POST-MARKETING SAFETY MEASURES IN JAPAN

East Asian Pharmaceutical Regulatory Symposium 2008,Tokyo（東京）

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April, 2008

Overview of PMDA

NAME: Pharmaceuticals and Medical Devices Agency

INAUGURATION : April 2004

MANAGEMENT: ・Effective operation under "Medium Term Plan" for 5 years' activities

・Subject to regular evaluation of performance by the Evaluation Committee organized by MHLW

FINANCE: Corporate accounting method and subdivided accounts according to the functions

Financial resources:

- User fee (Review and Inspection)
- Contribution Funds (Post-marketing, Relief)
- Appropriation from Gov. budget

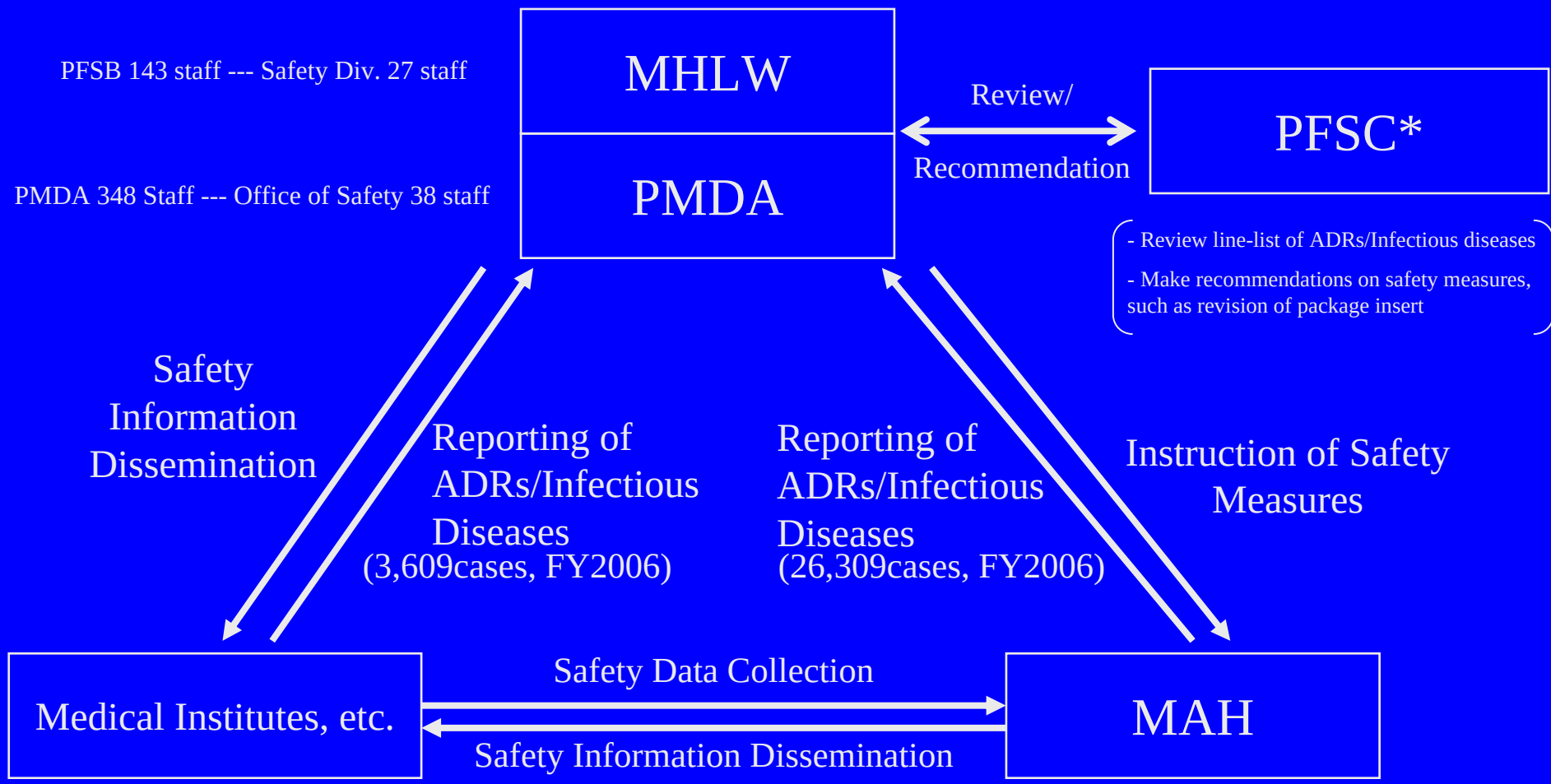
Organization of PMDA

3 Pillars of Safety Operations

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**

Post-Marketing Safety Scheme



* Pharmaceutical and Food Safety Council

Organization of Ministry of Health,Labour and Welfare

Ministry of Health, Labour and Welfare

- Social Insurance Agency
- Ministry Proper
  - Minister's Secretariat
  - Health Policy Bureau
  - Health Service Bureau
  - **Pharmaceutical and Food Safety Bureau (PFSB)** **143 staff**
    - General Affairs Division
    - Evaluation and Licensing Division
    - Safety Division **27 staff**
    - Compliance and Narcotics Division
    - Blood and Blood Products Division
  - Social Welfare and War Victim's Relief Bureau
  - Health and Welfare Bureau for the Elderly
  - Equal Employment, Children, and Families Bureau
  - Insurance Bureau
  - Pension Bureau
  - Director-General for Policy Planning and Evaluation

FY2008 Budget for Pharmaceuticals

(Pharmaceutical and Food Safety Bureau, MHLW)

- FY2008 Budget ¥8,882mil./$88.9mil.
  (Safety Div. ¥249.6mil./$2.5mil)

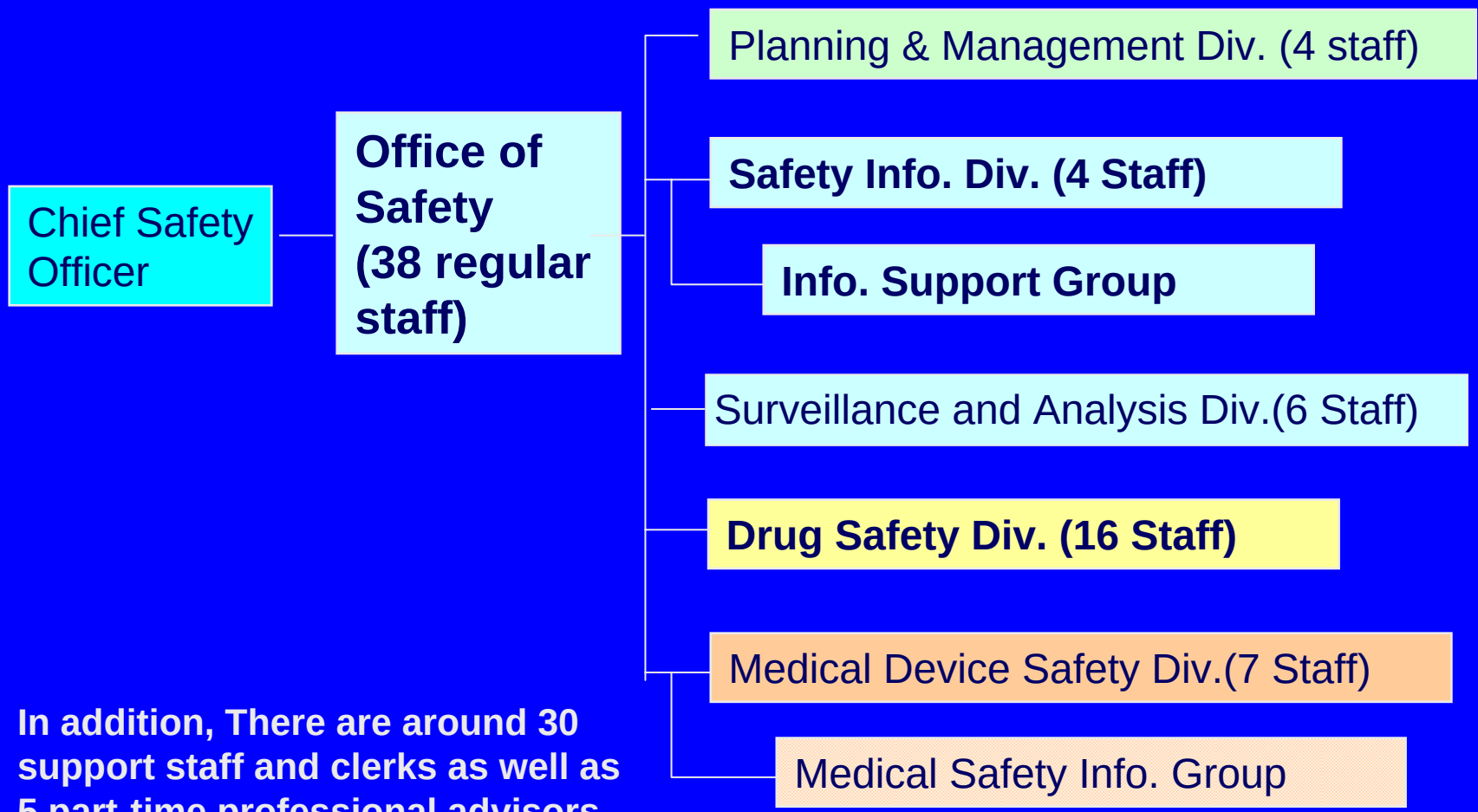
- FY2007 Budget ¥8,916mil./$83.5mil.
  (Safety Div. ¥243.4mil./$2.4mil)

  – Difference △¥34mil./$0.32mil.

