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# Pharmacovigilance in Japan.

—Overview & Specific drug safety issue—

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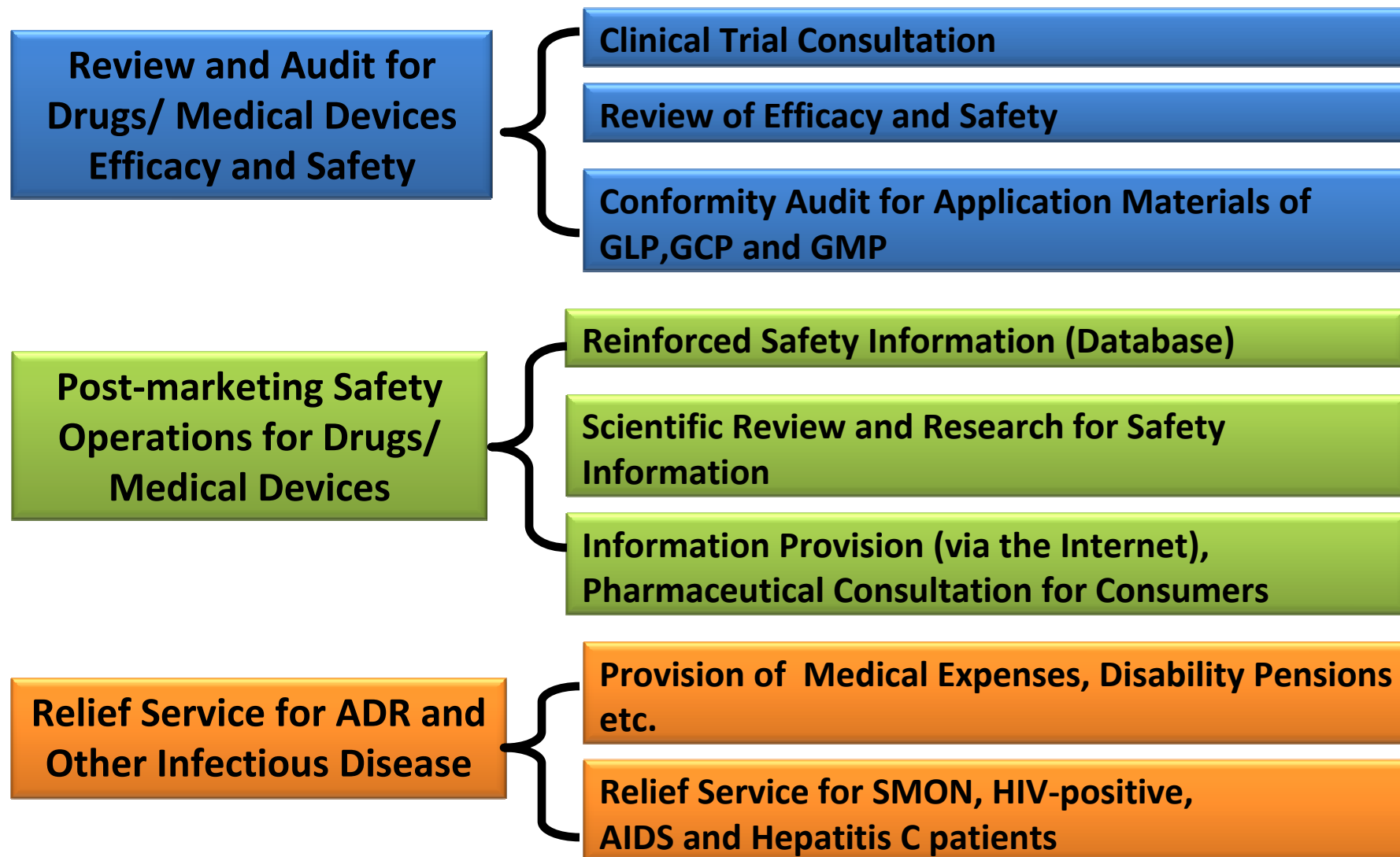
## Disclaimer

- Translation note
  - English and Japanese are not a perfect match
- The contents of this presentation represent the view of the speaker only and do not necessarily represent the official positions or policies of the PMDA

