



# Pharmacovigilance Activities in Japan

Pharmacovigilance: The Study of Adverse Drug Reactions and Related Problems

2-13 May 2011

WHO Collaborating Centre for International Drug Monitoring  
Uppsala, Sweden

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Office of Safety II

Pharmaceuticals and Medical Devices Agency

# Presentation Outline

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- Current picture of PMDA
- Pharmacovigilance Plan
- Risk Minimization Action Plan
- Challenges for the future

# Outline of PMDA

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- ▪ Date of establishment: April 1, 2004  
(former PMDEC established in 1997)
- ▪ Incorporated Administrative agency  
with non-civil servant status
- ▪ Authorized by Ministry of Health,  
Labour and Welfare (MHLW)
- ▪ Legal support by the law on PMDA
- ▪ The Chief Executive has been Tatsuya  
Kondo, M.D, Ph.D. since 01, April, 2008
- ▪ The Number of regular employees has  
been increasing

# The Number of the PMDA Staff

	April 1, 2004	April 1, 2005	April 1, 2006	April 1, 2007	April 1, 2008	April 1, 2009	April 1, 2010	At the end of the effective period for the Second Mid- term (end of FY 2013)
Total	256	291	319	341	426	521	605	751 (Plan)
Review Department	154	178	197	206	277	350	389	
Safety Department	29	43	49	57	65	82	123	

*Note1: The Review Department consists of the Director (Center for Product Evaluation), Associate Executive Directors (excluding Associate Executive Director responsible for Office of Regulatory Science), Associate Center Directors, Office of International Programs, International Liaison Officers, Office of Review Administration, Office of Review Management, Offices of New Drug I to V, Offices of Biologics I and II, Office of OTC/Generic Drugs, Offices of Medical Devices I and II, and Office of Conformity Audit, and Senior Specialists*

*Note2: The Safety Department consists of the Chief Safety Officer, Offices of Safety I and II, and Office of Compliance and Standards.*

# PMDA's Major Work Areas

**Review and Audit** for  
Drugs/ Medical Devices  
Efficacy and Safety

**Clinical Trial Consultation**

**Review of Efficacy and Safety**

**Conformity Audit for Application  
Materials of GLP, GCP and GMP**

**Post-marketing  
Safety Operations** for  
Drugs/ Medical Devices

**Reinforced Safety Information  
(Database)**

**Scientific Review and Research for  
Safety Information**

**Information Provision (via the  
Internet), Pharmaceutical  
Consultation for Consumers**

**Relief Service** for ADR and  
Other Infectious Disease

**Provision of Medical Expenses,  
Disability Pensions etc.**

**Relief Service for SMON, HIV-  
positive,  
AIDS and Hepatitis C patients**

# **Expanding PMDA's operations**

## **recommended by the Government Revitalization Unit (GRU)**

A working group of GRU which was established to reform the overall national administration reviewed PMDA's business program on April 27, 2010

