

POST-MARKETING SAFETY MEASURES IN JAPAN

East Asian Pharmaceutical Regulatory
Symposium 2008, Tokyo (東京)

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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**

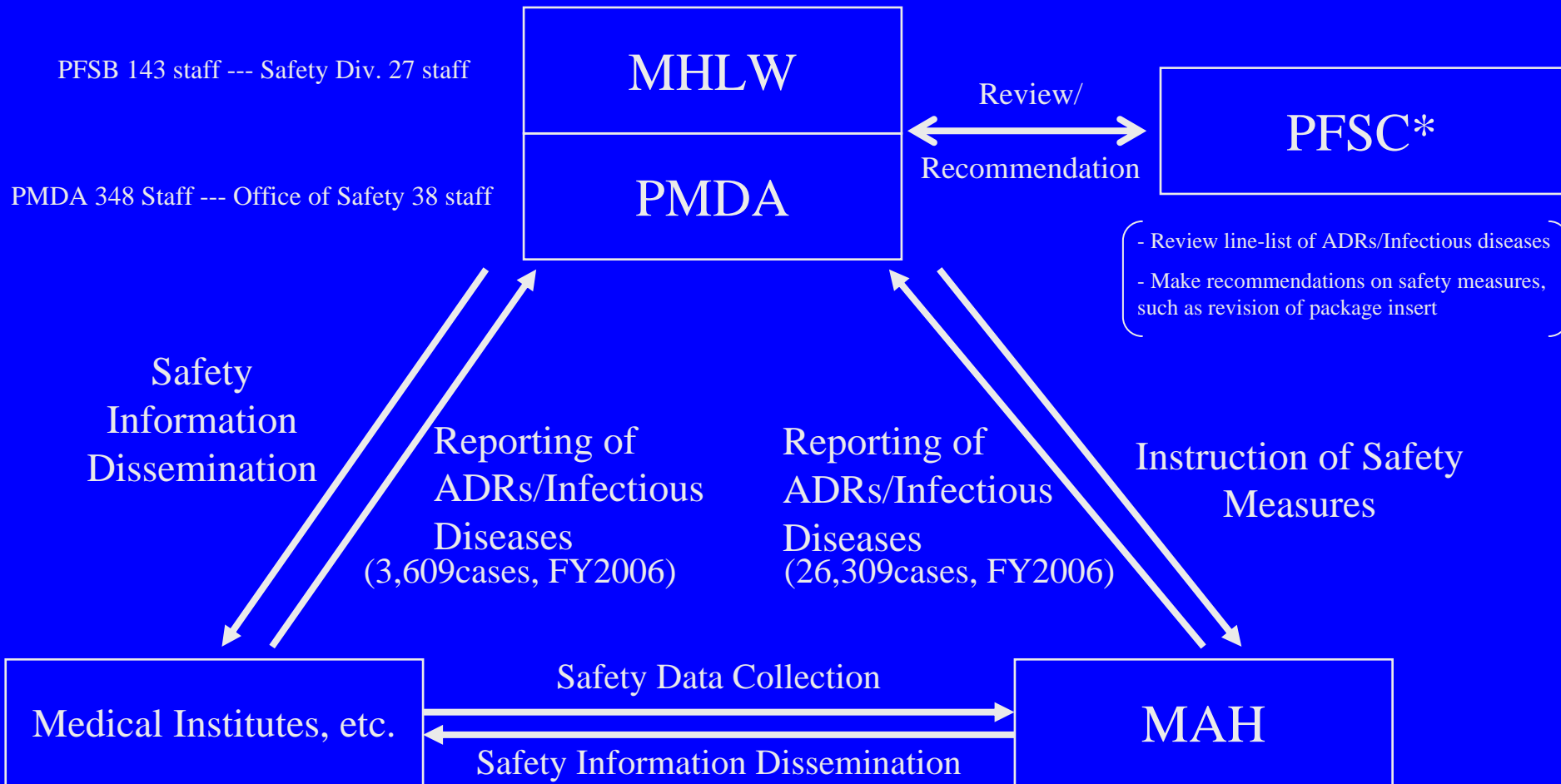
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graph LR; A[Post-marketing Safety Operations for Drugs/ Medical Devices] --- B[Reinforced Safety Information (Database)]; A --- C[Scientific Review and Research for Safety Information]; A --- D[Information Provision (via the Internet), Pharmaceutical Consultation for Consumers];
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Reinforced Safety Information (Database)

