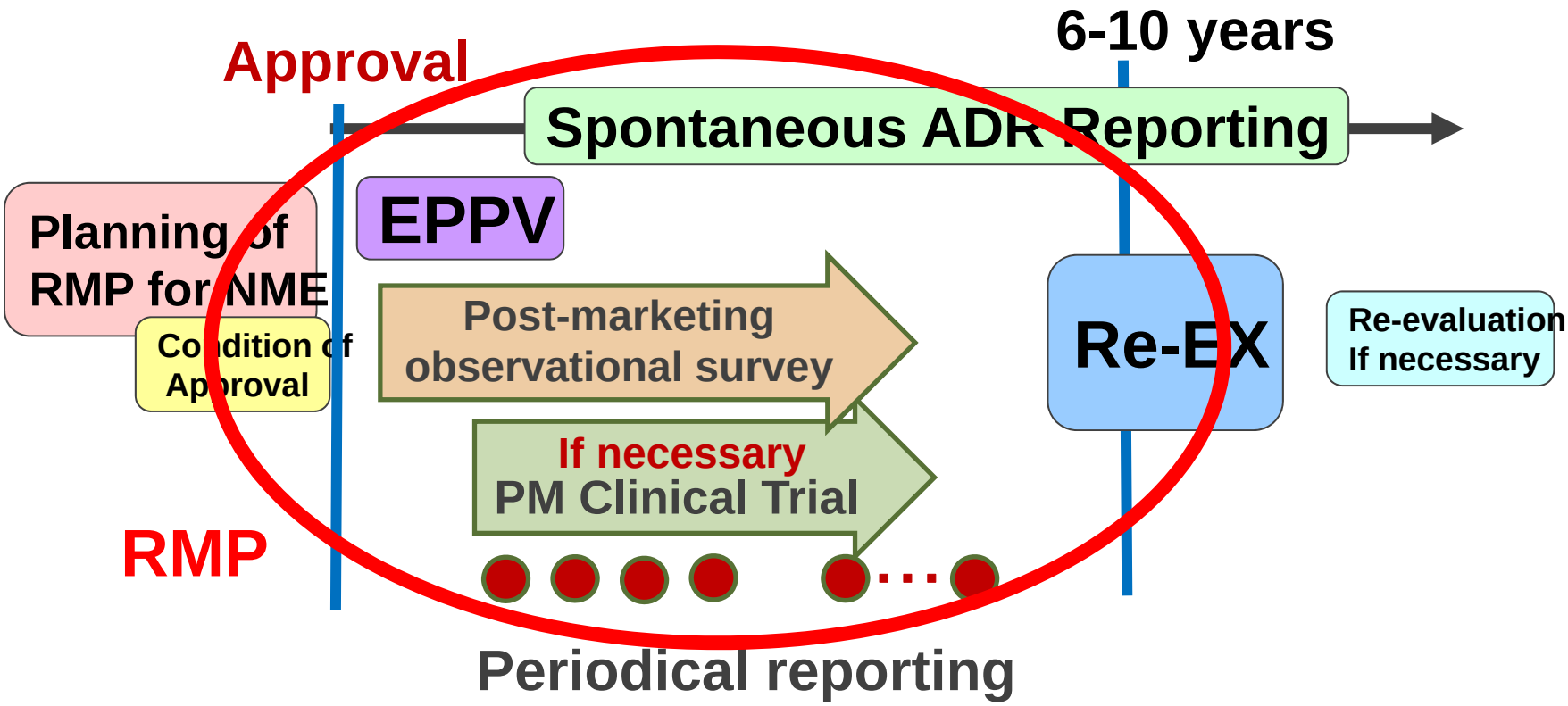
Today's Topics

- Overview of Japanese Pharmacovigilance Framework
- Risk Management Plan and Risk Managers
- New Initiatives for Safety Evaluation
  - --- Utilization of Electronic Healthcare Data
  - --- MID-NET Project
- New Regulation
  - --- Notification of Package Insert