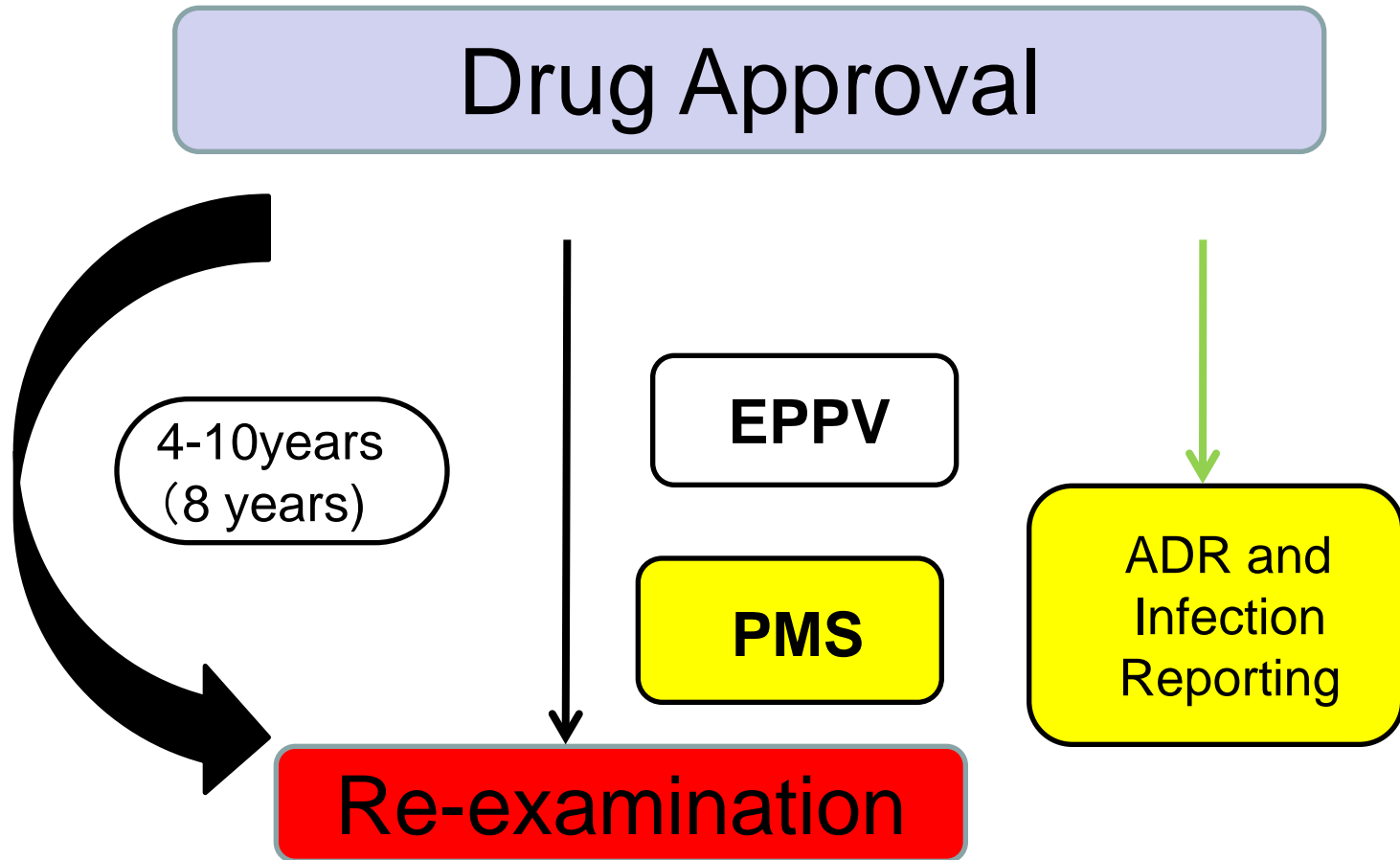
1. PMDA should expand its operations through the continued implementation of review services and safety measures.
2. PMDA was also instructed to improve its governance drastically.

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- ✓ Collection and Evaluation of ADRs
- ✓ Post Marketing Surveillance
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# The Framework for Post-Marketing Safety Operations