**Scientific Review and Research for Safety
Information**

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

Post-Marketing Safety Scheme



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

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

General Affairs Division

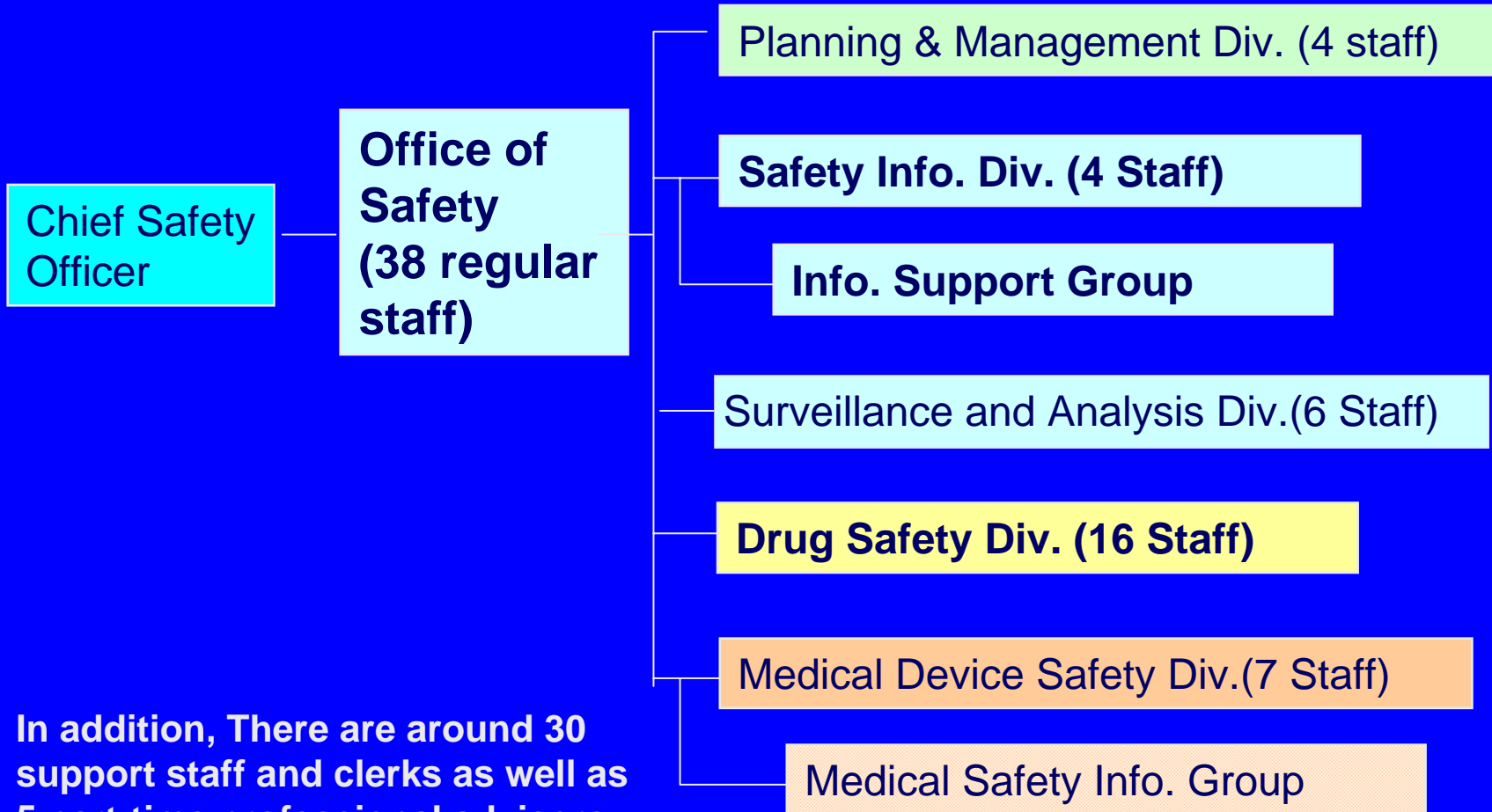
Evaluation and Licensing
Division

Safety Division **27 staff**

Compliance and Narcotics
Division

Blood and Blood Products
Division

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

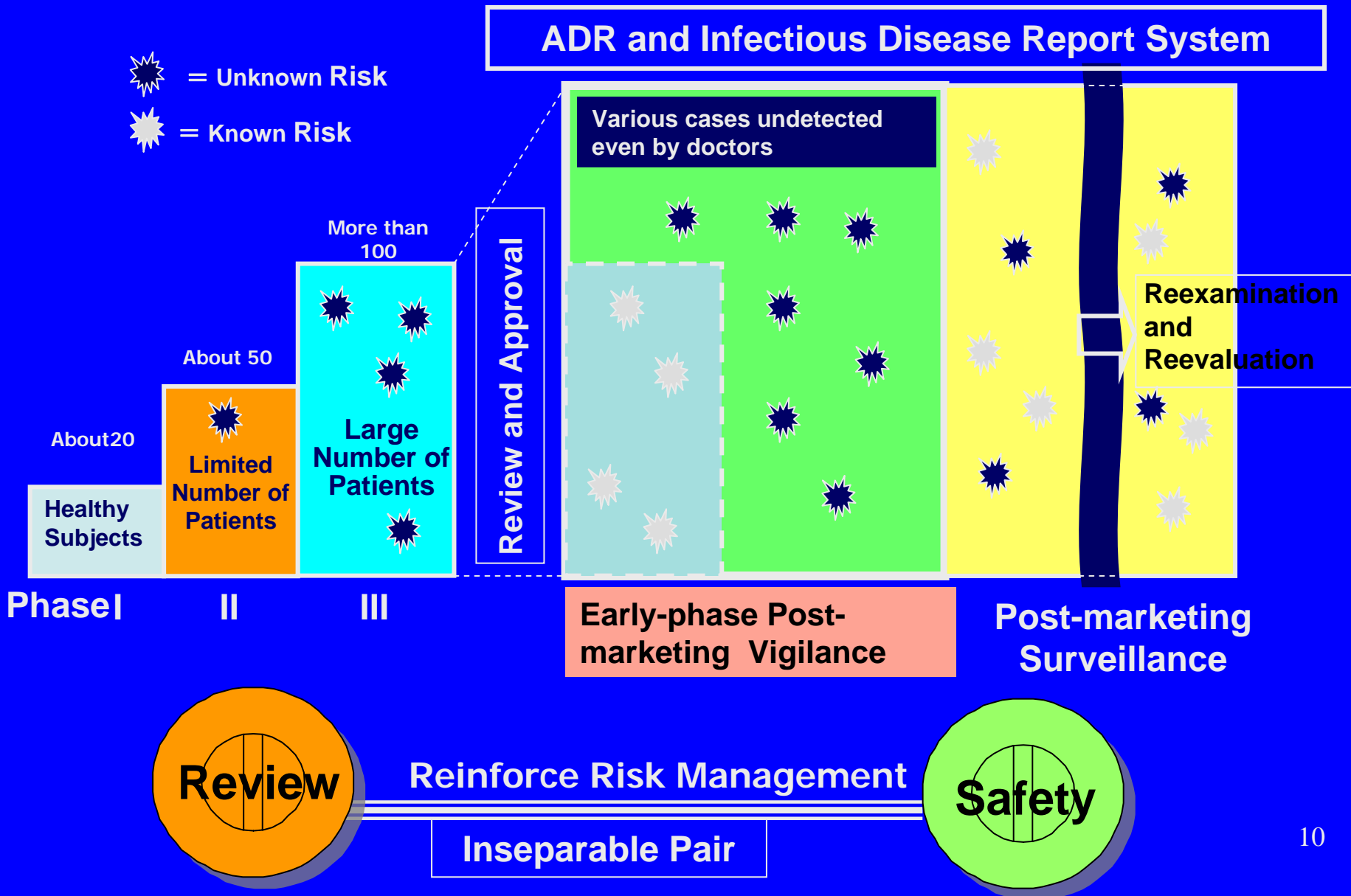
(Office of Safety, PMDA)