## Today's Topic

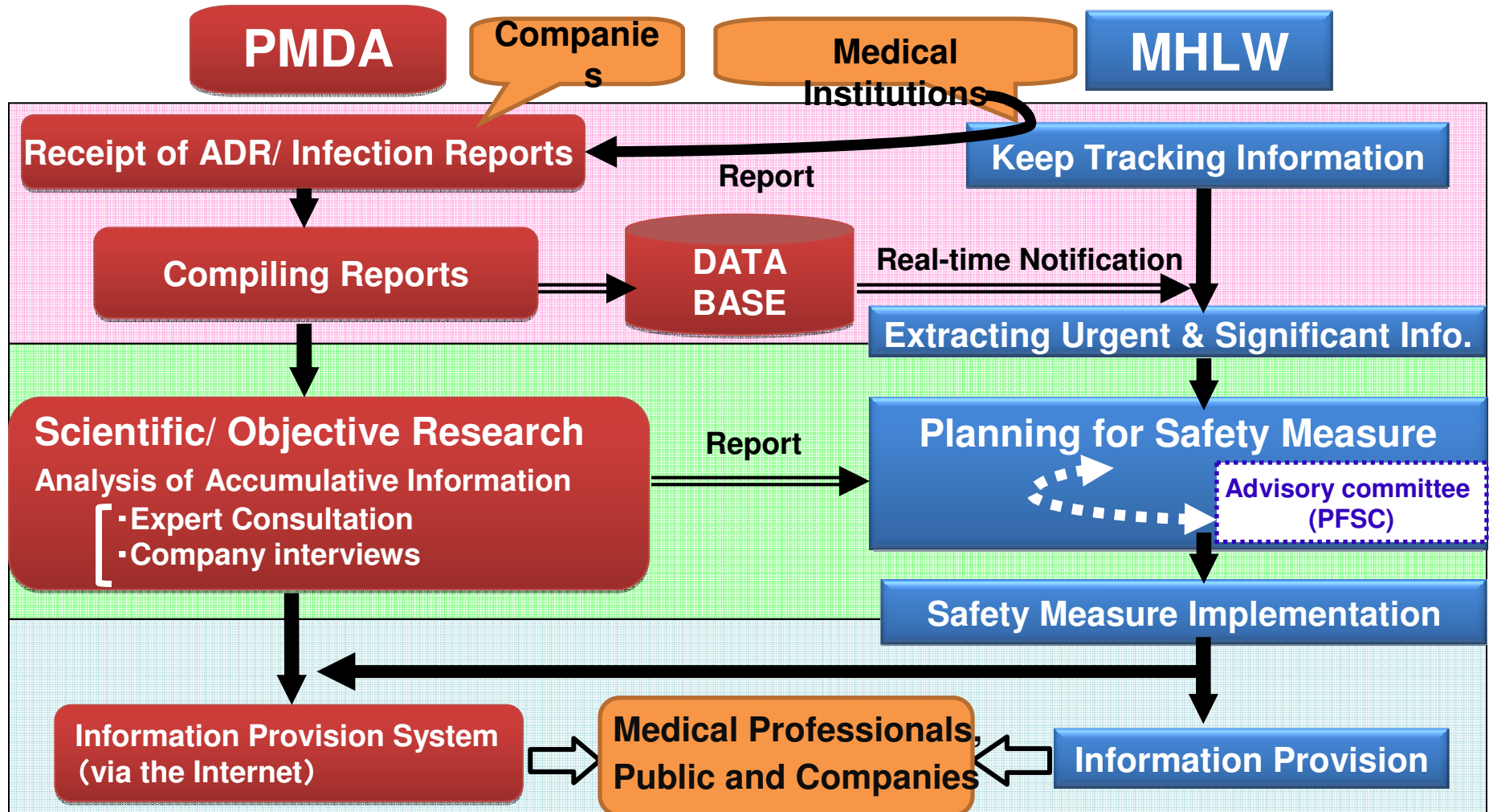
- Organization of PMDA
  - Pillars
  - Cooperation with Ministry of Health, Labour and Welfare (MHLW)
- Post-marketing activities in Japan
  - GVP
  - ADR report
  - EPPV
  - Re-examination
- Current situation of PhV plan & Risk Management
  - Risk Management Option in Japan
  - New Risk Management System in Japan