# Post-approval ADR Reporting Rule by Companies

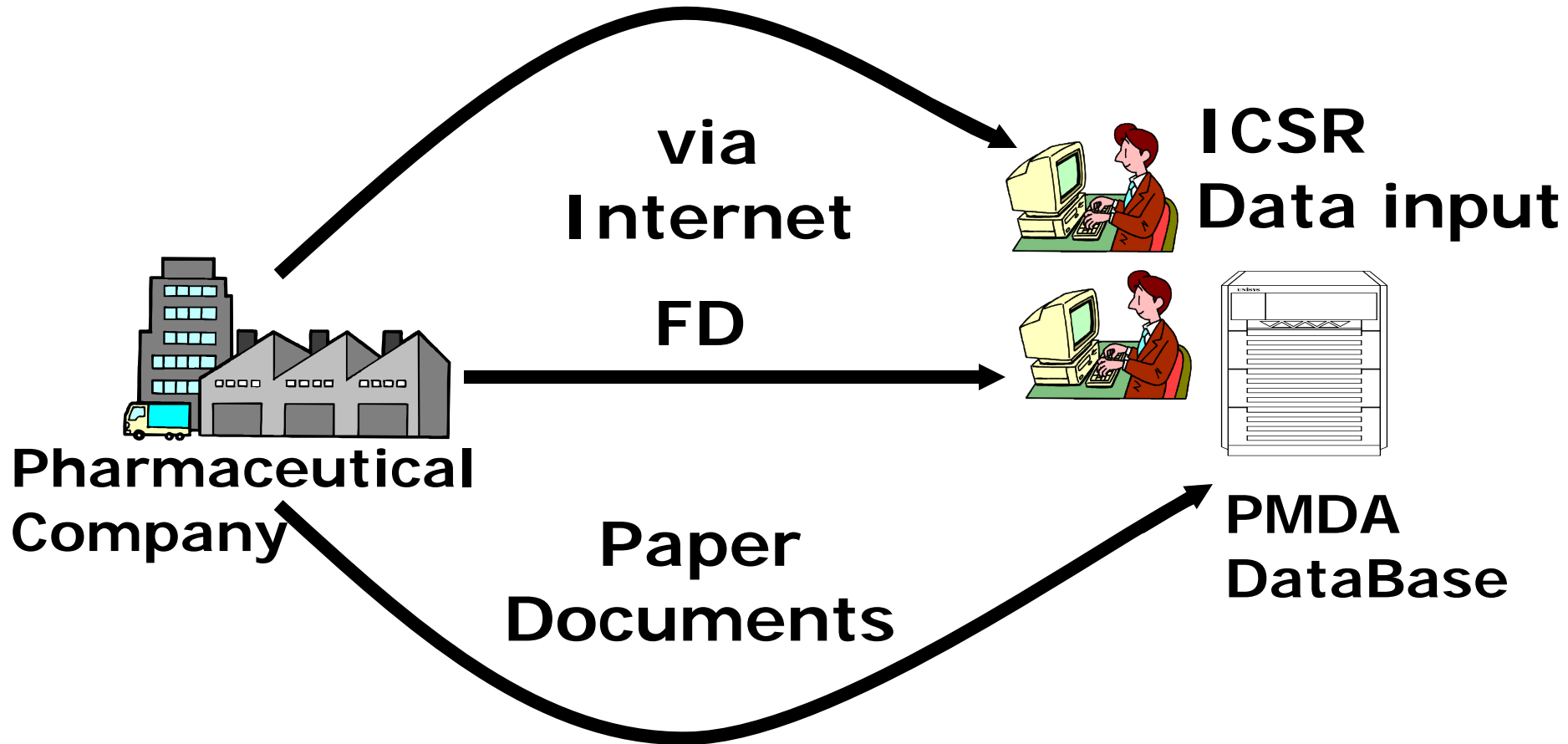
Serious-ness	Predict-ability	Time frame of report to PMDA
Serious	Not predictable	<b>15 days</b>
	Predictable	- Death etc.* <b>15 days</b> - Others <b>30 days</b>
Not serious	Not predictable	<b>Annually</b> (Annual Cumulative Report)
	Predictable	-