  – FY2008/FY2007 99.6%

NOTE: Japanese FY covers the period of Apr. 1 through Mar. 31.
$1=¥99.95 (as of Mar.19, 2008)

PMDA: Office of Safety --*Organization chart*--



In addition, There are around 30 support staff and clerks as well as 5 part-time professional advisors (MD and statistician).

FY2008 Budget for Pharmaceuticals

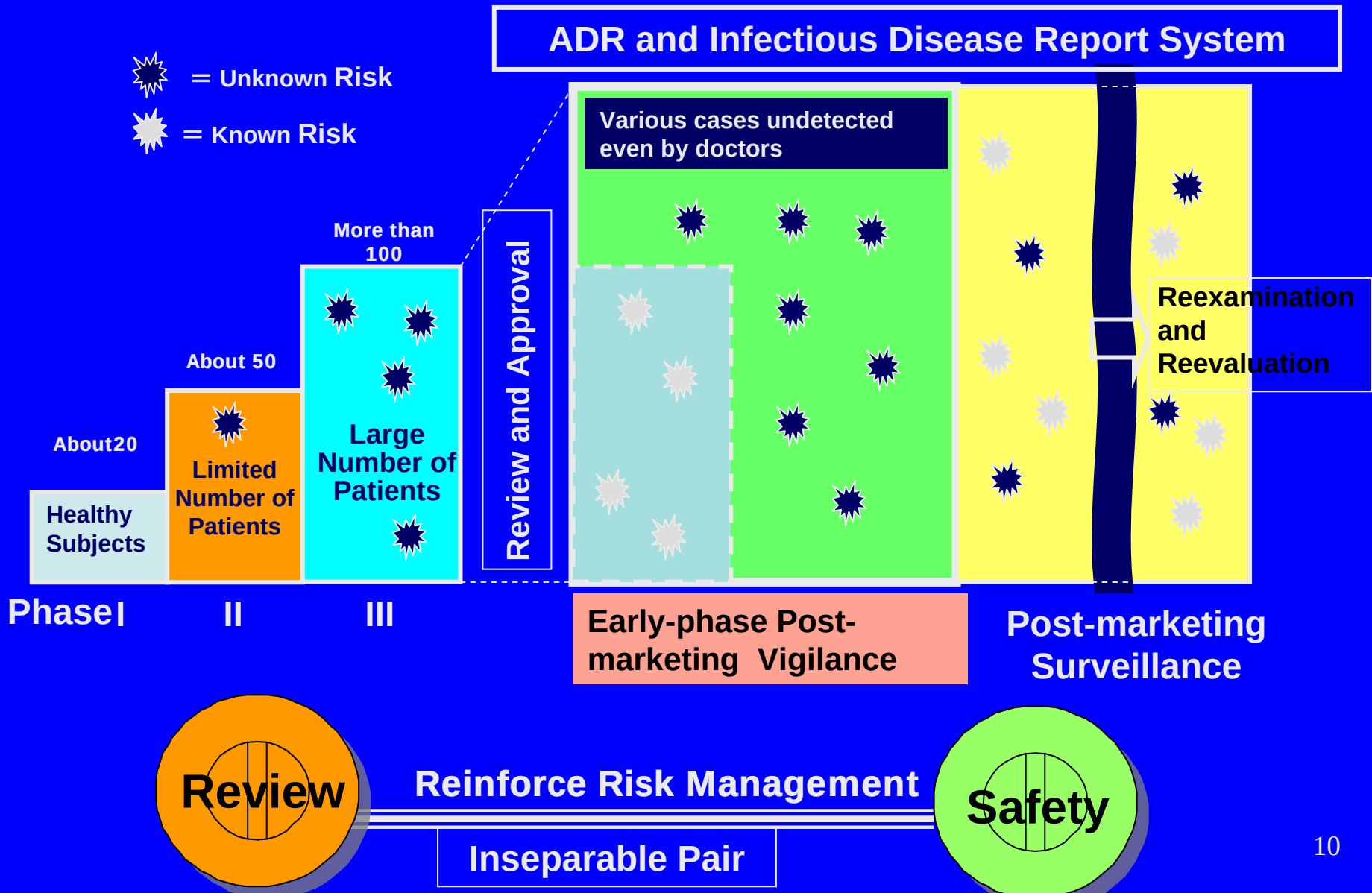
(Office of Safety, PMDA)

- FY2008 income from MAHs est. ¥ 1,280 Mil.
- FY2008 MHLW subsidy est. ¥ 252 Mil.
- Others est. ¥ 4 Mil.
- (total ¥ 1,536 Mil.)

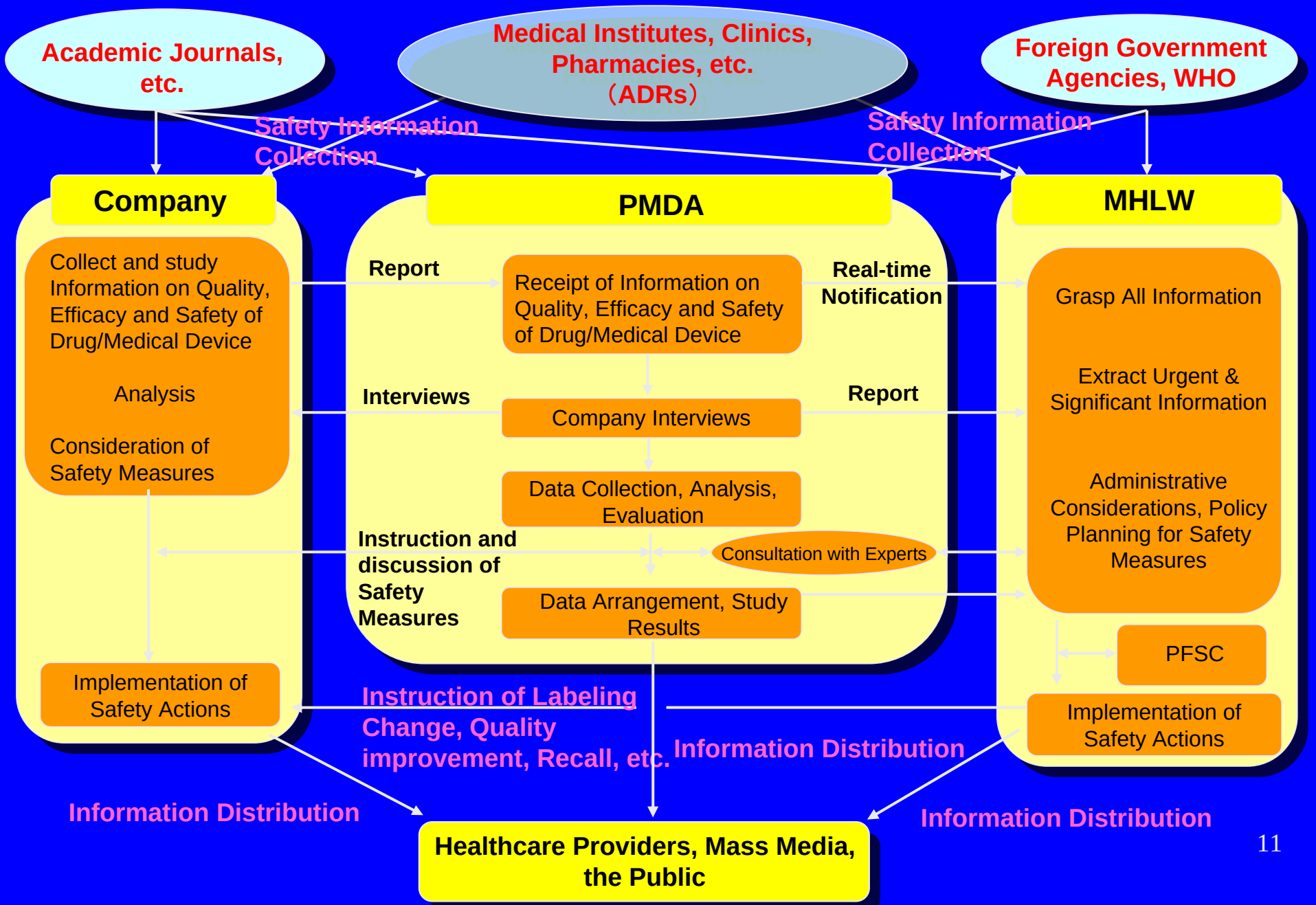
- FY2007 income from MAHs ¥ 1263 Mil.
- FY2007 MHLW subsidy ¥ 255 Mil.
- Others ¥ 5 Mil.
- (total ¥ 1,523 Mil.)