Overview of Japanese Pharmacovigilance Framework



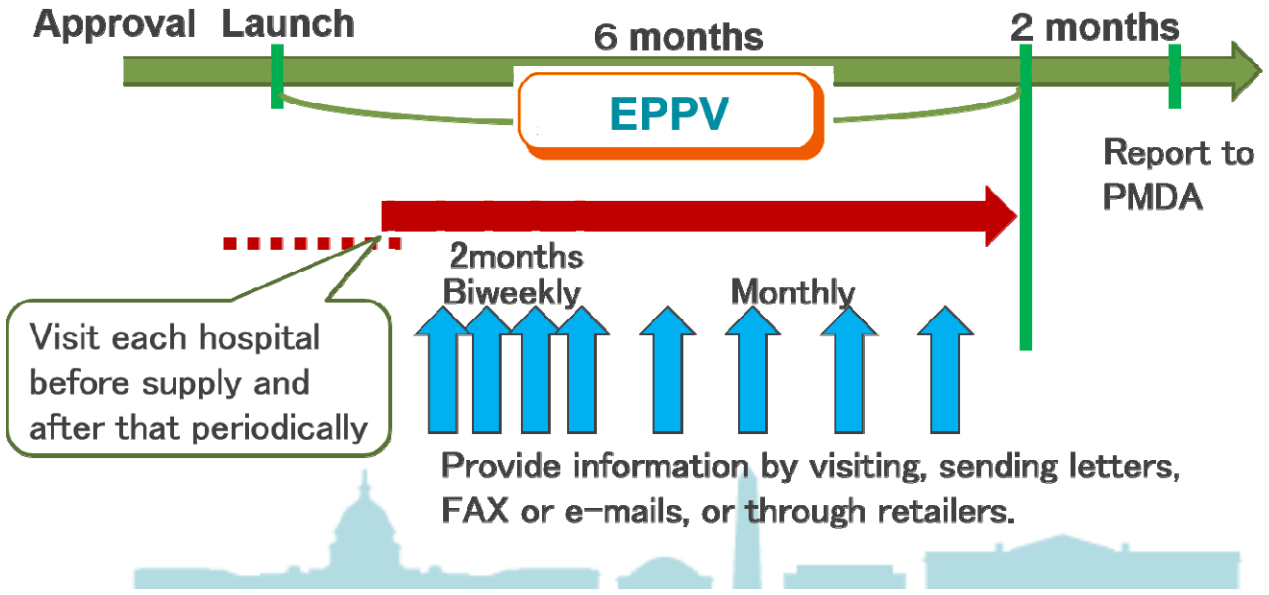
EPPV : Early Post-marketing Phase Vigilance (6 months intensive monitoring)

RMP : Risk Management Plan

Re-EX : Re-examination

Early Post-market Phase Vigilance

- Monitoring ADRs is critical in the first 6 months after the launch of a new drug.
- Marketing authorization holders are required to provide the safety information to health care professionals and to collect ADR information intensively for the time frame by visiting hospitals periodically.