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

\* - Death

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

# ADR Reporting by Companies

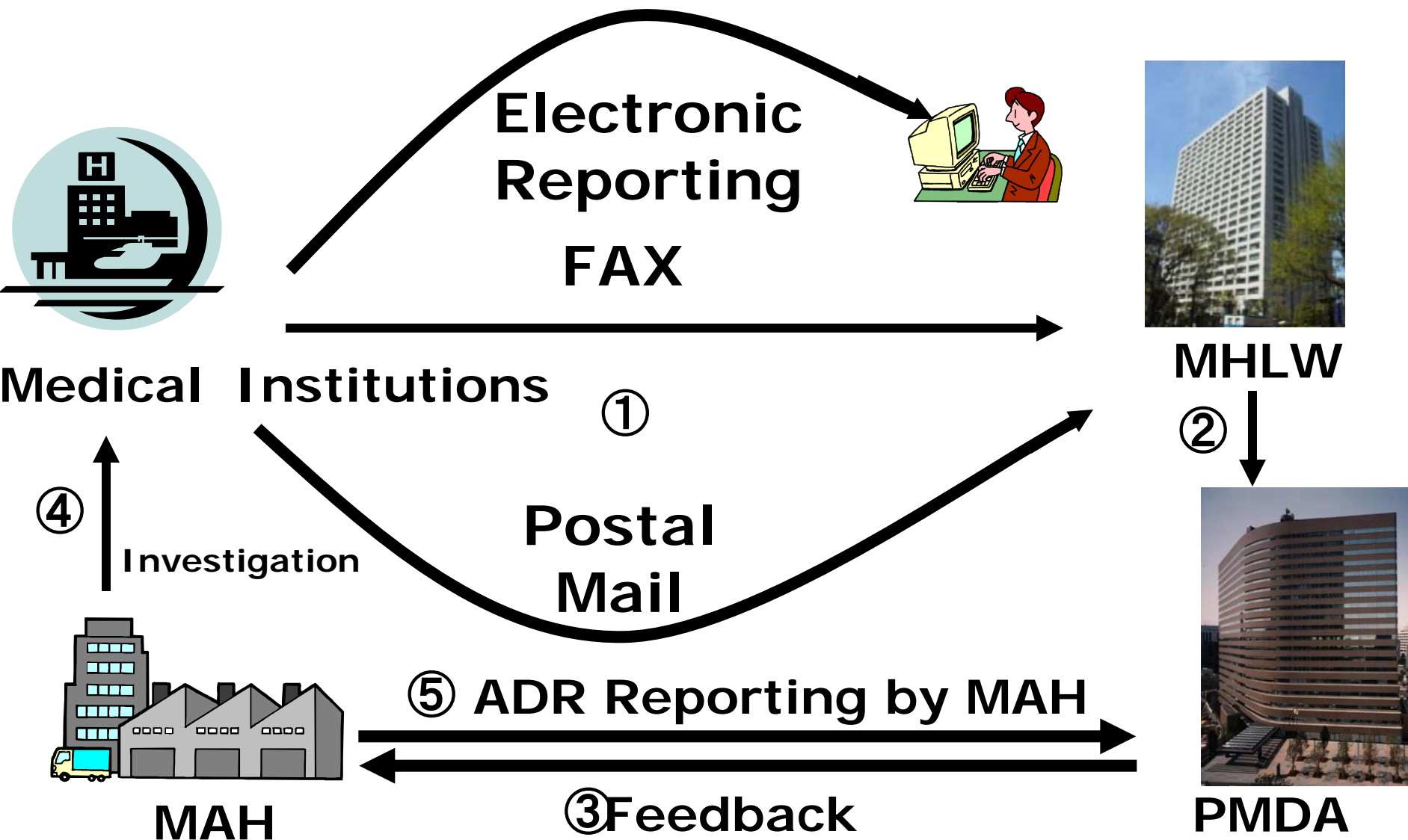


- ◆ Reporting by FD
- ◆ Reporting by paper documents
- ◆ Electronic reporting transmitted by internet