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

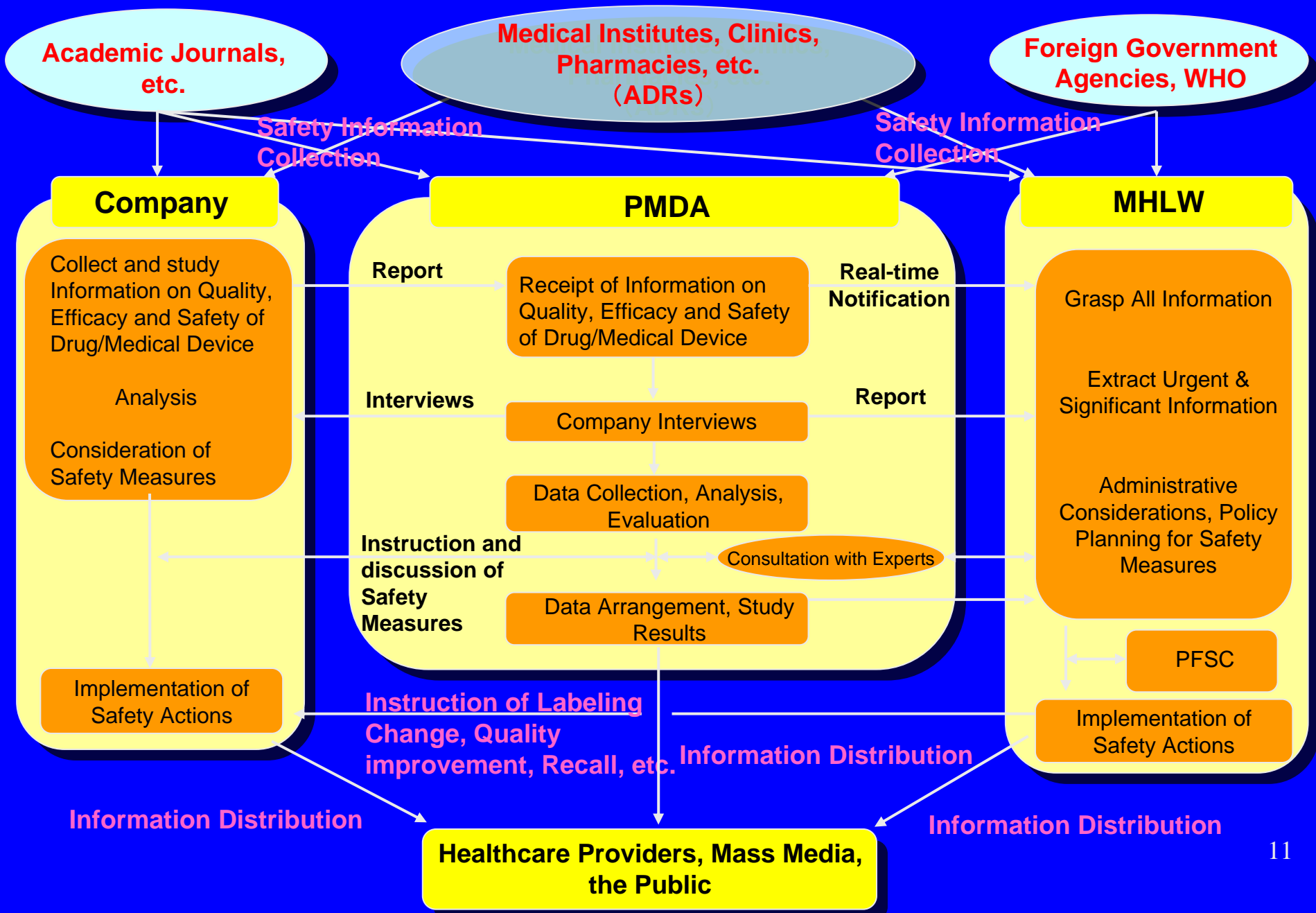
- FY2007 income from MAHs ¥ 1263 Mil.
- FY2007 MHLW subsidy ¥ 255 Mil.
- Others ¥ 5 Mil.
- (total ¥ 1,523 Mil.)