- Covering budget for Medical Devices Safety and partially for Quality (GMP/QMS and standard development)

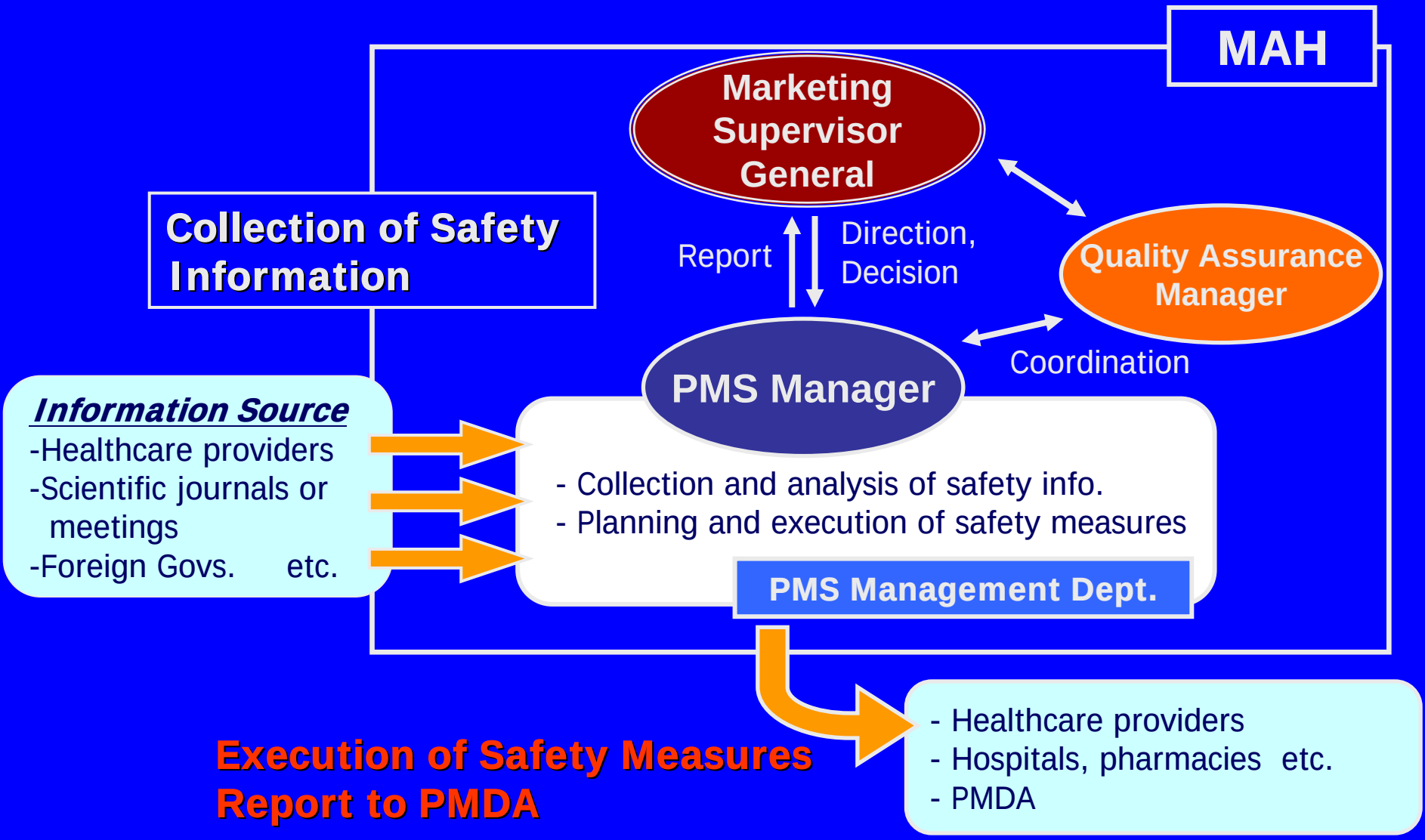
For “Safer” Drugs / Devices



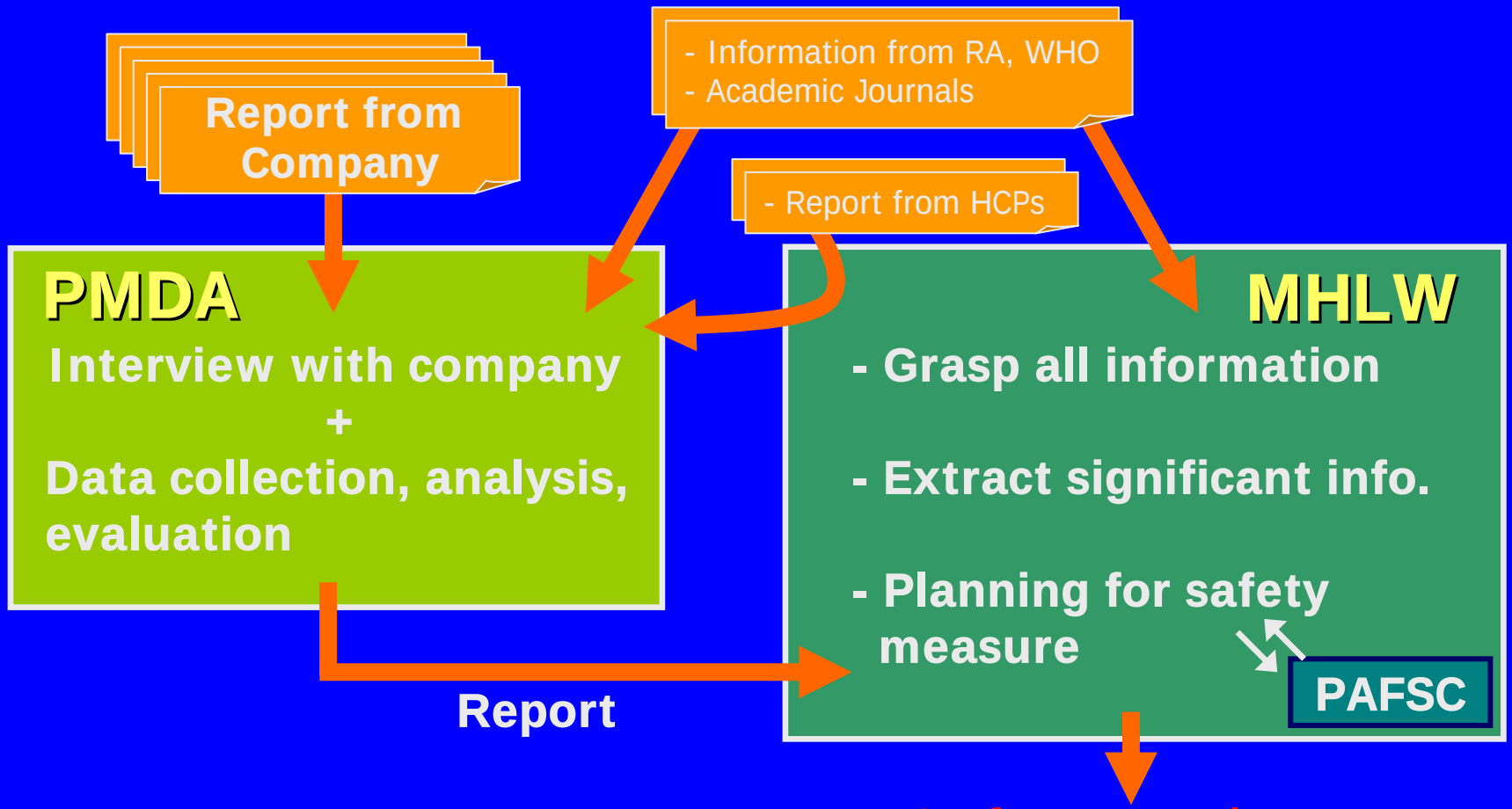
Vigilance Operation Flowchart



Outline of Information Flow (1)
(MAH)