# ADR Report from HCPs

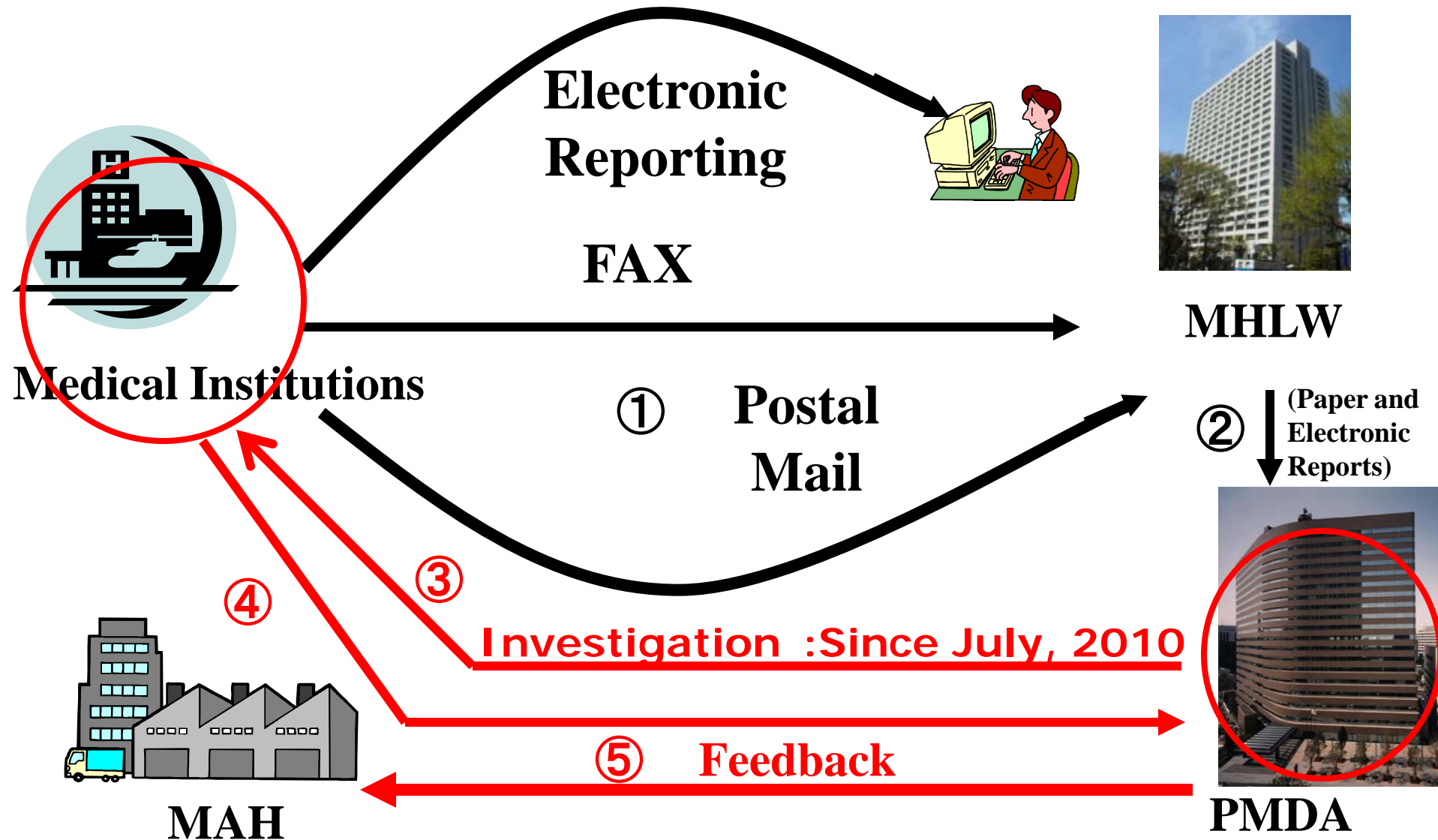
- Voluntary basis
  - since 1967: designated medical institutions
  - since 1984: designated pharmacies
  - since 1997: all medical institutions and pharmacies
- stipulated in PAL
  - since 2003
- HCPs shall report to MHLW when they
  - detect occurrence of any disorders suspected to be caused by ADRs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

# ADR Reporting by HCP **until July 2010**



# Direct Investigation by PMDA

(limited in the case of death or severe ADR)



# Numbers of Adverse Drug Reaction Reports

	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009
Companies: Japanese ADR	24,751	26,550	28,257	32,306	30,928
Companies: foreign ADR	65,316	77,346	95,036	116,662	141,386
Health Care Professionals	3,992	3,669	3,891	3,816	3,721

# PMDA Data Mining Method

- Current practice uses line listings
- Data mining positioned to supplement existing methods of signal detection
- Implement from April, 2009
- Determine cumulative frequency using count of reported cases
  - Not using count of events
- ROR to be main algorithm
- Chosen because:
  - Sensitivity was high during testing
  - Easy for assessors to understand and use

# Measures on Daily Evaluation of ADRs

- Assessment of **causality** of the following ADRs
  - Serious and not predictable
  - Serious and predictable
  - Death
  - ADR caused by new drug ingredient within 2 years after approval
  - ADR detected by Early Phase Post-marketing Vigilance (EPPV)
- Assessment of the accumulation of ADRs
- We discuss with MAH if we consider that we need to
  - Revise the package insert
  - Prevent serious ADRs and other medical safety issues
- PMDA also consolidates
  - Infections
  - Malfunctions as reported by HCP
  - Information from international sources such as ICH
  - Conference papers and research papers related to medical and pharmaceuticals sciences



# All Cases Surveillance

- One type of post marketing drug use investigations
- All patients who use the drug are needed to be registered by HCPs before the start of the use of the drug.
- The required numbers of patients is determined before approval
- Main target drugs of this system are historically orphan drugs
- Currently, most of oncology drugs are required to perform investigation of all users
- The characteristics of this system are:
  - Possibility to collect ADRs faster than ordinary drug use investigation
  - Possibility to evaluate the accurate incidence proportion of the ADR or risk factors of the ADR and so on
  - Possibility to provide information quickly about serious problems caused by the drug to all patients and doctors

# 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 active ingredients: 8 years (maximum 10 years)
- Surveillance and studies required for reexamination applications :  
in compliance with the GPSP, GCP or GLP depending on their objective.