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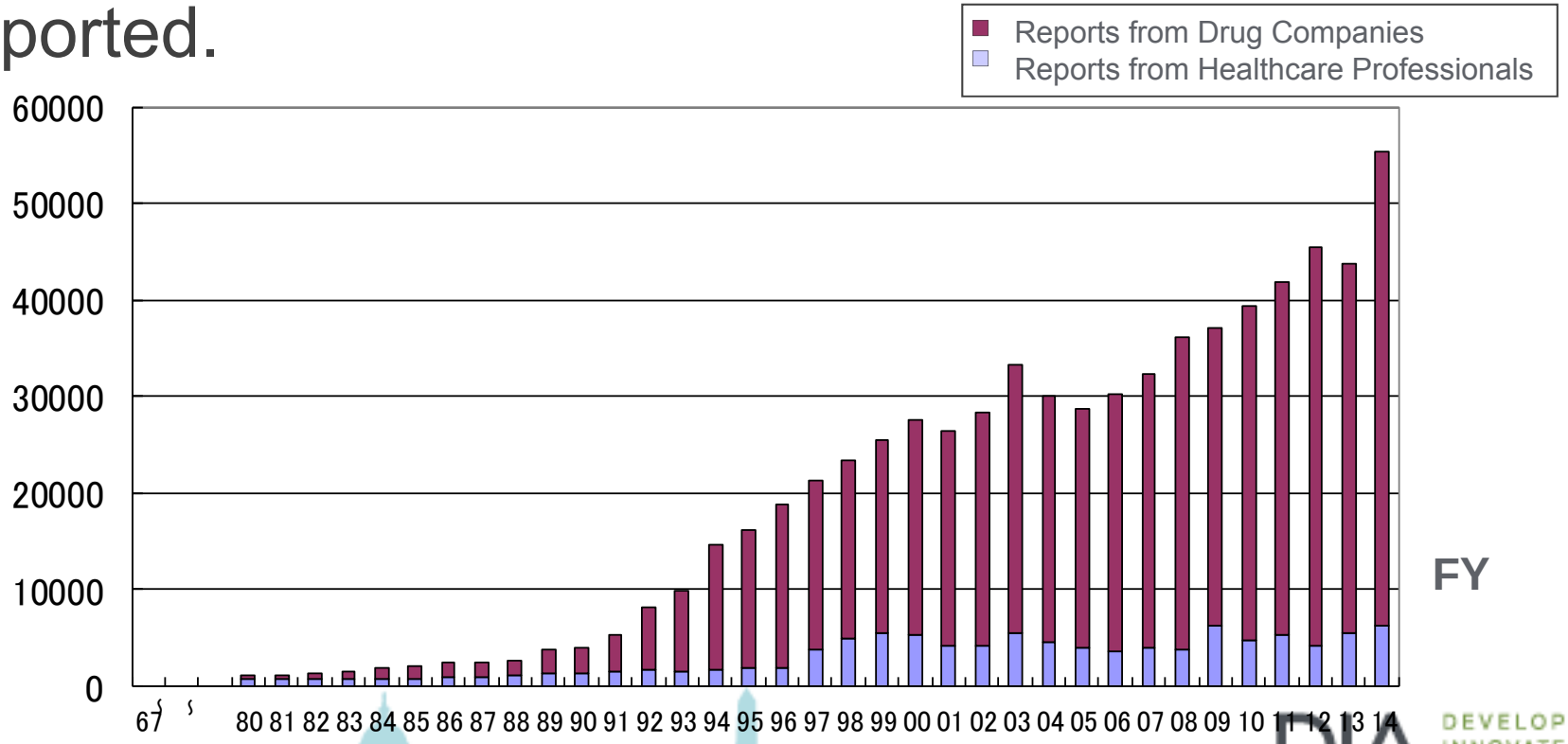
Spontaneous ADR Reporting

- MHLW and PMDA gather the ADR reports directly from health care professionals, and via drug companies.
- In FY2014, about 55,000 serious ADR cases were reported.



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Early Communication of Risk Under Review

PMDA holds an experts meeting every 5 weeks to consider revisions of labelling. Drug risk information under consideration will be put on this PMDA Risk Communications list.

PMDA Risk Communications

Drug Risk Information of Ongoing Evaluation Updated

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) (only available in Japanese language)	Risk Information Ongoing Evaluation	Related Information	Investigation Results
New January 23, 2015	abiraterone acetate	Hypokalaemia, thrombocytopenia, and rhabdomyolysis	–	–
	montelukast sodium	Thrombocytopenia	–	–
	telaprevir	Precautions concerning a risk of renal impairment	–	–
	memantine hydrochloride	Hepatic dysfunction and jaundice	–	–
	apixaban	Interstitial pneumonia	–	–

Risk Management Plan

- In order to ensure the safety of drugs, it is important to conduct an appropriate management of the risks of drugs throughout their life-cycle.
- J-RMP is a document summarizing the risk management for a drug.
- J-RMP is required for new drugs for which approval applications are submitted after April 1st, 2013, and for some of generic drugs after August 26, 2014 .

Risk Management Plan (ctd.)

- J-RMP should be reviewed at every milestone;
  - Submission of periodical reports
  - Completion of any post-marketing surveillance
  - Taking additional safety measures

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Risk Management Plan (ctd.)

Safety Specification

important identified risks
important potential risks
important unknown risks due to missing information

Pharmacovigilance Plan

Plan for activities of collecting information of individual risks

Routine: Collecting information of ADRs
Additional: EPPV
Post-marketing observational studies
Post-marketing clinical trials
Pharmacoepidemiologic studies, etc

Risk Minimization Action Plan

Plan for safety measures taken to minimize individual risks

Routine: Package insert
Patients Drug Guide
Additional: EPPV
Additional communications to HCP
Additional communications to patients
Special management of use
Special education of physicians, etc

Development of J-RMP

- At the time of approval application of new drugs and a part of generic drugs, a draft of J-RMP is required to submit to PMDA. Then, the applicant and PMDA review team and a risk manager discuss and agree on the J-RMP before the approval.