## **PMDA's Three Work Areas**

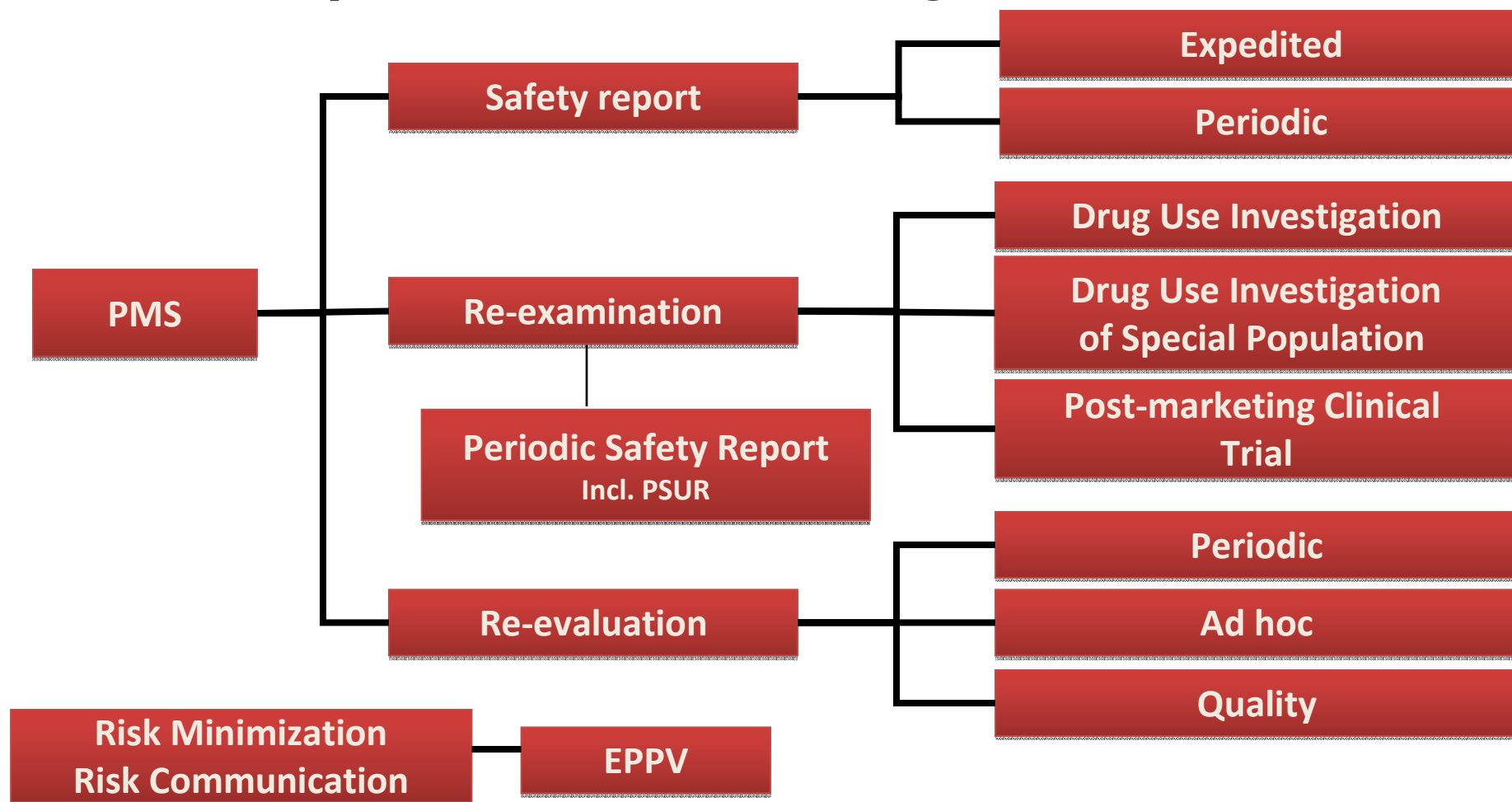


# Pharmacovigilance Operation Flowchart

## - MHLW/PMDA Cooperation -



# Japan's Post-marketing Activities



## Good Vigilance Practice for Prescription Drug

- Requirements for Personnel & Organization
  - Creation of Safety Management Department
  - Appointment of Safety Management Supervisor
- What GVP requires MAHs to do
  - Collection & Analysis of Safety Information
  - Planning & Execution of Safety Measures
  - Planning & Execution of EPPV\*
  - In-house Inspection
  - Training/Education of Relevant Staff
  - Preparation of SOPs on the above