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- ✓ Providing information
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# 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, and if occurred, immediately report to pharmaceutical companies
3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.

# Providing Information

- Package inserts: including information of revisions
- Recalls
- Urgent safety information issued by manufacturers (DHPL letter )
- MHLW press release
- Approval of new drugs
- Quality information for prescription drugs
- Pharmaceuticals and Medical devices safety information
- PMDA Medical Safety Information

# Pharmaceuticals and Medical Devices Safety Information

No. 277 February 2011  
**Executive Summary**

Published by  
Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare

Translated by  
Pharmaceuticals and Medical Devices Agency



Full text version of Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 277 will be upcoming soon. The contents of this month's PMDSI are outlined below.

## 1. Safety Measures for Gemtuzumab Ozogamicin (Genetical Recombination)

On June 21, 2010, it was published that gemtuzumab ozogamicin (Genetical Recombination), a therapeutic agent for acute myeloid leukaemia, was voluntarily withdrawn from the U.S. market. On the basis of the above, the MHLW reviewed the safety measures for gemtuzumab ozogamicin to be taken in Japan, and an expert discussion was held at the meeting of the Subcommittee of the Drug Safety, part of the Committee on Drug Safety, under the Pharmaceutical Affairs and Food Sanitation Council, on November 2, 2010. As a result, additional safety measures for the use of this drug have been taken. The details are described in Section 1 of the Full text document.

## 2. Important Safety Information

This section presents the contents of the revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notification dated January 11, 2011.

## Medical Safety Information

Pharmaceuticals and Medical Devices Agency



No. 17, May 2010

### Precautions in Handling of Prefilled Syringes

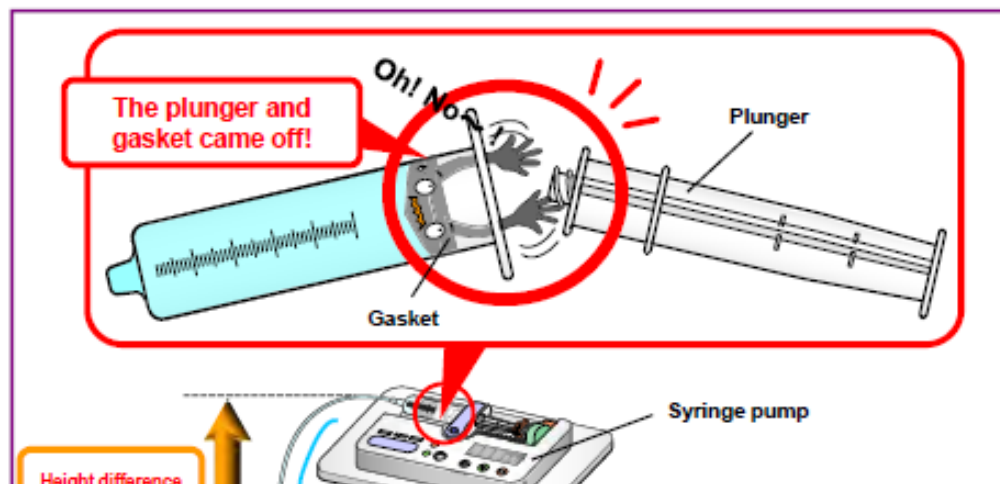
#### POINT

Key points for safe use

(Case 1) During administration of dopamine via a syringe pump, a pre-filled syringe's plunger came off from the gasket, and the drug solution ended up being injected too fast to a patient.

#### 1 Precautions when using prefilled syringes (Part 1)

- A prefilled syringe's plunger is screwed into the gasket and connected together. The connection may become loose during use, so be very careful.