Development of J-RMP

- When PMDA judges that additional activities are necessary, MAH is required to conducting appropriate post-marketing safety measures based on the agreed J-RMP as a condition of an approval.
- Sharing a J-RMP document among healthcare professionals is important to ensure post-marketing safety of drugs.
- J-RMP is made public via PMDA website at the earliest availability.

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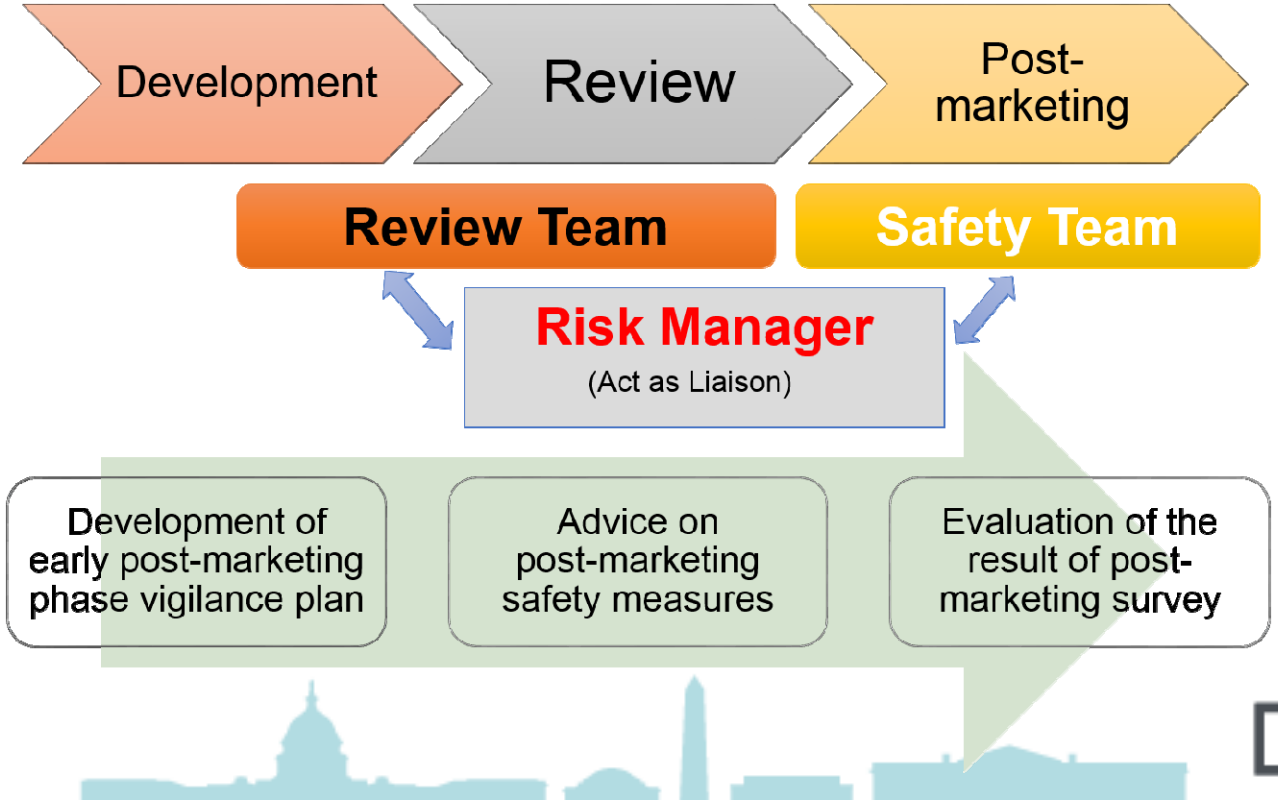
Risk Managers in PMDA

- Risk Managers are liaison officers between the review teams and the post-market safety teams to develop the suitable safety measures.
- PMDA has 14 risk managers for 12 review teams.



MIHARI Project

- “MIHARI” means a guard or a watch in Japanese.
- MIHARI Project is
  - To utilize electronic healthcare data (health insurance claim data, medical records, etc) in order to evaluate possible safety issues more quickly and more securely.
  - Launched in FY2009.