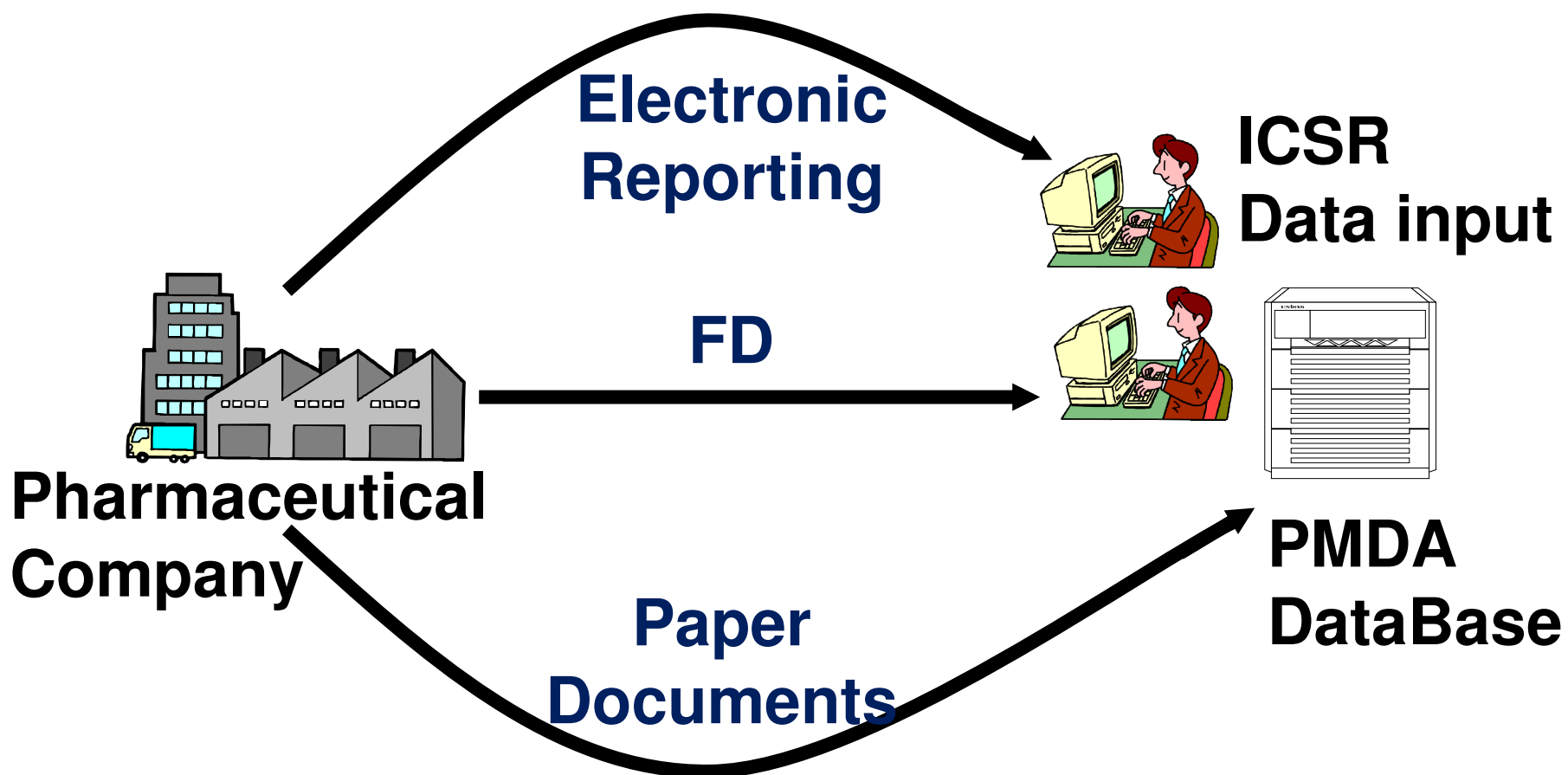
\*Early Phase Post-marketing Vigilance

## GVP Requirements

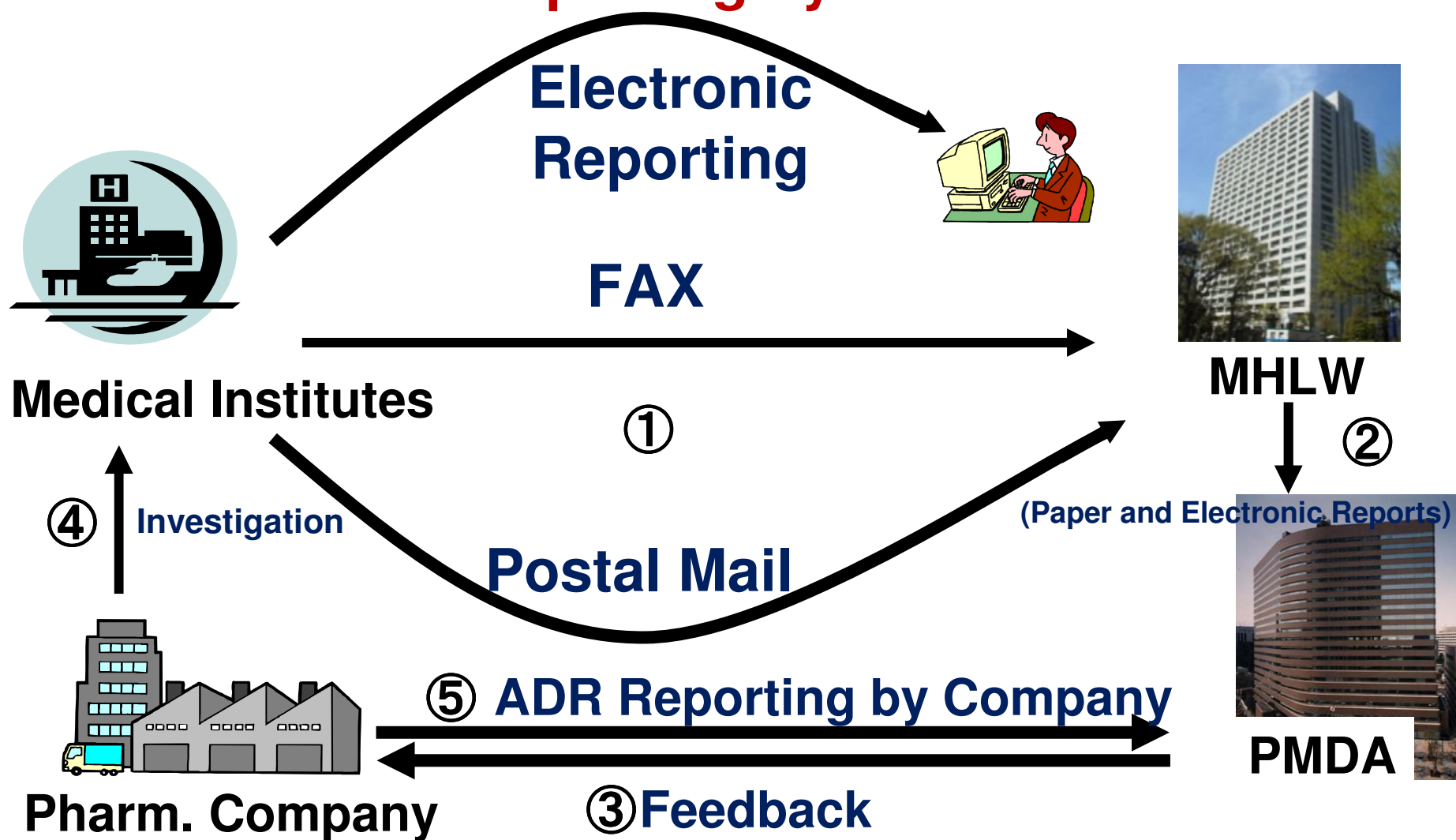
	Prescription Drugs	Drugs other than Prescription ones	Quasi Drugs, Cosmetics etc.
<b>Organization and Personnel</b>	<ul style="list-style-type: none"> <li>a) Creation of Safety Management Department</li> <li>b) Qualified Safety Management Supervisor (over 3 yrs experience)</li> </ul>	<ul style="list-style-type: none"> <li>a) Not mandatory</li> <li>b) Safety Management Supervisor (no qualification required)</li> </ul>	Same as on the left
<b>SOP etc.</b>	Preparation of SOPs	Same as on the left	Not mandatory
<b>Collection of Information for Safety Management</b>	<ul style="list-style-type: none"> <li>a) Health Care Professionals</li> <li>b) Scientific Papers</li> <li>c) MHLW, PMDA, etc.</li> <li>d) Foreign authorities, etc.</li> <li>e) Other Companies</li> <li>f) Others</li> </ul>	Same as on the left	b) and f) are required for Quasi- Drugs and Cosmetics
<b>In-house Inspection, Education/Training</b>	Required	Same as on the left	Not mandatory