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

For "Safer" Drugs / Devices

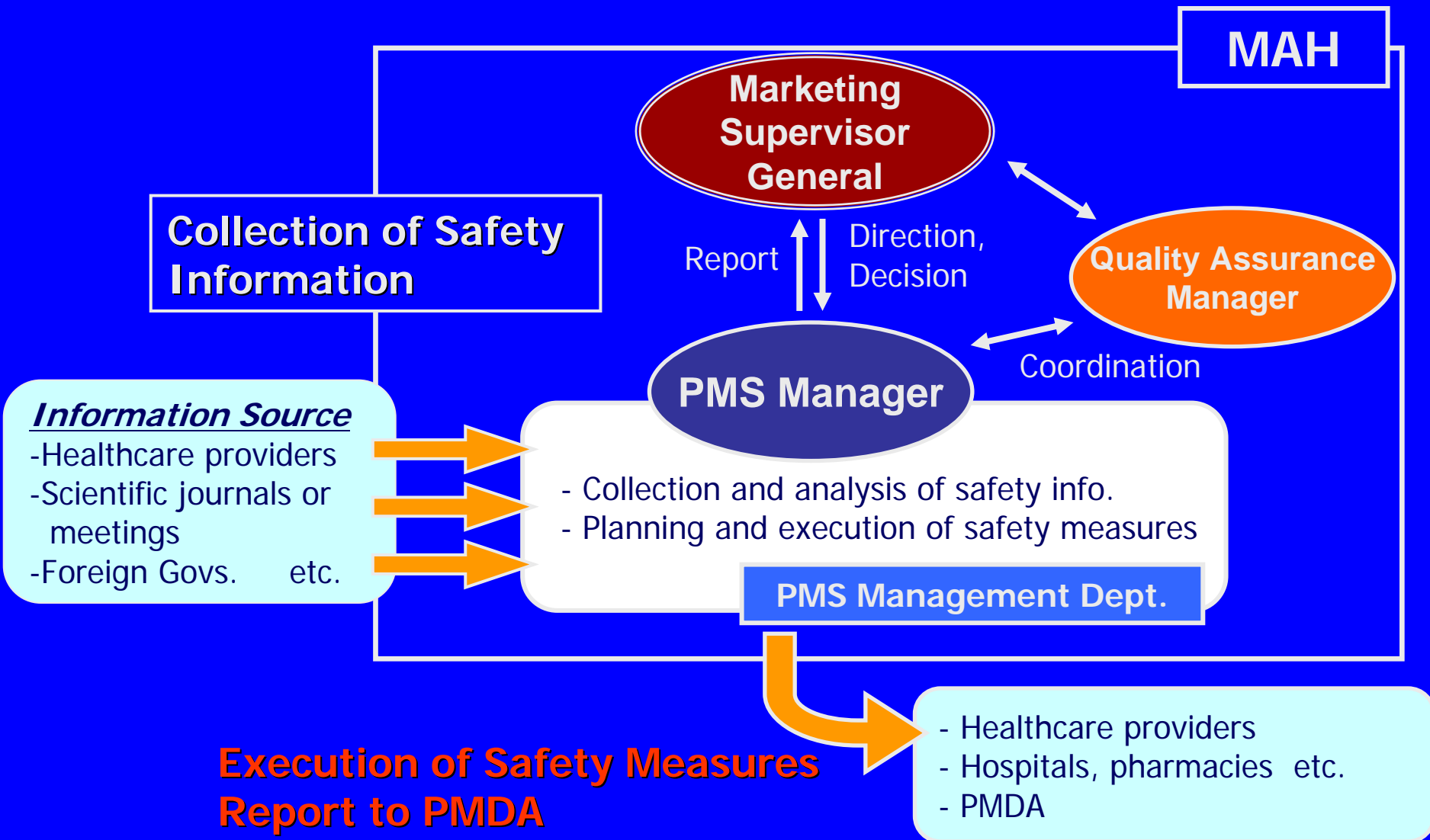


Vigilance Operation Flowchart

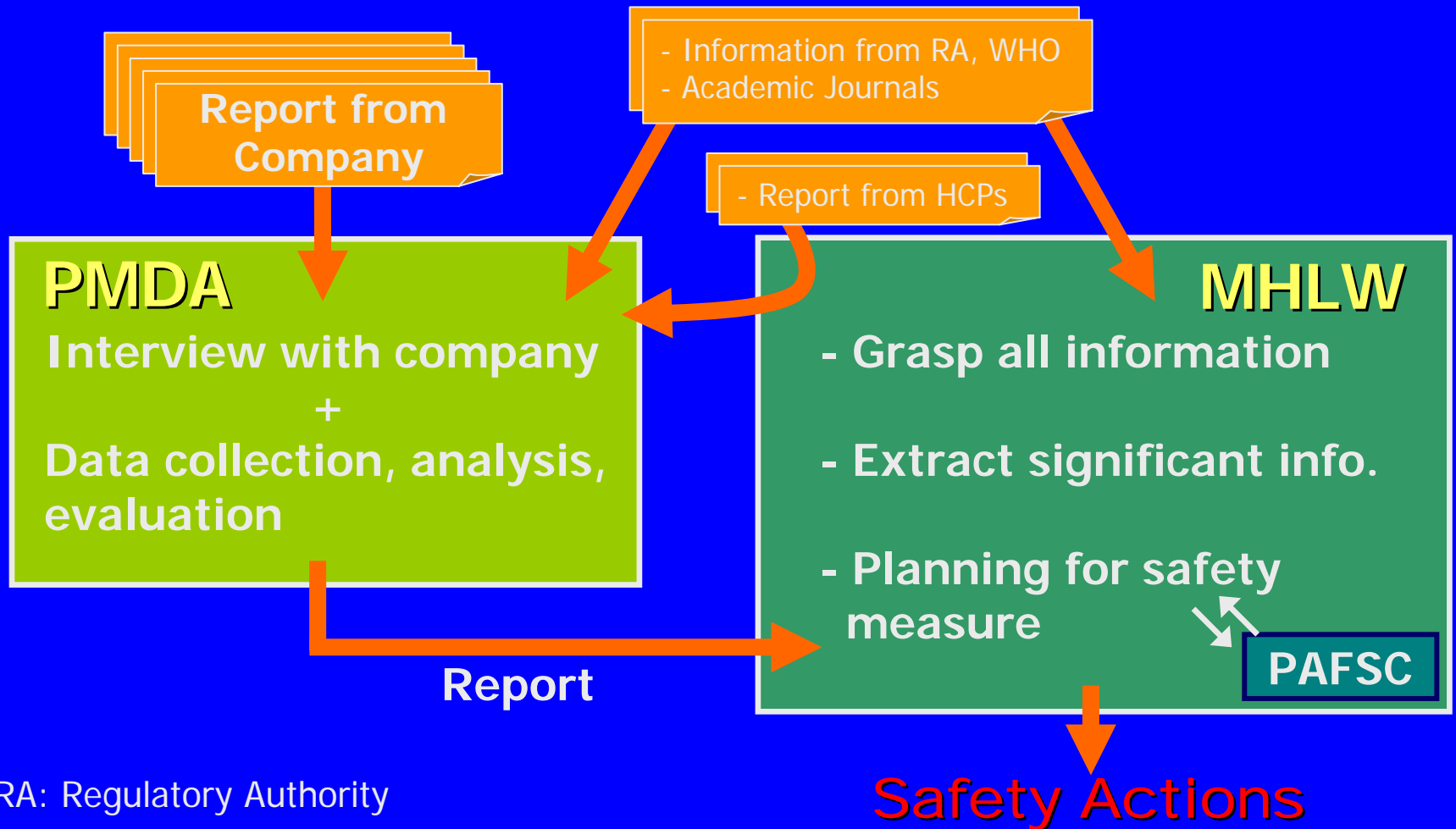


Outline of Information Flow (1)

(MAH)