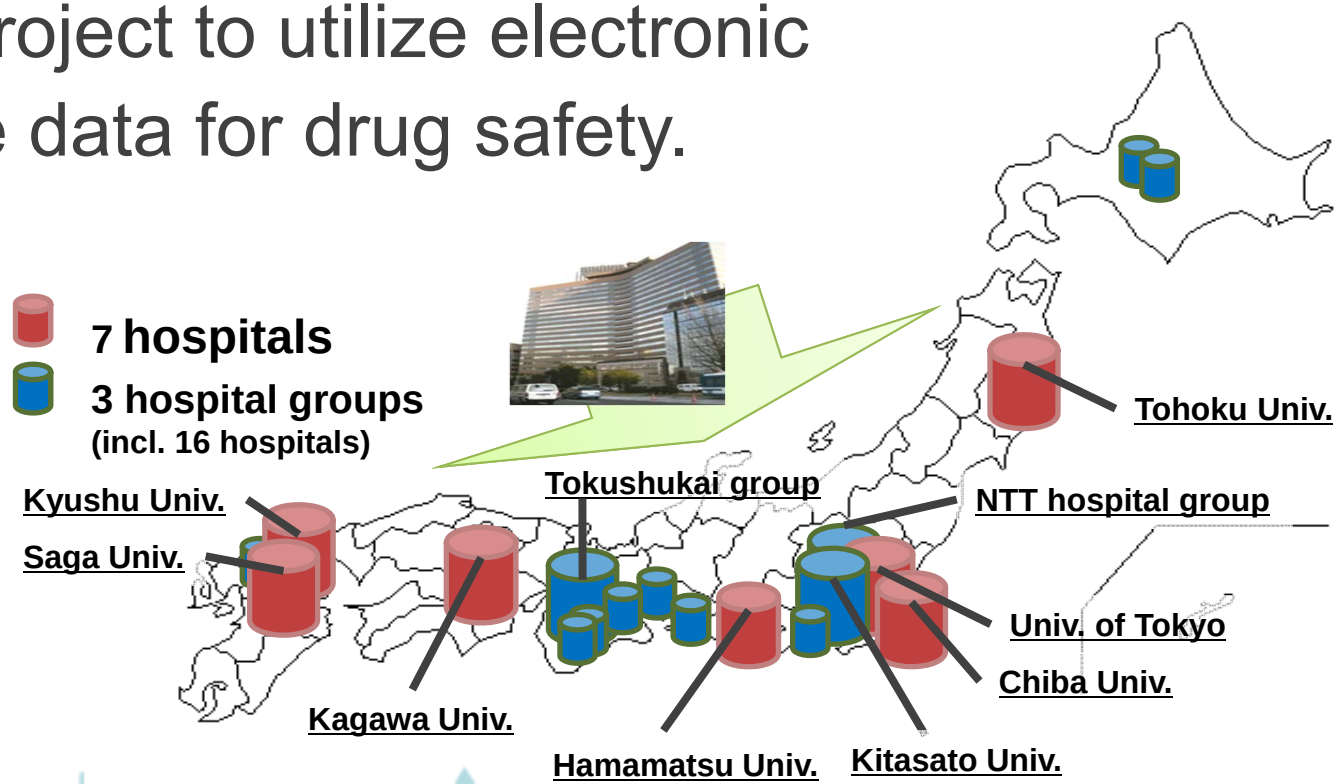
MIHARI
Medical Information for Risk Assessment Initiative

MIHARI Project

- Since 2009, we have conducted pilot studies
  - To ensure access to existing electronic healthcare data (EHD) such as medical records and health insurance claim data.
  - To develop pharmacoepidemiological methodology and technique to use EHD for quantitative risk evaluation of drugs and for evaluation of impact of regulatory safety actions.

MID-NET Project

- MID-NET（Medical Information Database Network） is a national project initiated by MHLW to establish the DB network for MIHARI Project to utilize electronic healthcare data for drug safety.