## ADR Reporting by Companies



## ADR Reporting by HCPs



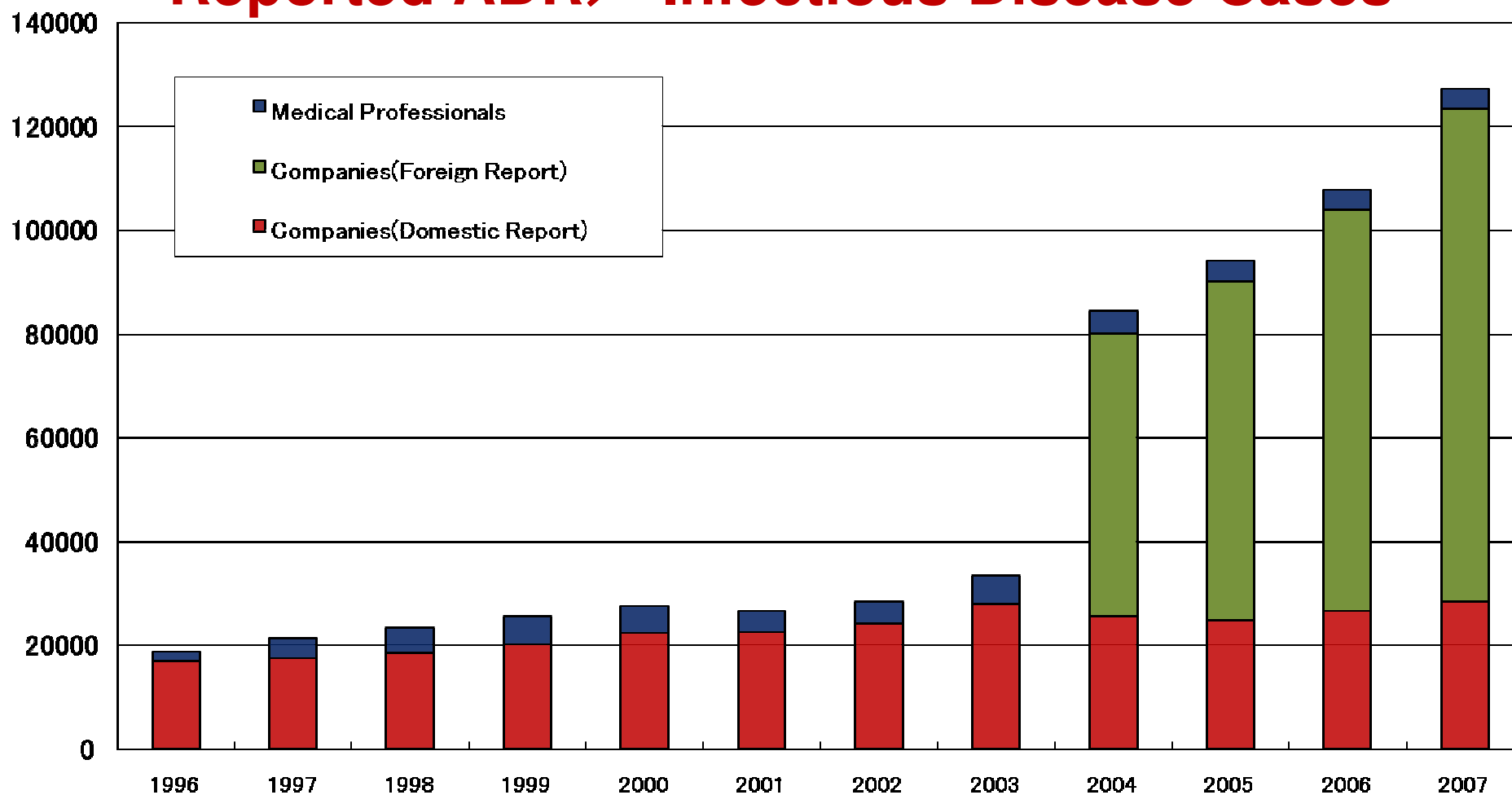
## ADR Reporting Rule

Seriousness	Predictability	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 PAL)
- No timeframe defined for HCP reporting

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

## Reported ADR / Infectious Disease Cases



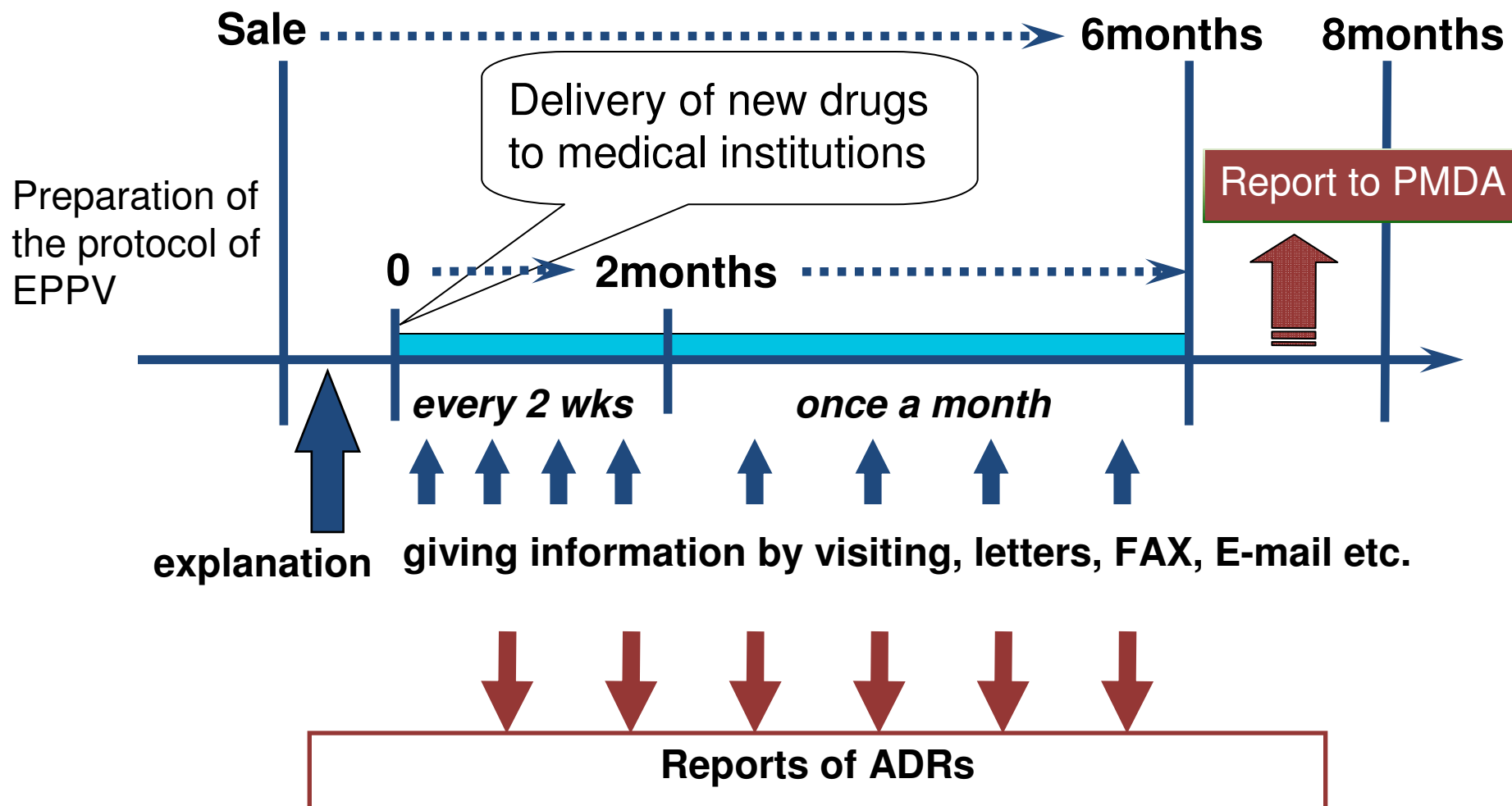
Note :Foreign reports by drug makers are not included in and before FY03'.  
Annual Cumulative Reports are not included.