# We also offer

- **Publications of data** of all cases of adverse reactions and malfunctions reported by companies after April 1, 2004
- “PMDA Medinavi”: **E-mail information** delivery services providing latest safety information to the health care professionals
- **Telephone consultation** services for consumers
- Publication of **drug guide for patients**
- Giving advice to companies about **drug medication guide for doctors** focused on safety and how to use issued by manufactures



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# Challenges

- Take more **proper** measure to provide information
  - Patients-friendly, user-friendly
  - Optimal timing
- More **actively**
  - Collecting information
  - Analyzing information
- Seeking more **efficient and appropriate** method of post marketing safety operations in Japanese Society
- **Global perspective**: share information under international cooperation, collection and evaluation of safety information internationally

# MIHARI project

*"Medical Information for Risk Assessment Initiative"*

## What does the MIHARI project address ?

- Ensure access to several kinds of electronic health information (i.e. medical records, insurance claim data)
- Develop pharmacoepidemiological methodology to use electronic health information for evaluation of risk for adverse drug reactions
- Develop methodology to use claim data etc. for evaluation of impact of regulatory actions on drug utilization
- Make safety information from post marketing studies electronically available and to create a database
- Expand accessibility to adverse drug reaction data from outside PMDA for research activities



**MIHARI**

# Providing Information on the Proper Use

■ PMDA Request for Proper Use of Drugs  
[http://www.pmda.go.jp/english/service/safety\\_info.html](http://www.pmda.go.jp/english/service/safety_info.html)

No. 1 August 2010

## PMDA Request for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency



No. 1 August 2010

### Compliance with conduct of laboratory tests before and after administration of salazosulfapyridine

Salazosulfapyridine (sulfasalazine) is used for the treatment of rheumatoid arthritis and ulcerative colitis. Periodic hematological, liver function, and renal function tests should be performed to prevent adverse drug reactions (ADRs) such as blood disorders and hepatic dysfunctions.

It is well known that salazosulfapyridine may cause blood disorders and hepatic dysfunctions. These ADR alerts are included in "Important Precautions" and "Clinically Significant Adverse Reactions" sections of the package insert. However, among recently reported cases, there still seems to be some cases where ADR symptoms due to salazosulfapyridine became serious because the laboratory tests were not performed at the timings described in the package insert (See "Typical Clinical Cases"). Timely laboratory tests as described in the package insert must be performed when administering salazosulfapyridine.

#### "Typical Clinical Cases"

(Case 1) A female patient in her 50s with rheumatoid arthritis. WBC was 7600/mm<sup>3</sup> before starting salazosulfapyridine (enteric tablets). Administration of salazosulfapyridine was started at 250 mg and increased to 500 mg on Day 9 of administration. On Day 36 rash accompanied by redness appeared on the upper arms, chest, and back. WBC decreased to 900/mm<sup>3</sup> (lymphocyte 84%). Drug-induced agranulocytosis was suspected, and the patient was admitted to a sterile room. No laboratory tests were performed during treatment until the symptoms appeared.

(Case 2) A male patient in his 40s with rheumatoid arthritis. WBC was 6900/mm<sup>3</sup> before starting administration of salazosulfapyridine (enteric tablets). On Day 43 of administration of salazosulfapyridine 1000 mg, the patient was admitted to the hospital for pyrexia and pharynx pain. WBC was 500/mm<sup>3</sup> upon admission. The patient was diagnosed with sepsis based on a blood culture showing staphylococcus. No laboratory tests were performed during treatment until the symptoms appeared.

(Case 3) A female patient in her 50s with rheumatoid arthritis. WBC was 5380/mm<sup>3</sup> before starting administration of salazosulfapyridine (enteric tablets). Administration of salazosulfapyridine was started at 500 mg concomitant with other drugs (loxoprofen sodium and rebamipide) and increased to 1000 mg on Day 14 of administration. Cold symptoms occurred on Day 36. On Day 38, WBC was 280/mm<sup>3</sup>. The patient was diagnosed with leukopenia and admitted to the hospital. No laboratory tests were performed during treatment until the symptoms appeared.

In patients treated with salazosulfapyridine;

- ADRs may be overlooked without periodic laboratory tests. ADRs may become serious if left untreated!
- Be sure to perform periodic laboratory tests!



<http://www.pmda.go.jp/english/service/request.html>

# Thank you for your attention