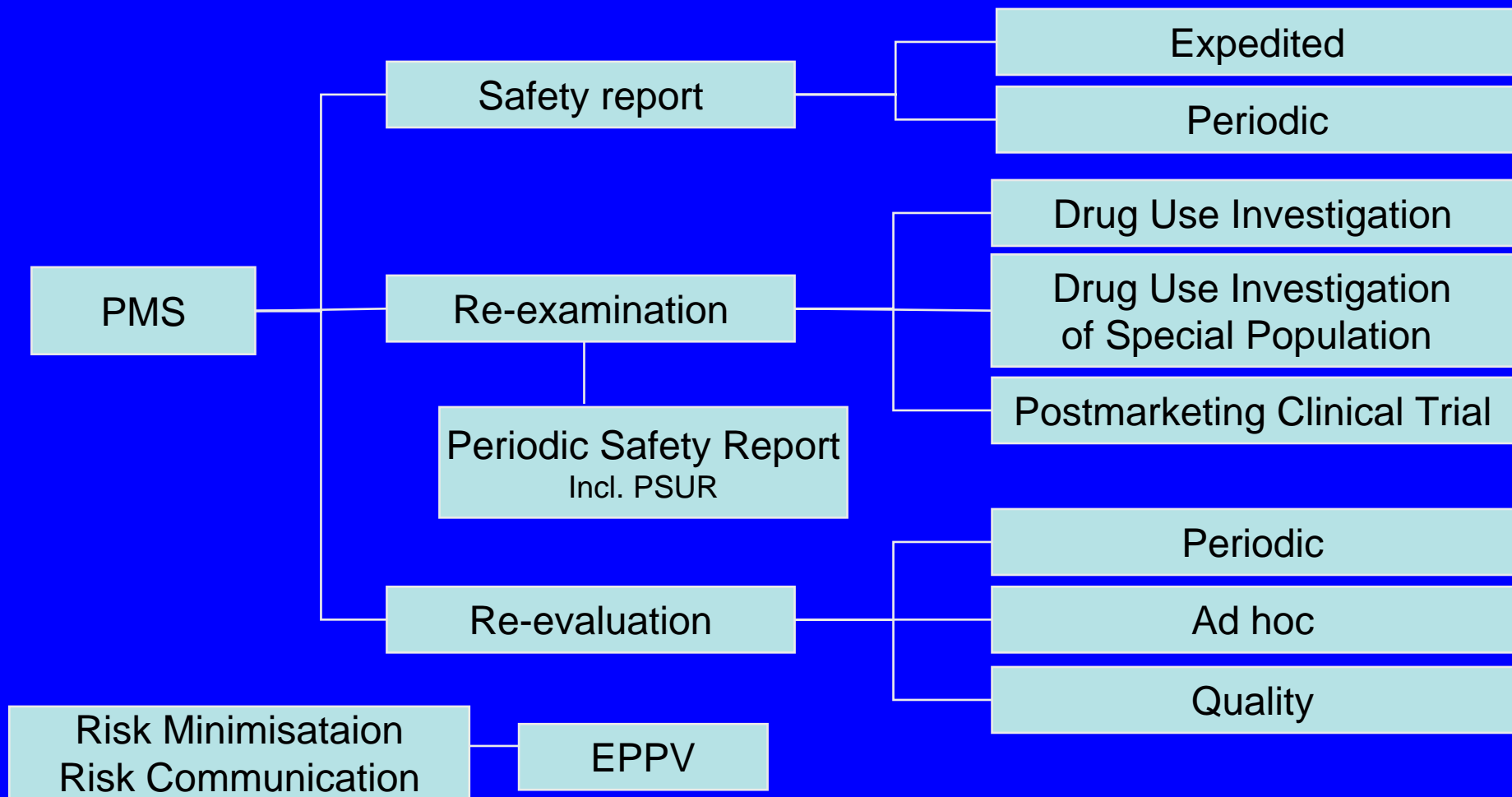
Outline of Information Flow (2)