## **Early Post-Marketing Phase Vigilance : EPPV**

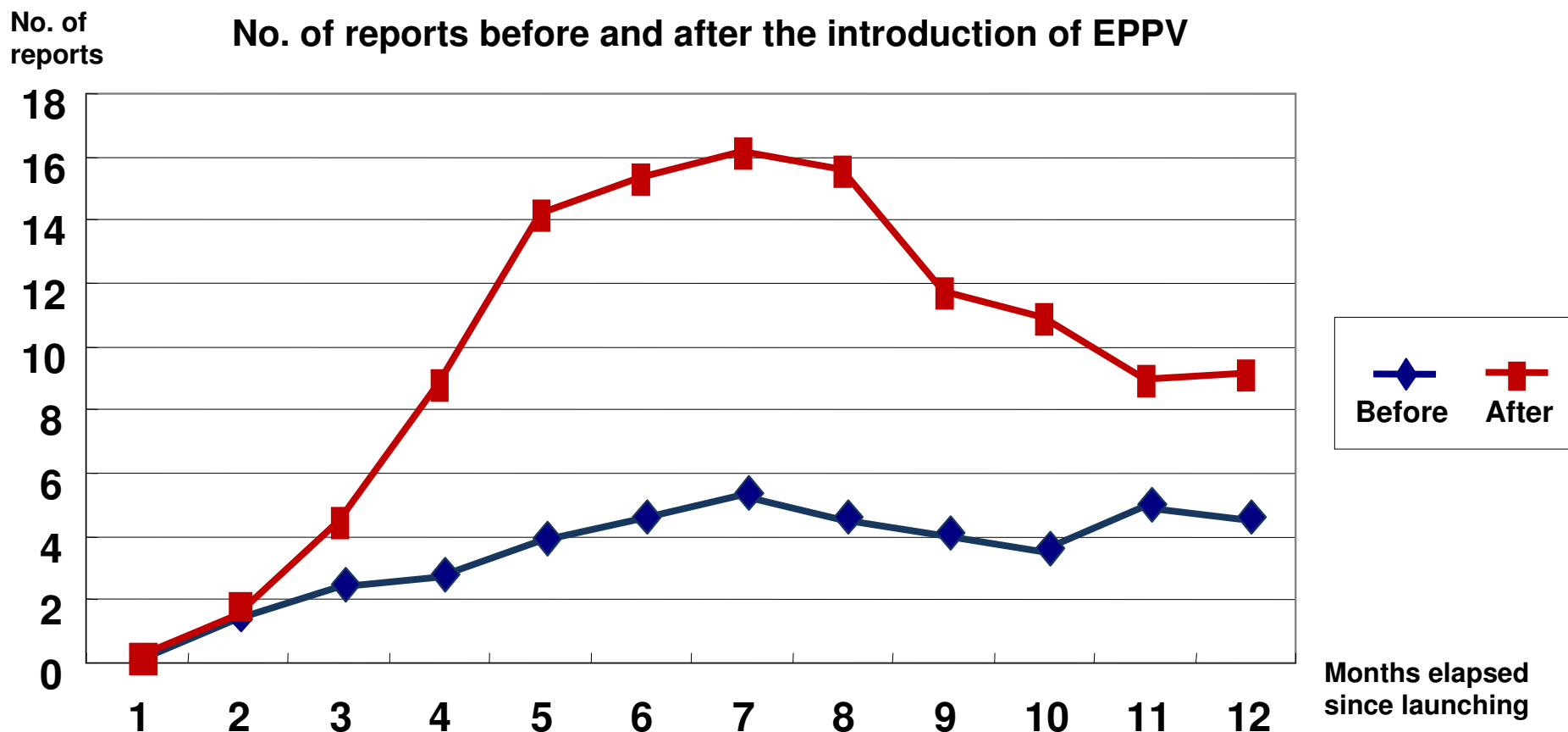
Enforced on Oct 1, 2001

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.

## Early Post-Marketing Phase Vigilance : EPPV



## Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV (average per month)



EPPV was introduced in October 2001.

Number of before-EPPV is based on 30 new active ingredients launched between Apr. 2000 and Mar. 2001.