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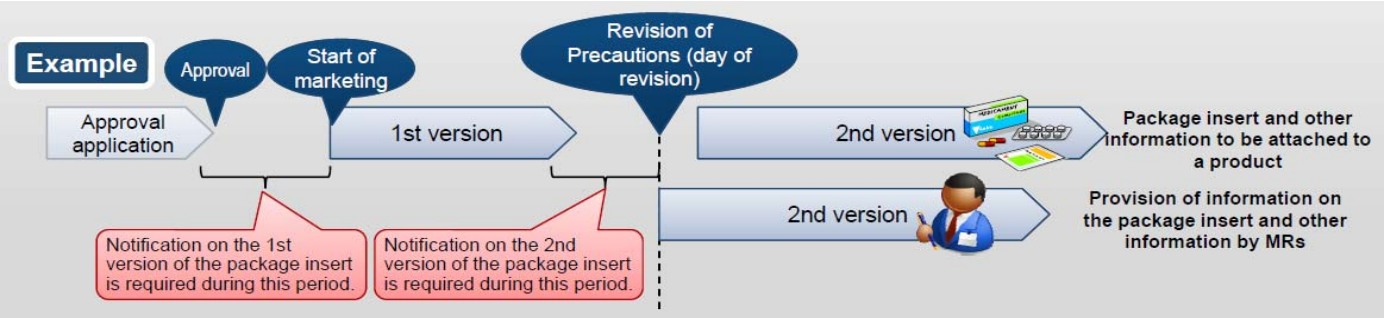
MID-NET Project

- Electronic healthcare data at 10 hub medical institutions will be retrieved and standardized for analysis and evaluation of ADR.
- A standardized database of EHD and an analysis system has been already established in each of 10 co-operating medical institutions.
- Data quality check and system validations are now being conducted.
- Full-scale utilization of the MID-NET data is expected to start in 2018.

Notification and Publication of PSI

- A new regulation on notification and publication of product safety information has been introduced into the Pharmaceuticals and Medical Devices Law and came into effect in November, 2014.
- MAHs are required to make prior notification of product safety information at the start of marketing and at the time of their revisions.
- After the notification, MAHs shall immediately publish the package insert on the PMDA website.



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Items to be notified

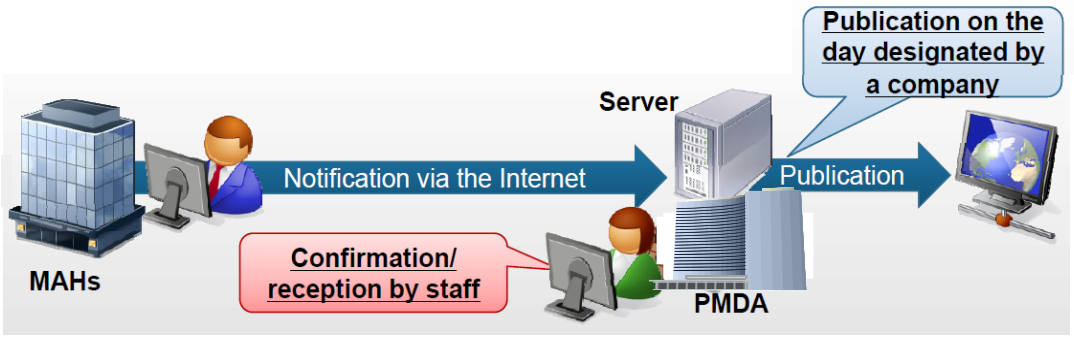
- Among sections in package insert, sections listed below by red and underlined letters shall be notified.

1 Date of preparation or revision
2 Japan Standard Commodity Classification Number
3 Therapeutic category
4 Regulatory classification
5 Name
6 Warnings
7 Contraindications
8 Description
9 Indications
10 Dosage and administration
11 Precautions
- **Precautions related to the indications**
- **Precautions related to the dosage and administration**
- **Careful administration**
- **Important precautions**
- **Drug interactions**
- **Adverse reactions**
- **Geriatric use**
- **Use during pregnancy, delivery or lactation**
- **Pediatric use**
- **Effects on laboratory tests**
- **Overdosage**
- **Precautions concerning use**
- **Other precautions**

12 Pharmacokinetics
13 Clinical studies
14 Pharmacology
15 Physicochemistry
16 Precautions for handling
17 Conditions for approval
18 Packaging
19 References and request for literature should be made to:
20 Name and address of manufacturer or importer

Practically

- The contents of product safety information are reviewed by a review team and a risk manager during approval review, and after approval, they are revised based on the consultation between PMDA and MAH based on the information collected in post-marketing surveillance.



Practically

- Based on the consultation with PMDA, MAHs notify the package insert including product safety information to PMDA electronically via the Internet and then the package insert is published on the PMDA website.

PMDA English Website

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

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Thank You

Tomiko TAWARAGI

Chief Safety Officer

Pharmaceuticals and Medical Devices Agency

tawaragi-tomiko@pmda.go.jp