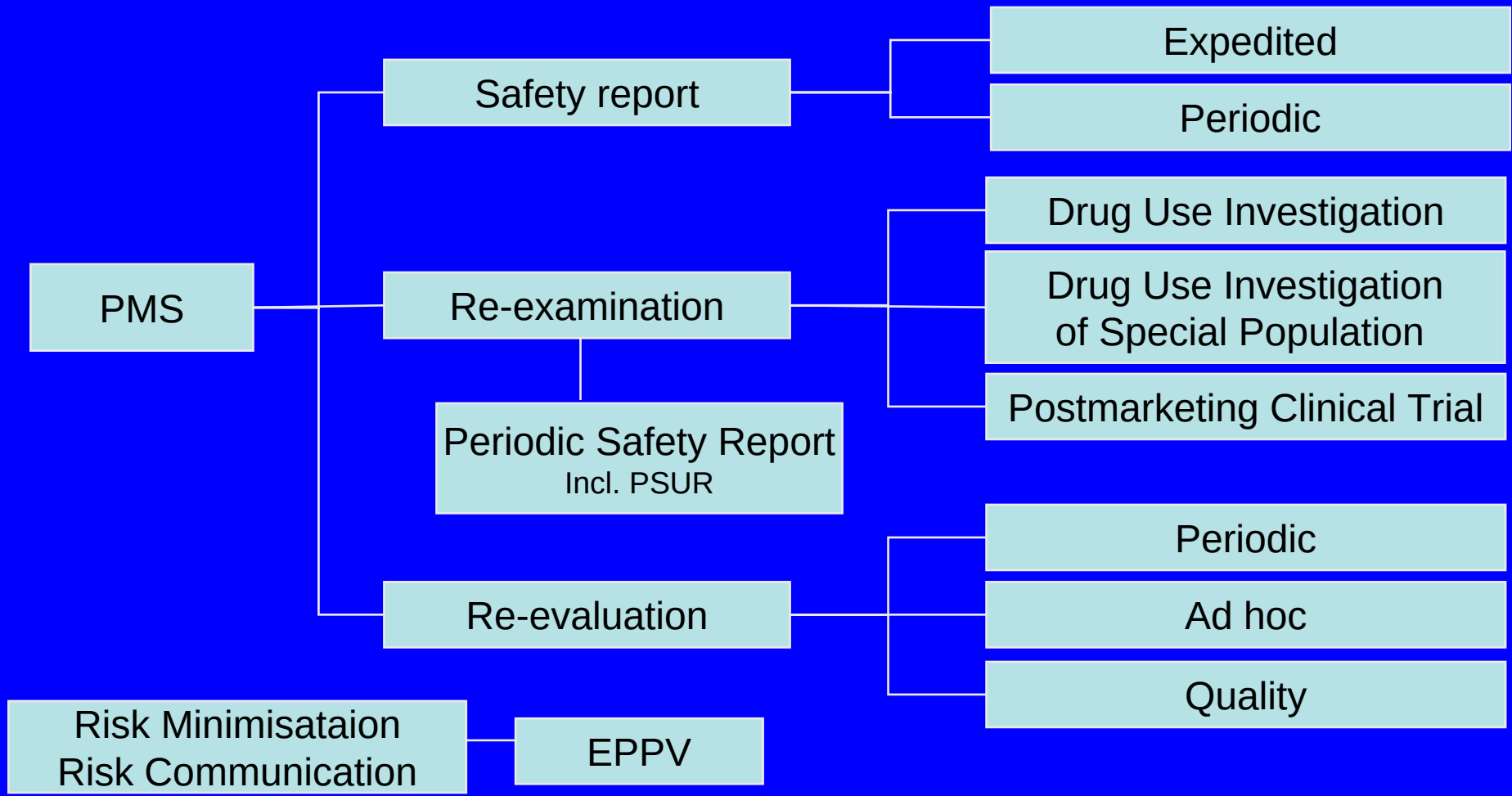


Outline of Information Flow (2)

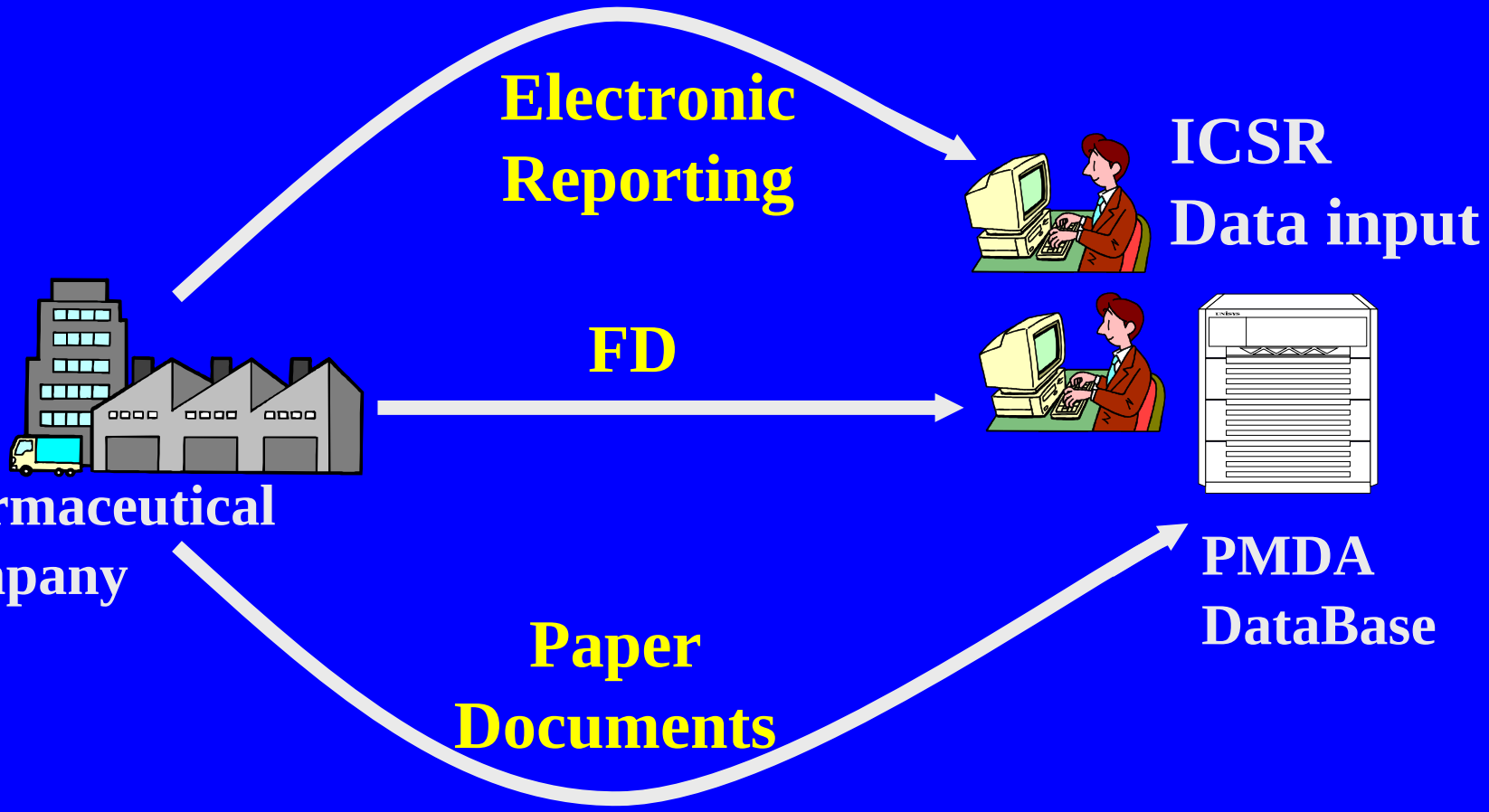


RA: Regulatory Authority

JP Postmarketing activities



ADR Reporting by MAH



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

ADR Report from HCP

- 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
  - detect occurrence of any disease suspected to be caused by adverse reactions
  - confirm that it is necessary to prevent occurrence or spread of hazards

ADR Reporting by Med. Inst.