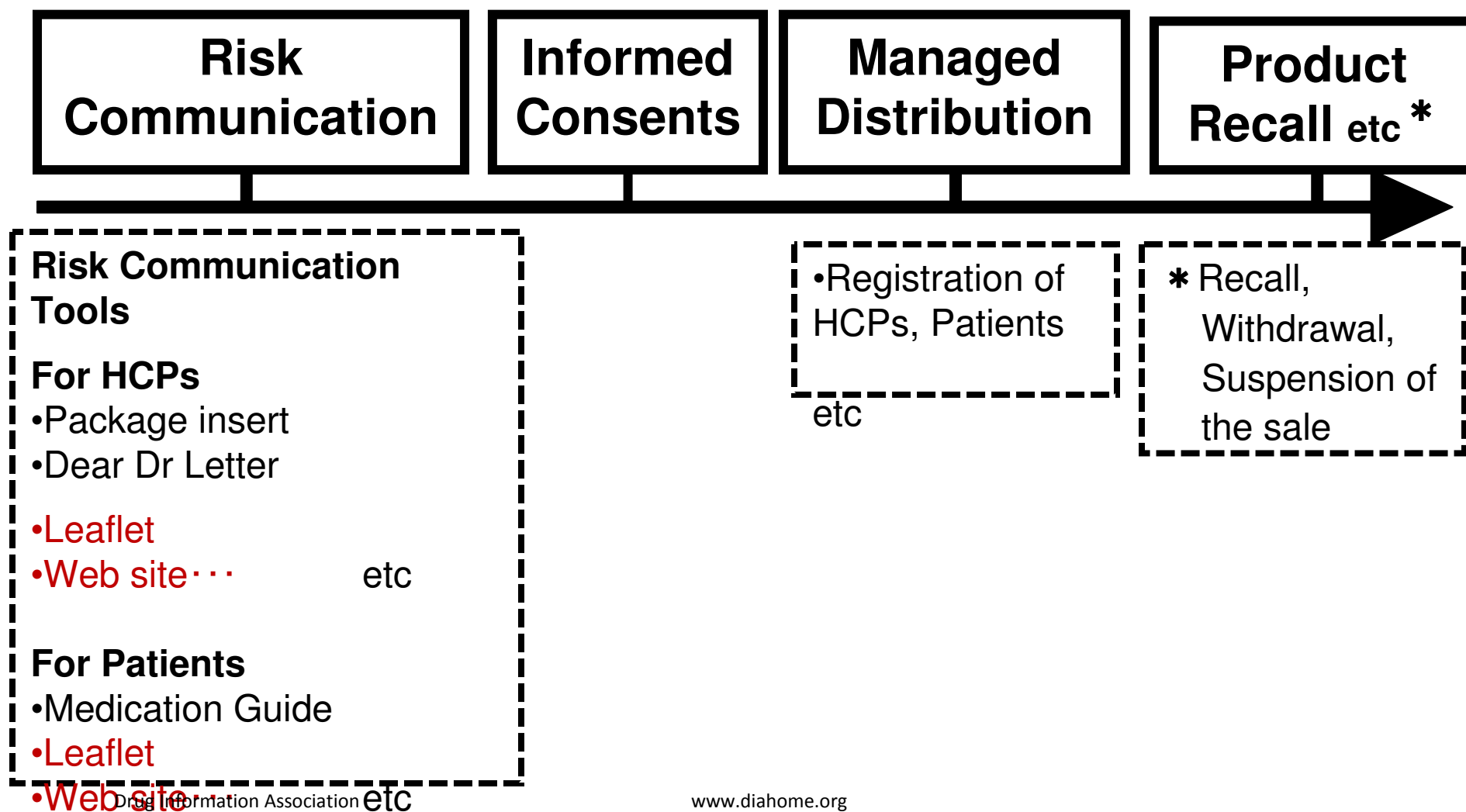
Number of after-EPPV is based on 22 new active ingredients launched between Oct. 2001 and Oct. 2002.

## Re-examination

- The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval.
- The surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP (GPSP), GCP or GLP depending on their objective.
- The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs.
  - Reexamination period of drugs containing new active ingredients: 8 years (maximum 10 years) 0



## Risk Management Options in Japan



## Example . Thalidomide

### **T.E.R.M.S** : Thalidomide Educations and Risk Management System

- Goal
    - To minimize the risk of Thalidomide exposure during pregnancy in women
  - Elements
    - Education
    - Managed Distribution
      - Registration of Physicians, Pharmacists, Patients
    - Periodic Pregnancy Test
    - Periodic Confirmation of Understanding
- ... etc