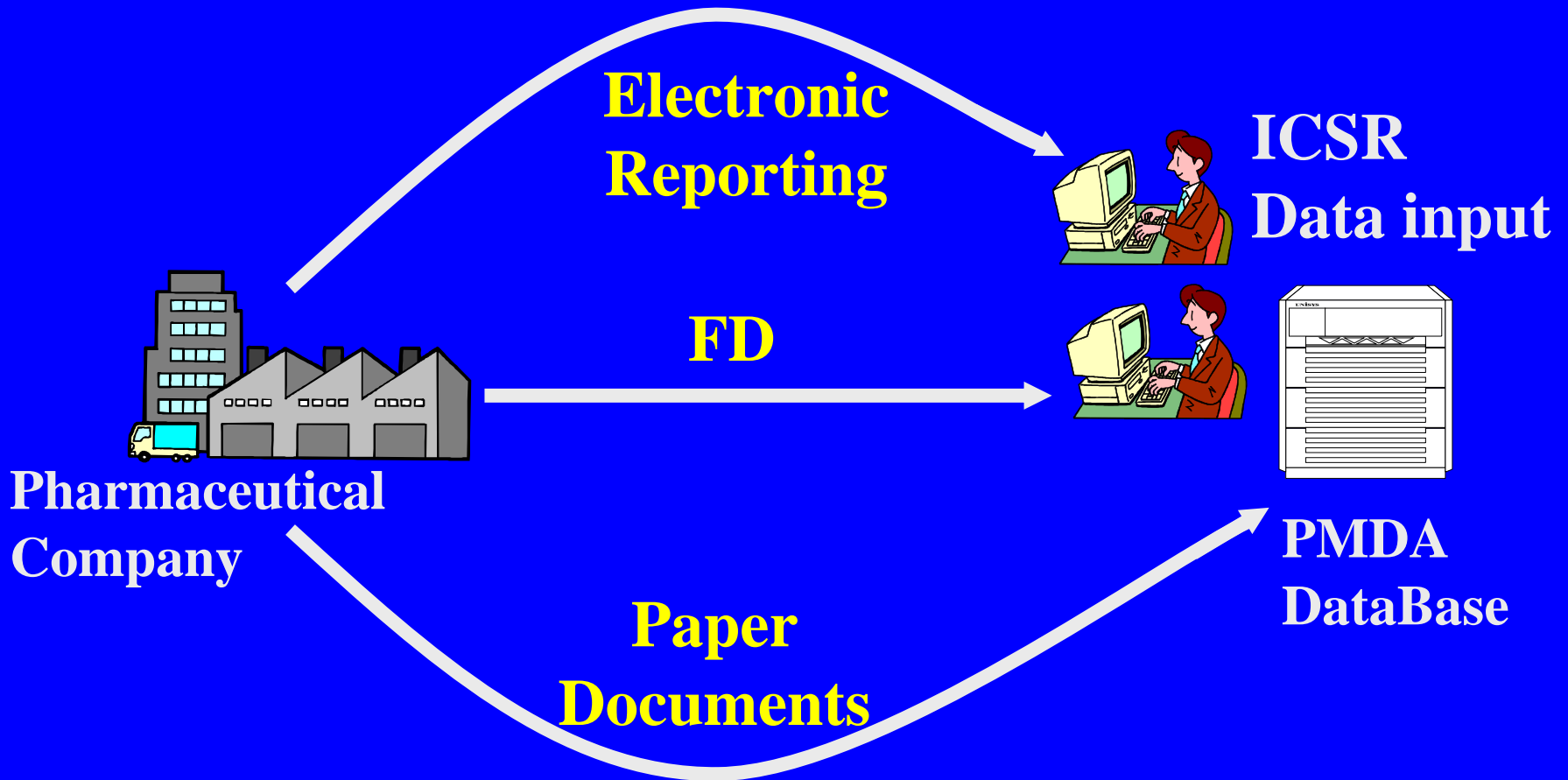
RA: Regulatory Authority

(Administrative Advice for revision of package insert etc.)

JP Postmarketing activities



ADR Reporting by MAH

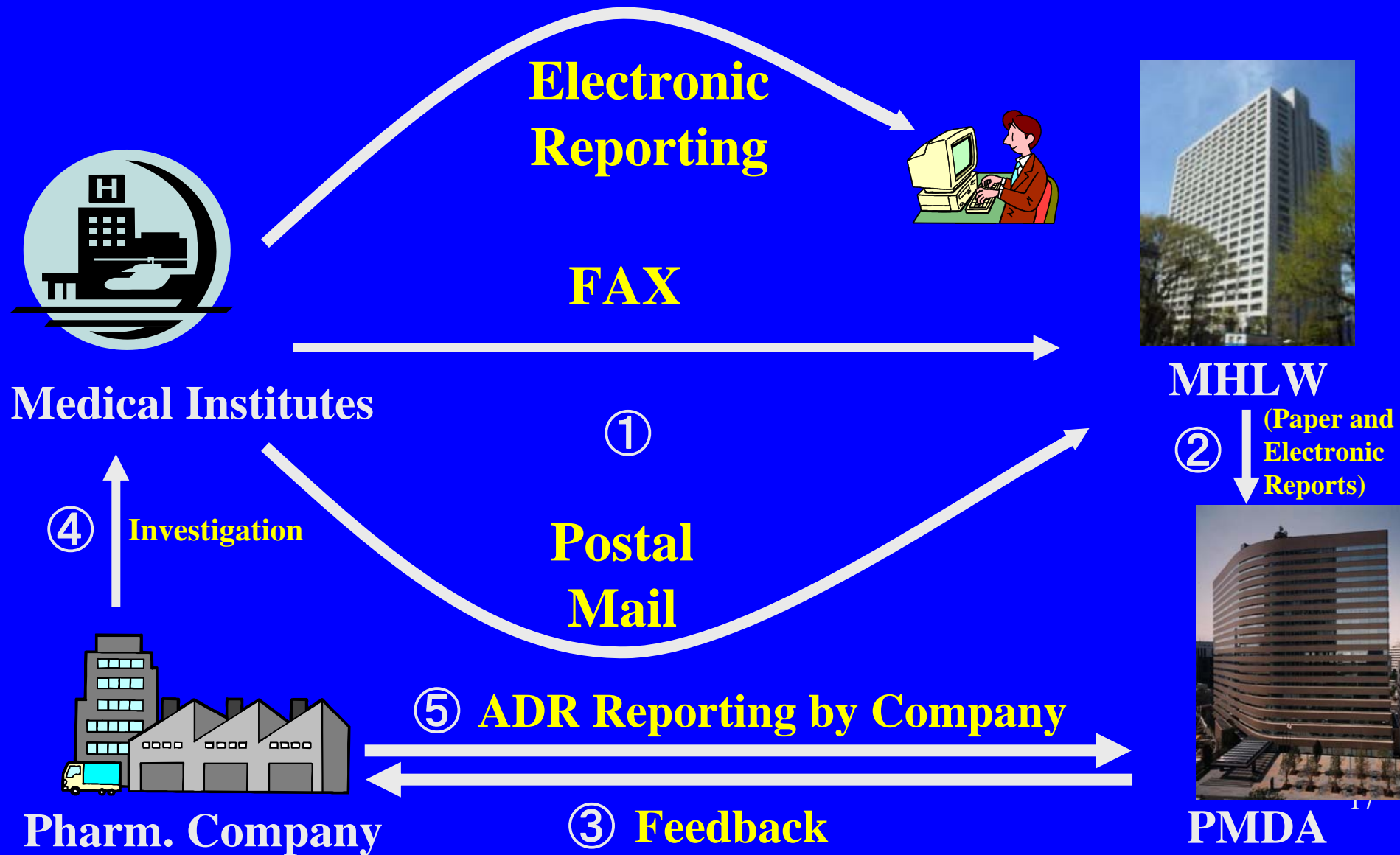


- ◆ Electronic reporting transmitted by internet
- ◆ Reporting by FD
- ◆ Reporting by paper documents

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.