Medical Institutes

Electronic Reporting

FAX

①

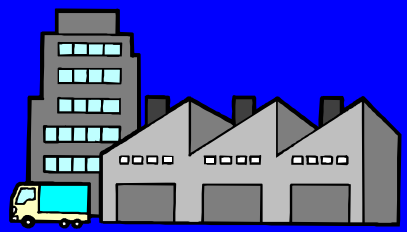
Postal Mail

MHLW

② **(Paper and Electronic Reports)**

PMDA

④ **Investigation**



Pharm. Company

⑤ ADR Reporting by Company

③ Feedback

ADR Reporting Rule (Drug)

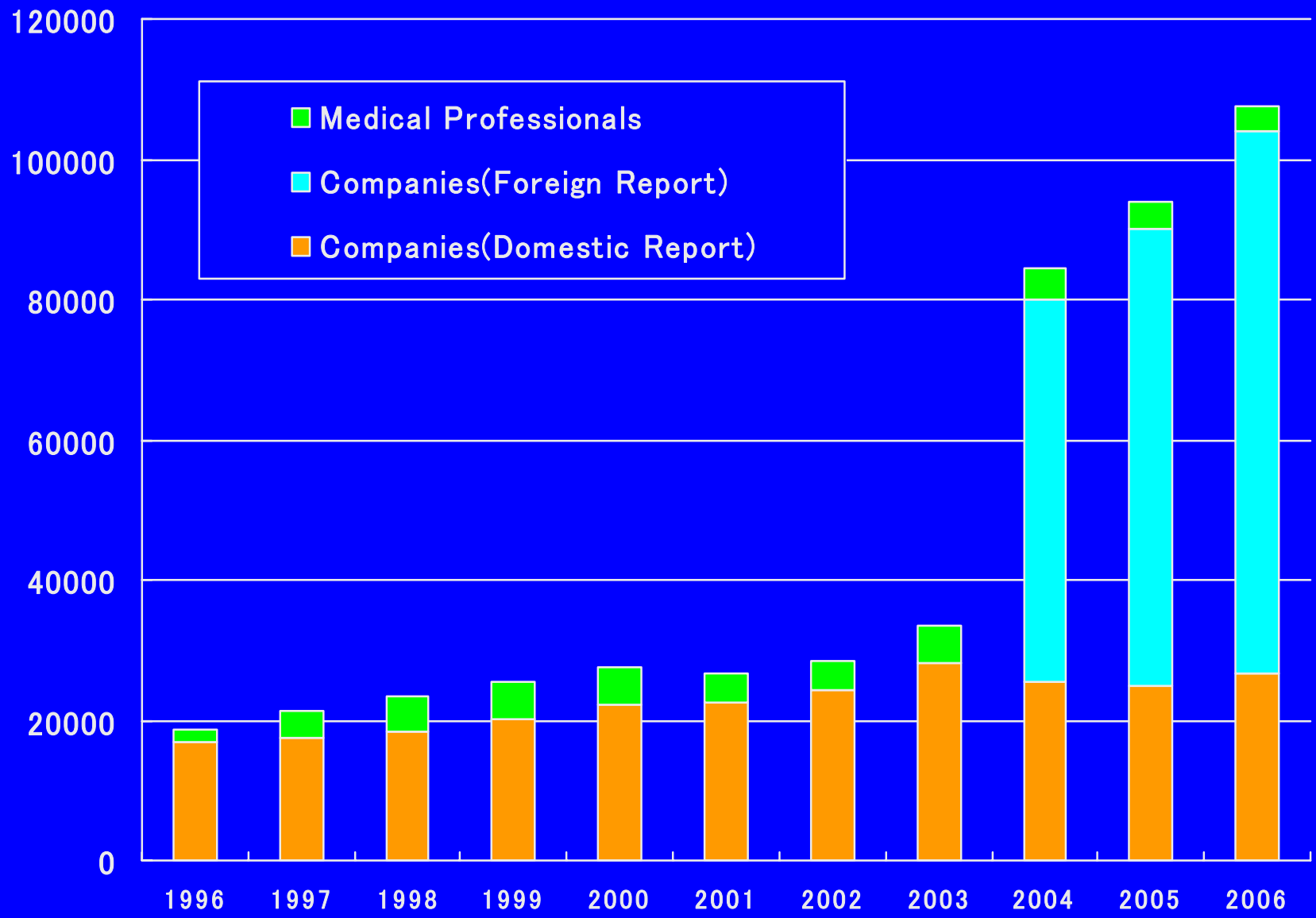
Serious-ness	predictability	Time frame of report to PMDA
Serious	Not predictable	**15 days**
	Predictable	- Death etc.* **15 days** - Others **30 days**
Not serious	Not predictable	**Annually** **(Annual Cumulative Report)**
	Predictable	-

- 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)

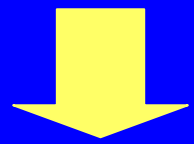
Reported ADR／ Infectious Disease Cases



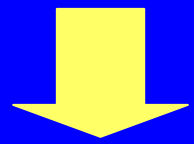
Note :Foreign reports by drug makers are not included in and before FY03'.

Course of Post-marketing Safety Measures

- After-the-Fact Measures (Measures taken after the incidence of ADR)



- Prognostic Measures (Measures taken for drugs/patients with possible incidence of ADR)



- Preventive Measures (Measures taken for high-risk situation (high-risk patients etc.))

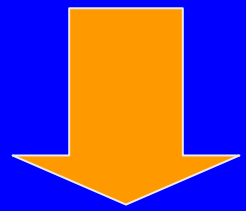
Safety Measures

- Revision of a package insert
- Recall/withdrawal, suspension of the sale
- Improvement of the products to prevent reoccurrence of the AE

- Administrative Instruction/Advice by PMDA/MHLW to MAH to revise safety information in package insert; “Precautions for Use,” “Boxed Warning,” etc.
- Dissemination of information on ADR/AE incidents and measures against them (e.g., publication of “Pharmaceuticals and Medical Devices Safety Information” and “Urgent Safety Information” by MHLW) etc.

Early Phase Post-marketing Vigilance (EPPV)

- Promote proper use of new drugs
- Detect serious ADRs earlier
- Take safety measures quickly



- Protect patients from ADRs

Early Post-Marketing Phase Vigilance : EPPV

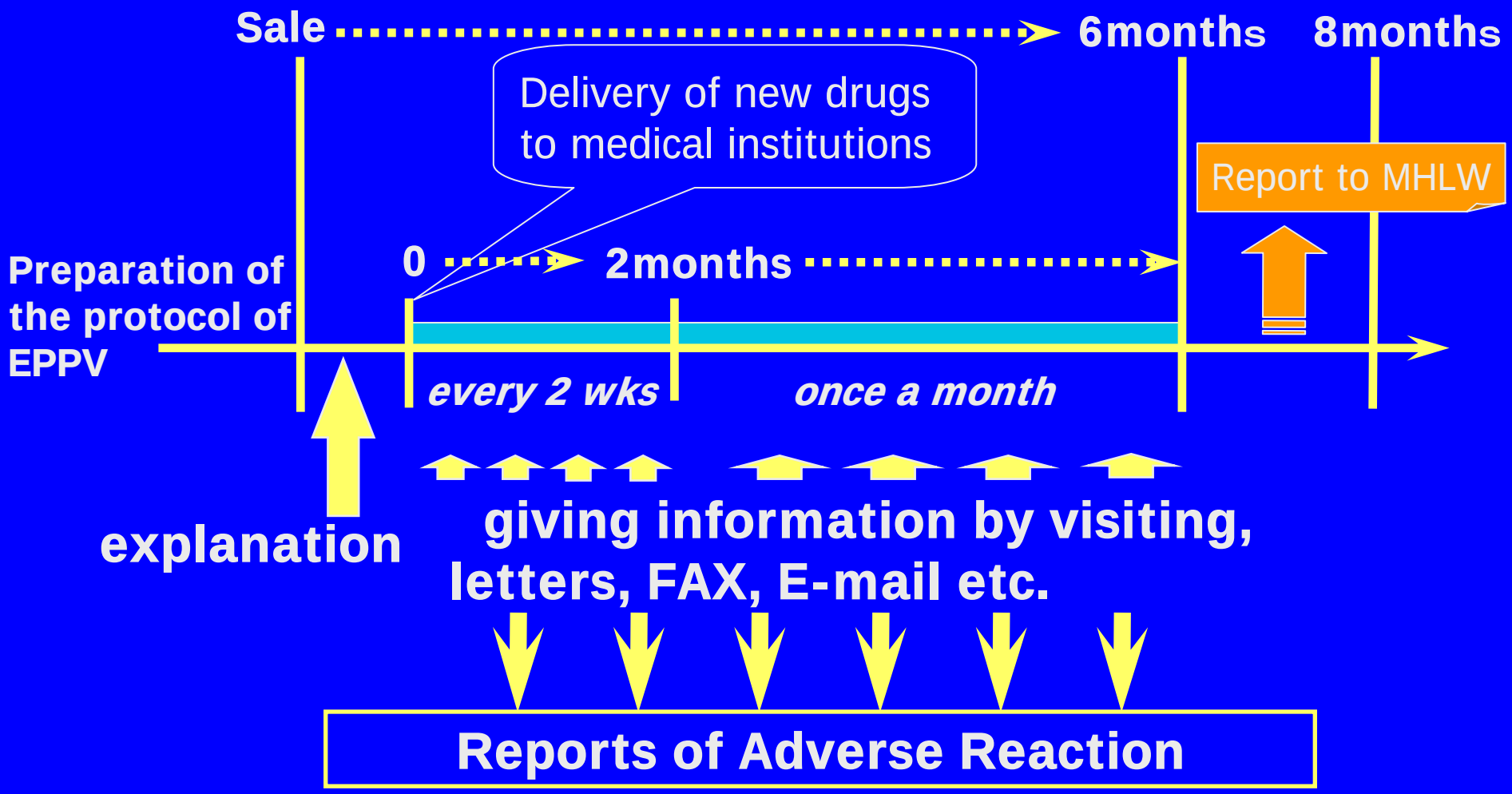
Enforced on Oct 1, 2001

1. To ensure necessary information for appropriate use (contraindication, careful administration etc) is explained to the medical institutions 2 weeks before delivery.