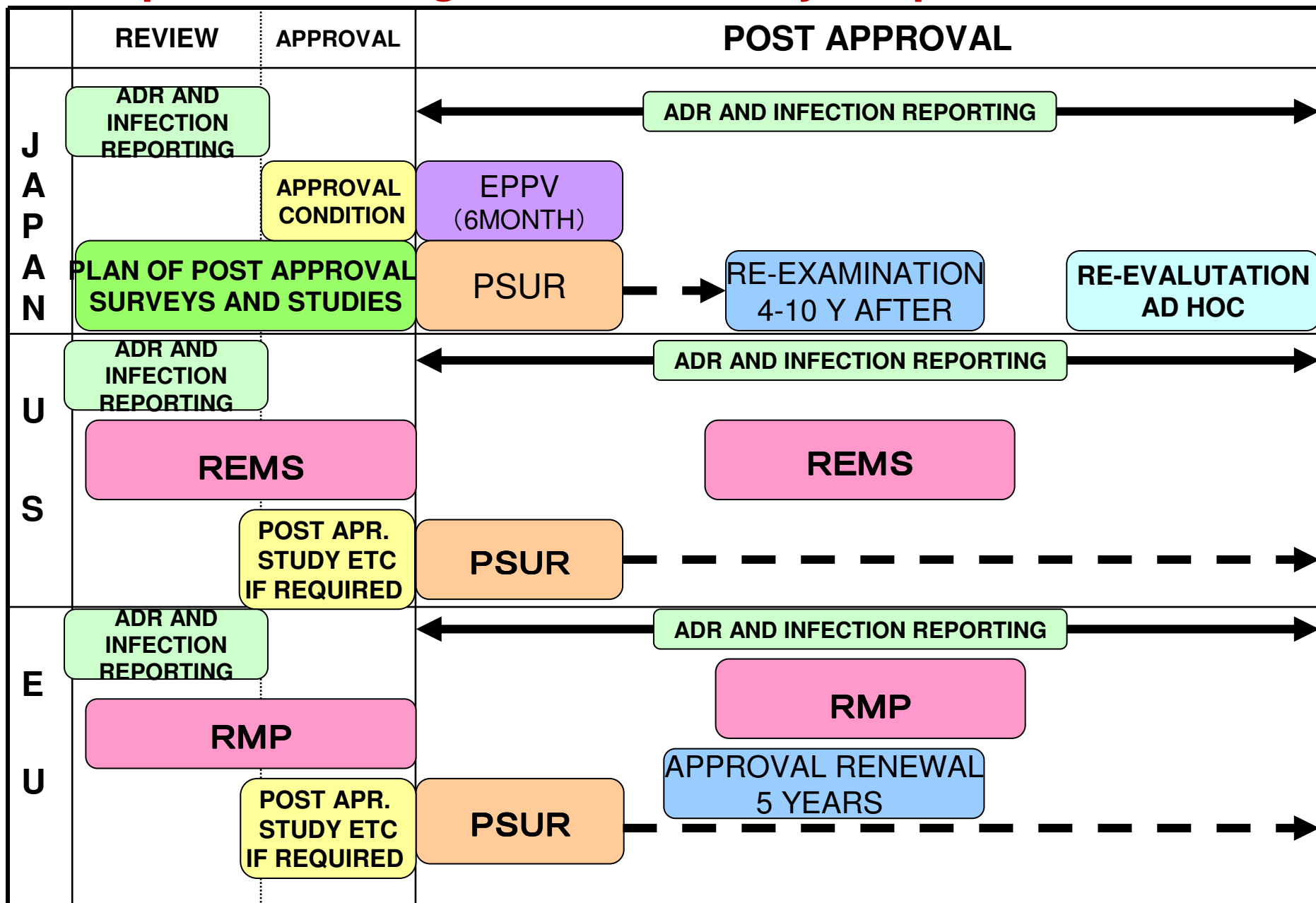
## Risk Management on Review

- Brand name
  - To avoid misuse
- Package
  - To avoid misuse
- Risk communication tool
  - For healthcare professionals & patients
  - Package insert, leaflet, website ...etc.
- Other Risk Management Option
  - Informed Consents
  - Managed Distribution

## PhV Plan and J-NDA

- Pharmacovigilance plan is a component of CTD ( if the plan has been prepared)
  - PMDA recommend to prepare PhV plan until NDA submission through consultation
- PhV is an important discussion point under review
  - Description on review report
- Monitor and review the data
  - Submission of a local periodic report with PSUR

# Comparison of Regulation on Safety : Japan, US and EU



## **New Risk Management System in Japan**

- Seamless evaluation of risk & benefit balance from FIH to post-approval
  - Through lifecycle of a drug
- Early detection of safety signal
  - Accumulation of information
  - Seamless assessment
  - Development of New Methods
- Make Timely and Appropriate Safety Actions to Minimize Risks

## Risk Manager System

- Purpose of RM System
  - PMDA will collect, compile, evaluate and manage all the safety information on new drugs from development to post approval stages to give guidance and advice to companies on PMS at early stage and in a timely manner.
- PMDA RM System will help the life cycle management of drugs in safety aspect
  - Identification of safety profile from development stage
  - Guidance and advice on designing post-approval surveys, studies and other activities at review stage
  - Evaluation and advice on outcome and problems of post-approval surveys, studies and other activities etc

## **Participation of Safety Team in Review Process under New Risk Management System (Future)**

- **Collection, compilation, assessment and follow up of all the safety information related to a drug**
  - Non-clinical and clinical data (pre- and post-approval )
  - ADR DB + epidemiological data
  - History of safety actions (pre-caution revision, Dear HCP letters etc.)
  - Related literatures
- **More scientific and active interaction and discussion with review team**
  - Creation of safety assessment team corresponding to review team(s)
  - Team of different expertise
  - Discussions based on scientific evidence (epidemiology data, ADR DB analysis)



## Participation of Safety Team in Review Process under New Risk Management System (Future)(cont'd)

- **Active participation in review process**
  - Participation in review process from clinical trial consultation to make contribution to clinical safety assessment
  - More responsibility for assessment of post approval survey and studies including PSUR and re-examination Non-clinical and clinical data (pre- and post-approval )
- **Identification of safety profile of new drug and its incorporation in review report**
  - Identified risks that require further evaluation
  - Potential risks that require further evaluation

## **Participation of Safety Team in Review Process under New Risk Management System (Future)(cont'd)**

- **Guidance and advice on drafting PMS plan attached to CTD**
  - Starting discussion at early stage of review process (even at clinical trial consultation)
  - Concrete design of post approval surveys/studies and PMS plan at approval
- **Follow up of PMS plan at post approval stage**
  - Assessment of results of post approval surveys and studies
  - Assisting evaluation and decision on result of approval conditions
  - More involvement in EPPV, PSUR, Re-examination

***Pilot study of new system is starting in selected stages of review process from 2009.7***

## Possible Benefits of New Risk Management System

- Efficient preparation of effective PMS plan
- Consistent safety management throughout lifecycle both in PMDA and companies
- Preventing withdrawal of new drugs (at early stage)
- Completion of lifecycle of a drug
- Protection of patients especially at early stage of marketing

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**Thank you for your kind attention!**