ADR Reporting Rule (Drug)

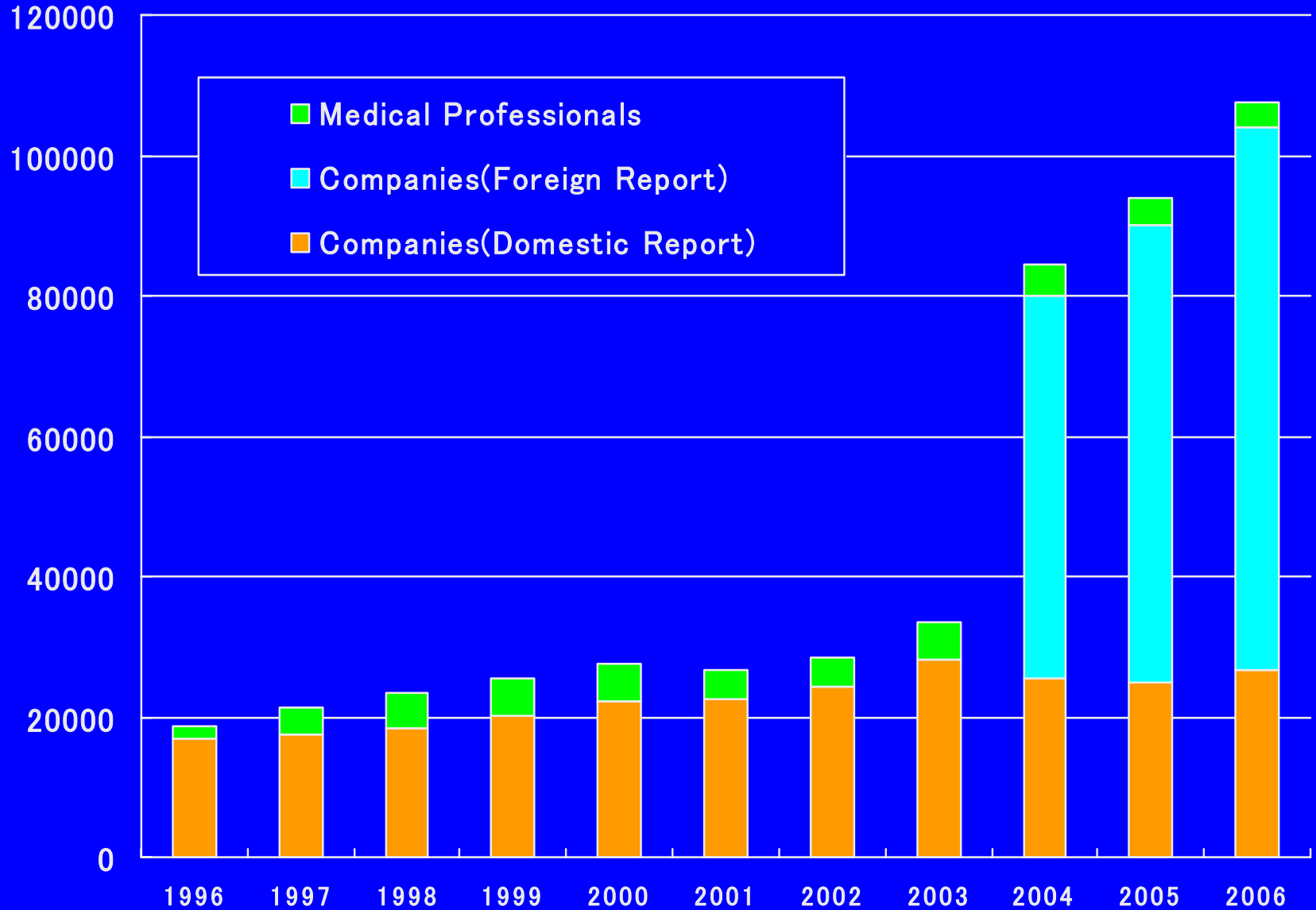
| Seriousness | predictability | Time frame of report to PMDA |
|-------------|-----------------|---|
| Serious | Not predictable | 15 days |
| | Predictable | - Death etc.* 15 days - Others 30 days |
| Not serious | Not predictable | Annually (Annual Cumulative Report) |
| | Predictable | - |

- 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)

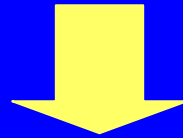
Reported ADR / Infectious Disease Cases



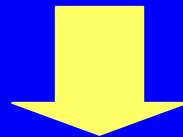
Note :Foreign reports by drug makers are not included in and before FY03'.

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.))