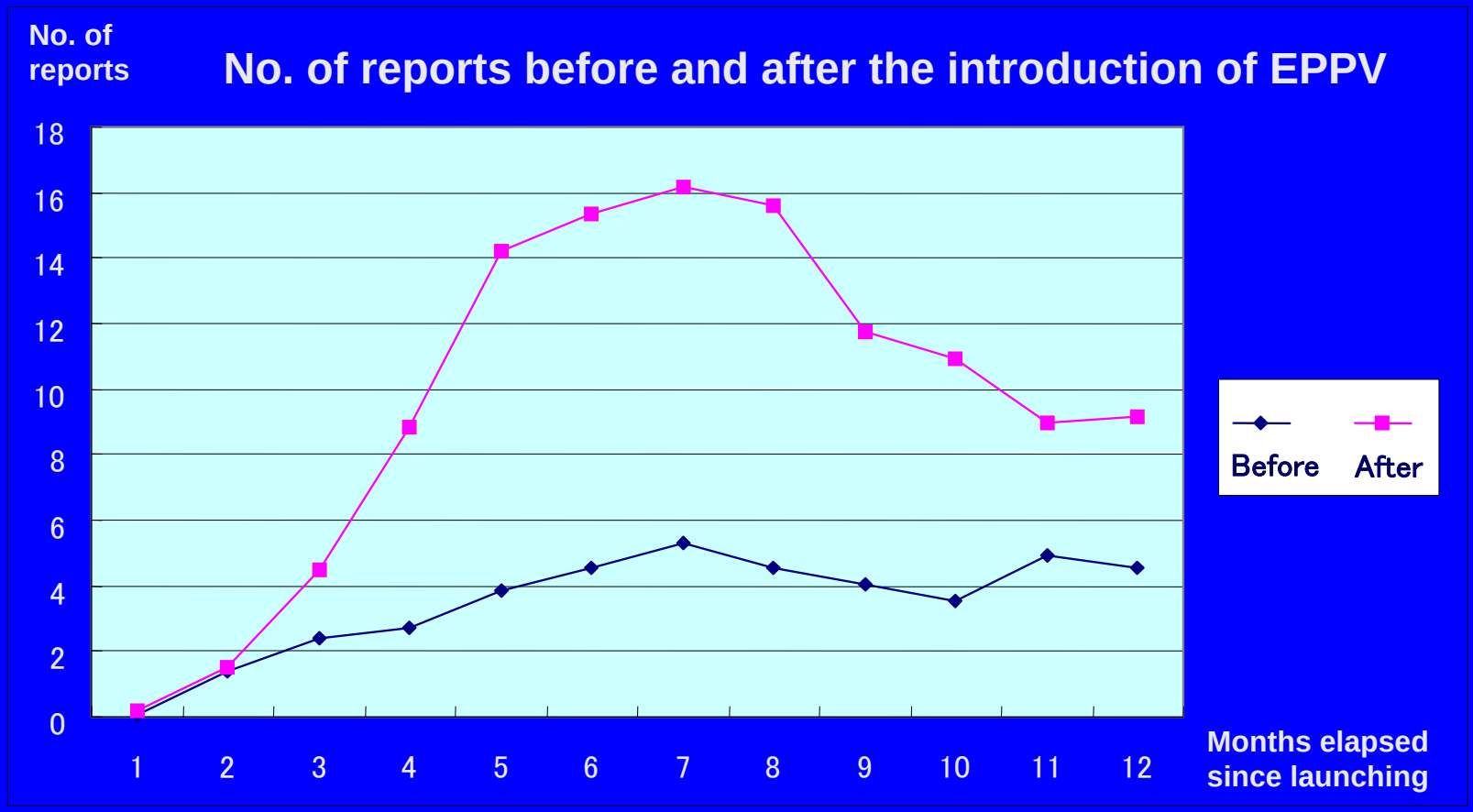
2. To request medical institutions to use the drugs carefully and report serious ADRs, if occurred, immediately to pharmaceutical companies

3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.

Early Phase Post-marketing Vigilance, EPPV



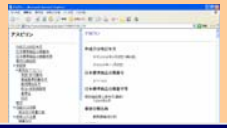
Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV (average per month)



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.

PMDA Information Web site

For Health Care Professionals



Package Inserts for Pharmaceuticals or Medical Devices

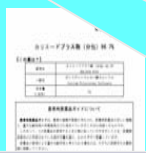
Reports of suspected adverse events or suspected Defect s

Doctor letters and Safety Information

Information on approvals of Drugs/Devices

Recalls

Information about the free mail system provided by



Pharmaceutical Guidance for patients

For Patients and the general public

Q&A on Pharmaceutical

Consultation on Drugs /Devices

Measures against the Serious Adverse Events

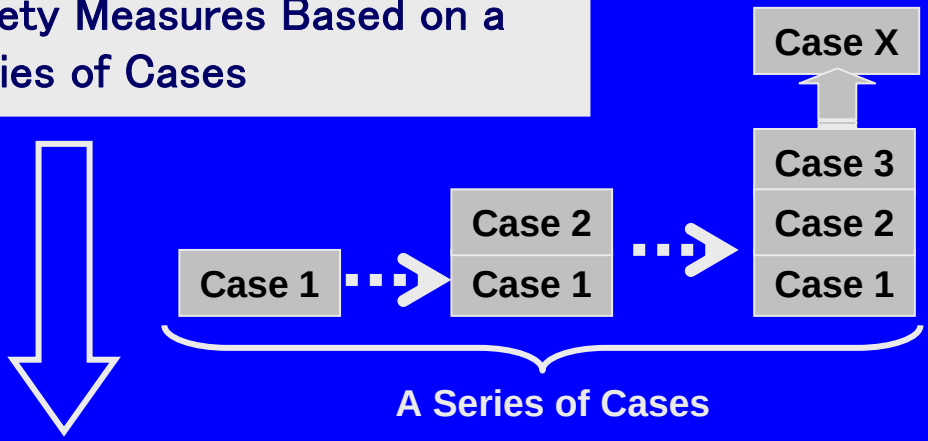
Package Inserts for OTC Drugs

Information distributed by MHLW/PMDA

- Revision of package insert by MHLW
- Documents of Committees/Working groups available on the MHLW website (Japanese only)
- Pharmaceuticals and Medical Devices Safety Information by MHLW (PMDSI English version to be available by PMDA)
- Pharmaceuticals and Medical Devices Information Website (PMDInfoWeb, Japanese only) by PMDA
  - Package insert, guidance for patients, rules of ADR reporting, pieces of ICSRs and etc.

Improvement of Safety Measures

Safety Measures Based on a Series of Cases



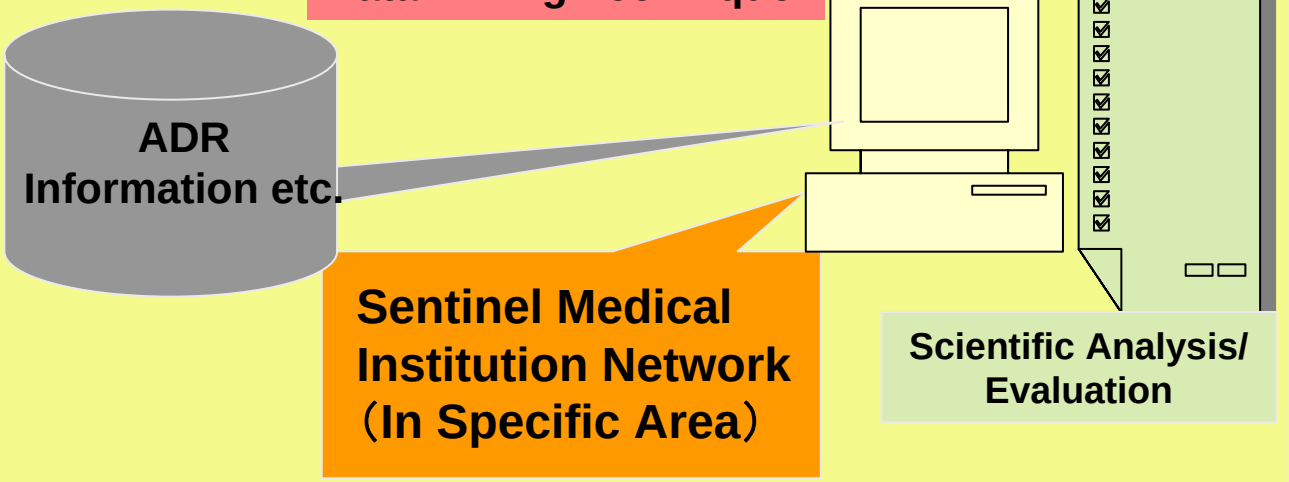
MHLW
Implementation of Safety Measures

Prospective/ Preventive Safety Measures

PMDA

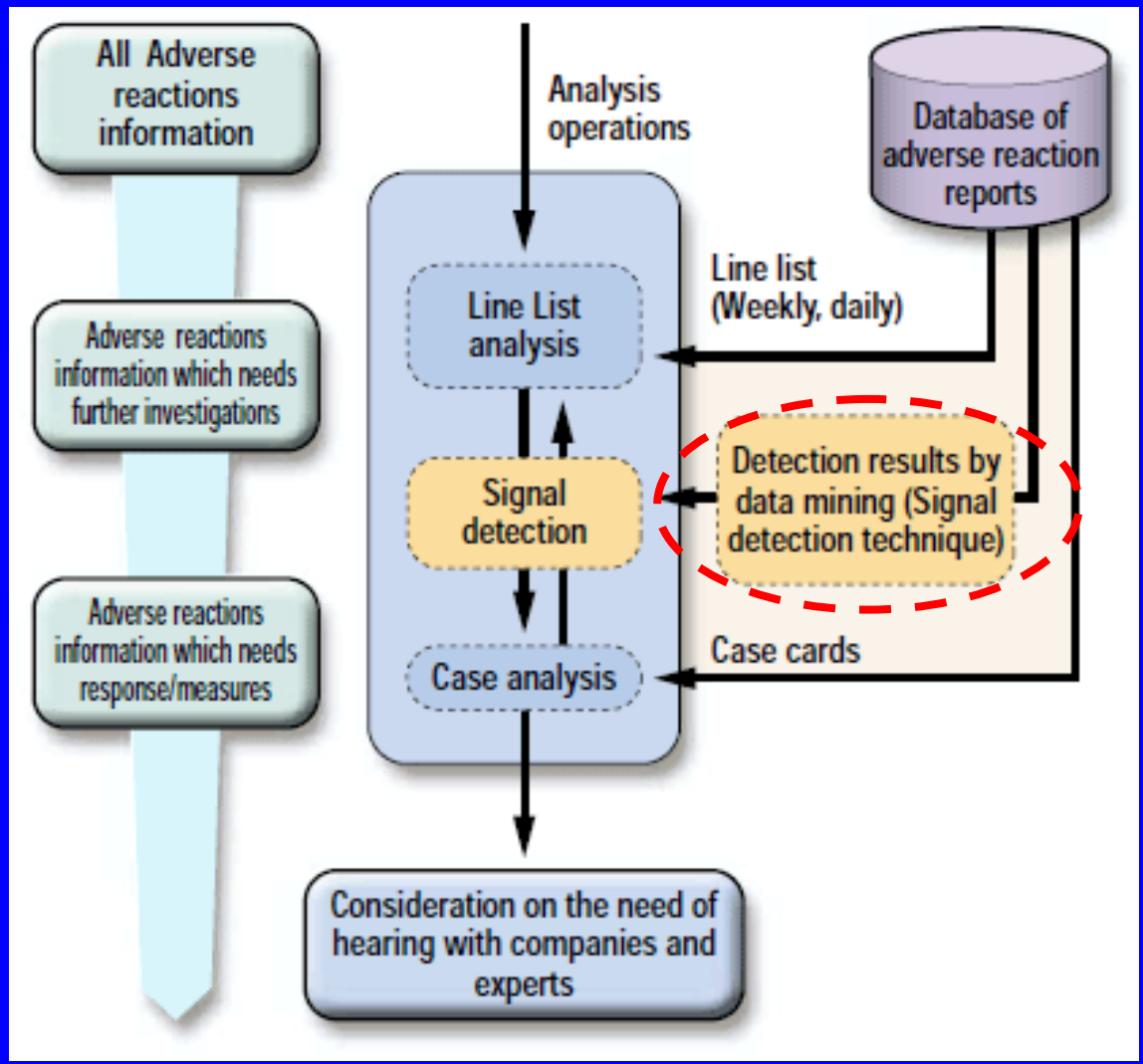
Data Mining Technique

Risk Extraction

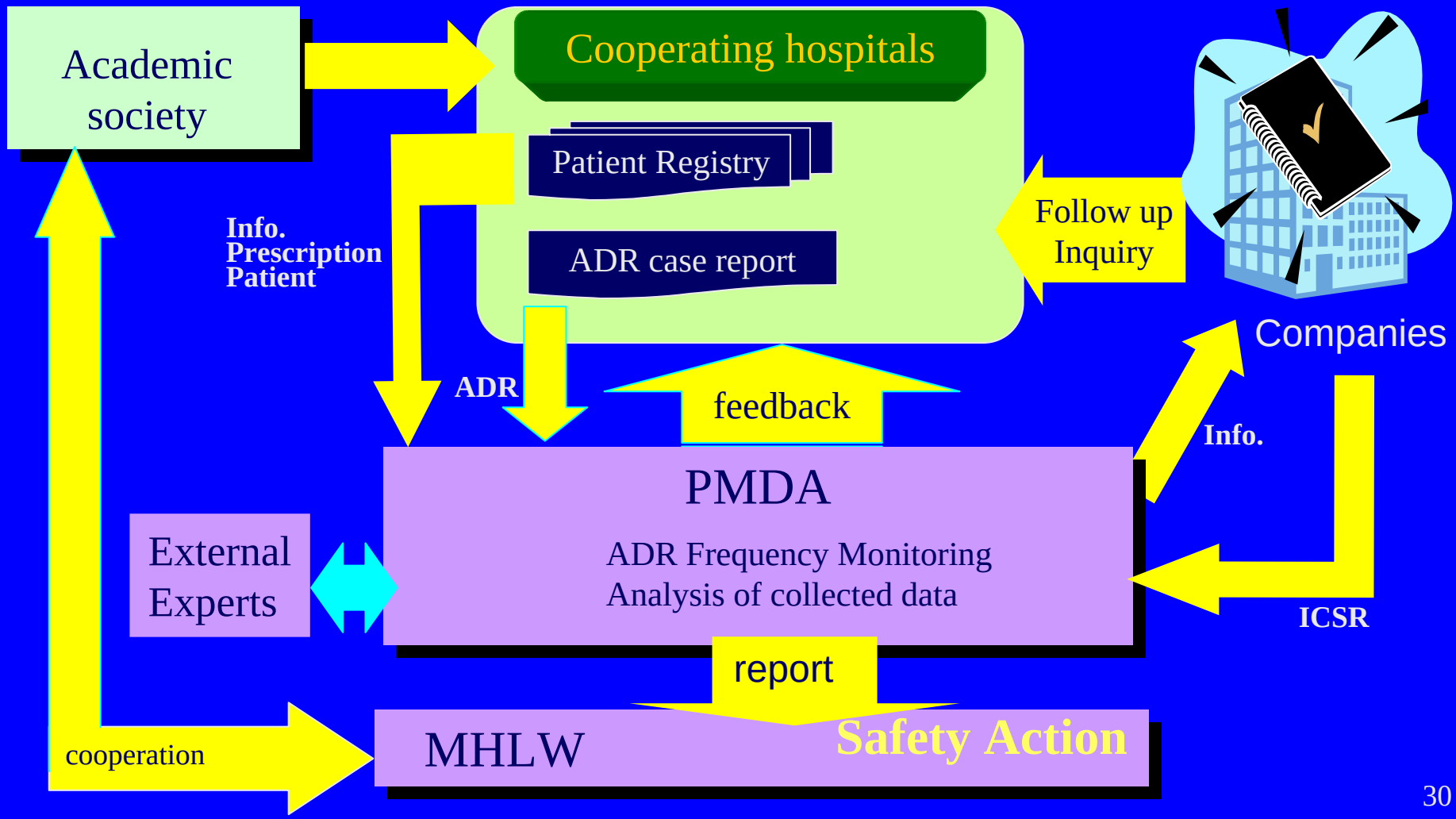


MHLW
Implementation of Safety Measures

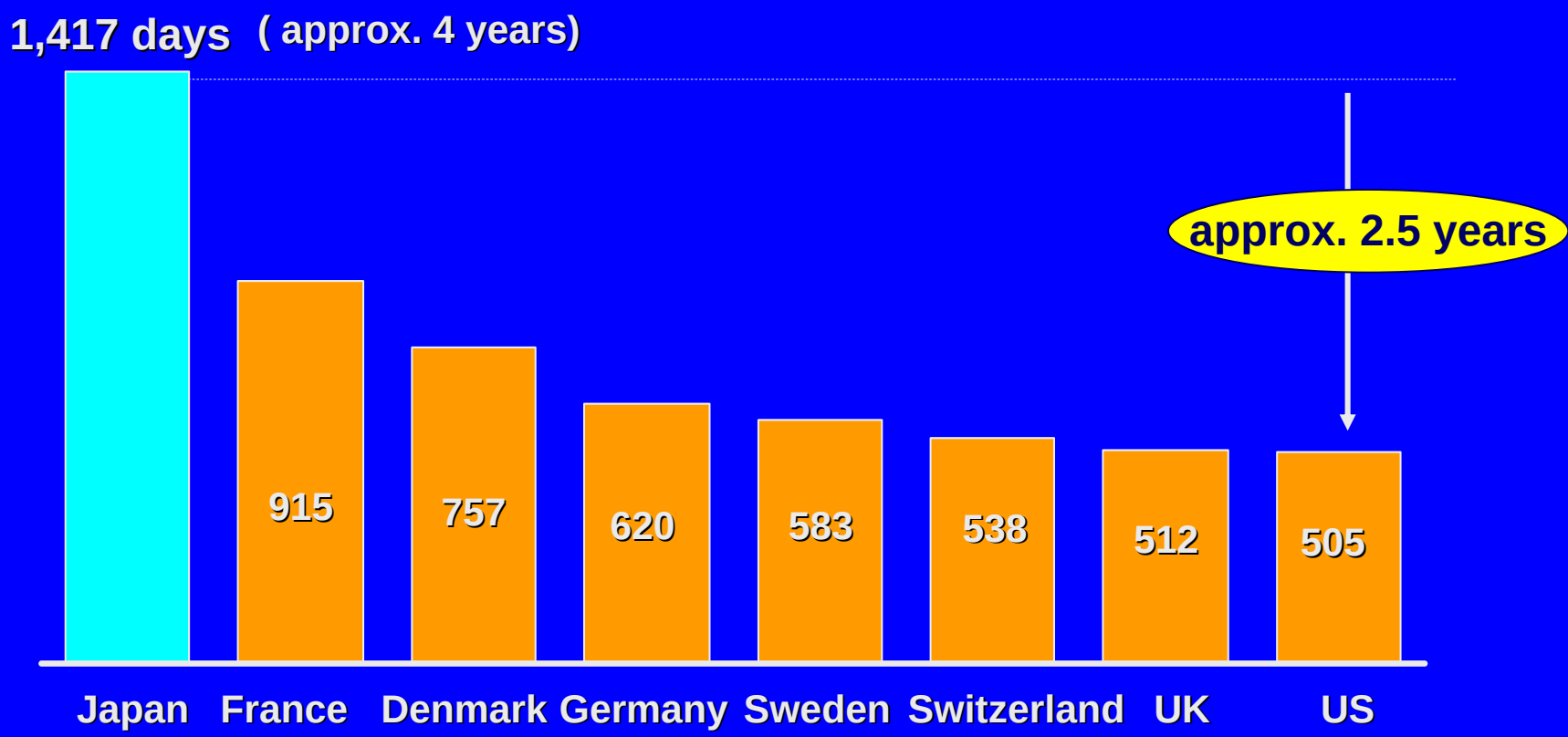
Application of Data Mining Method to Post-marketing Safety Operations



Sentinel Medical Institution Network for Oncology Combination Therapy Surveillance



Present situation of “Drug Lag”



∗ Average days to launch 100 world best selling products in each country after their first launch.
Because different combinations of 100 world best selling products are marketed in different countries, average days are calculated based on the products actually marketed in each country.

Source : JPMA Office of Pharmaceutical Industry Research.
Research paper No. 31

Measures and policies to reduce the drug lag
Target Setting FY 2007 ~ 2011 (5 years)

Aims: To reduce the "drug lag" by a total of 2.5 years by 2011
through 1.5 year and 1.0 year reductions respectively
in the development and approval times;
and to cut down the marketing lag to 500 days in line with the U.S.

Development time

Current time lag of application between Japan and US/ EU: 4.3 years (median)

Approval review time

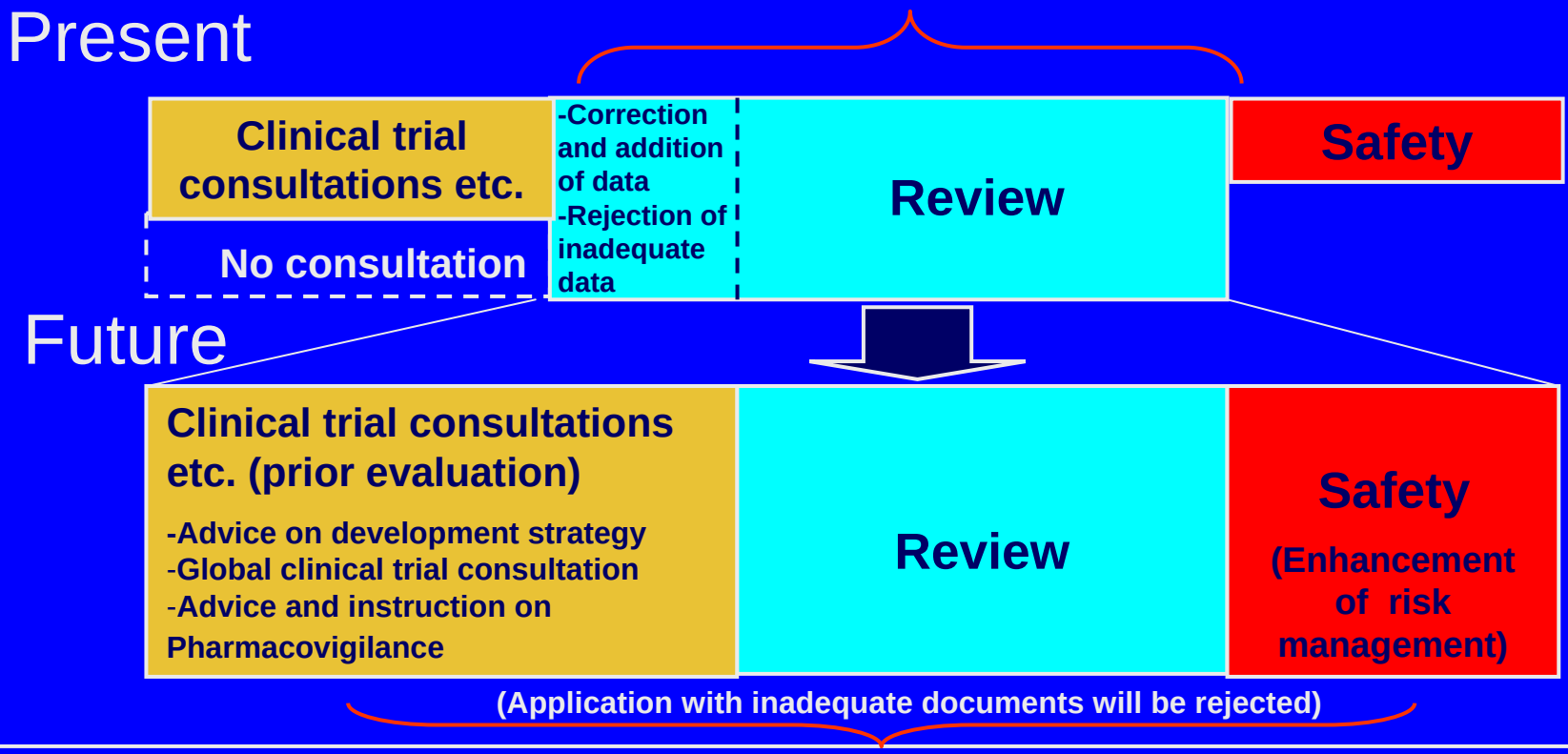
Present total review time of standard products :22 – 24 months (median)

To reduce current time lag of application between Japan and US/ EU by 1.5 years

To reduce Total TC (median) for standard products applied after FY2004 by 1.0 year

To reduce a total of 2.5 years

Total risk management system for Consultation, Review and Safety



I. Enhancement of CT consultation

- -Conduct the review of toxicity and pharmacology etc. beforehand as a part of consultation
- -Advice on development strategy at the early stage of development, clarification of review policy
- -Enhanced measures for global collaborative clinical trial and state-of-the-art science and technology

II. Review with selected focuses

- -Focused on essential evaluation of efficacy and safety

III. Enhancement of safety measure

- -Start giving advice and instruction on pharmacovigilance from the consultation stage

Cooperation between review and safety (Current)

Future Perspective :

Total Management of Safety Information from developing stage to Post Marketing Phase

- to create a system in PMDA to manage all safety information from development and review stage to post marketing phase by strengthening cooperation between OND and Office of Safety with a view to giving timely and effective guidance and advices on safety measures

- Contribute to Life Cycle Management of Drugs
  - Identification of Safety Specification of New Drugs
  - Design of Post Market Studies and Investigations to address the specification
  - Assessment of the results of studies and investigations

Our Mission（MHLW／PMDA）

To Ensure **Faster** Access to

More Effective and **Safer**

Pharmaceuticals, Medical Devices

for the Public

Improving Public Health