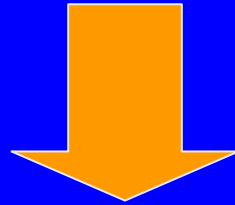
Safety Measures

- 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



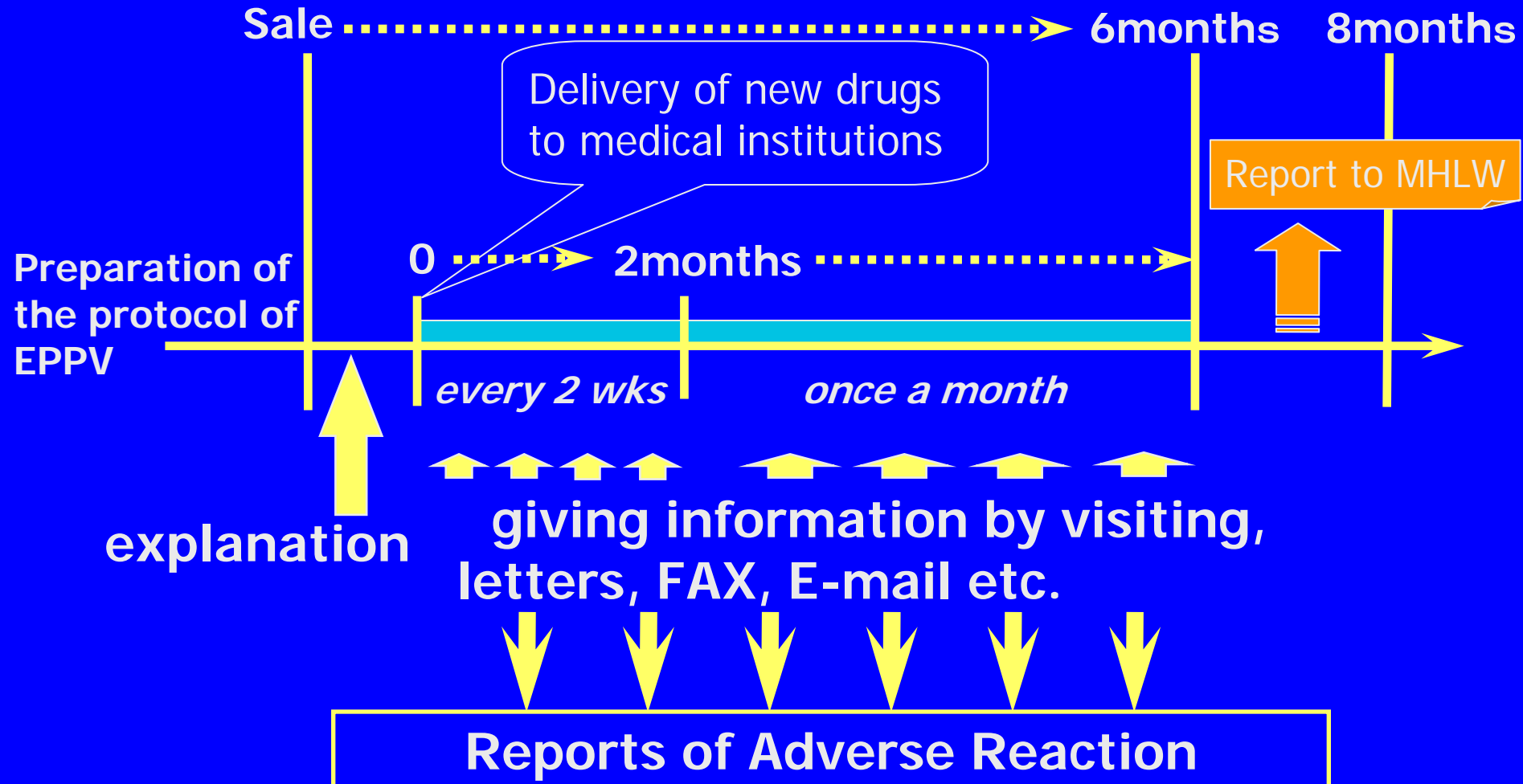
- Protect patients from ADRs

Early Post-Marketing Phase Vigilance : EPPV

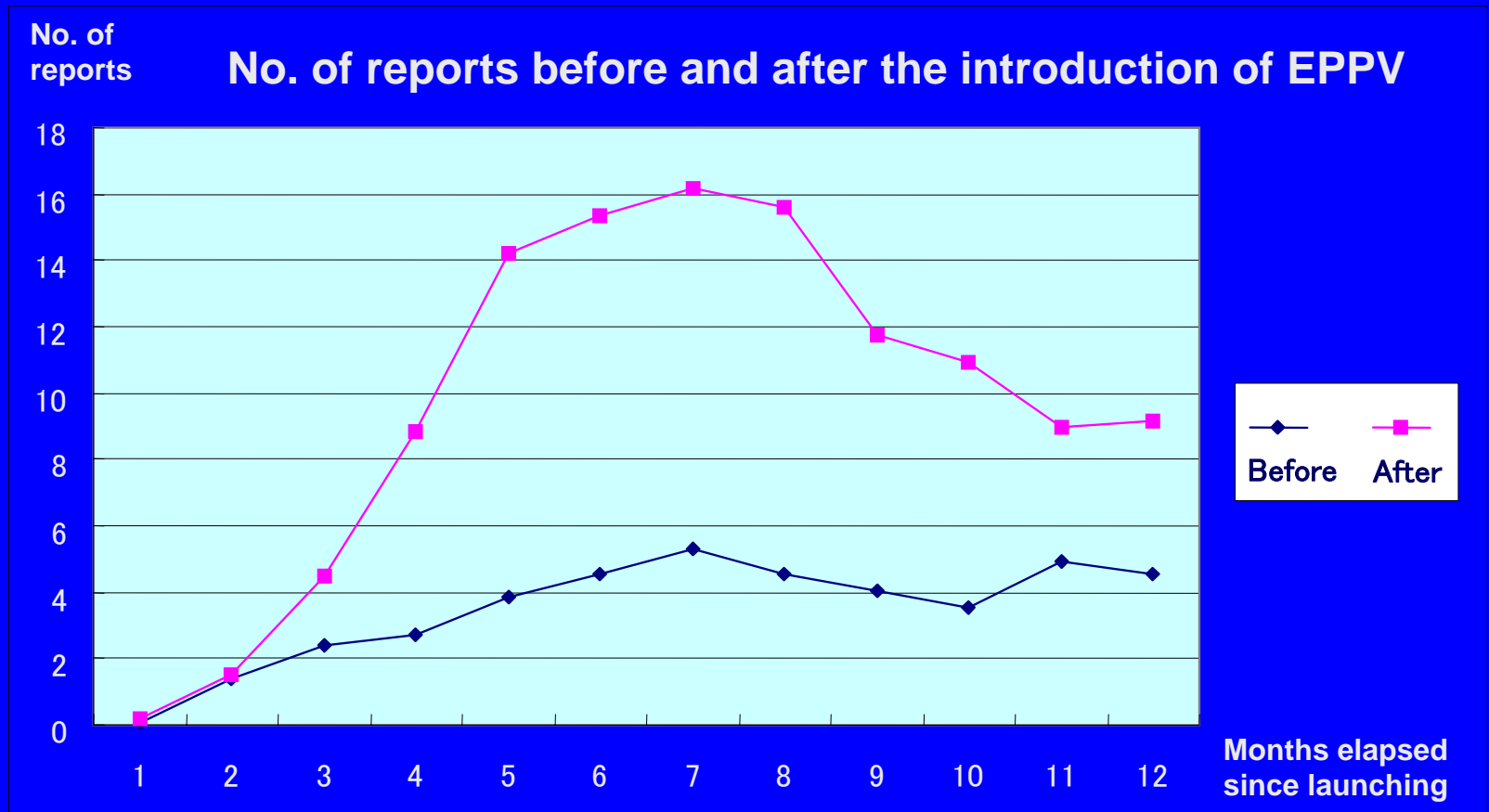
Enforced on Oct 1, 2001

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

For Patients and the general public

Package Inserts for Pharmaceuticals or Medical Devices

Information for the general public

Q & A on Pharmaceutical

Reports of suspected adverse events or suspected Defects

Information for the Health Care Professionals

Consultation on Drugs / Devices

Doctor letters and Safety Information

Measures against the Serious Adverse Events

Information on approvals of Drugs/Devices

Recalls

Information about the free mail system provided by

Pharmaceutical Guidance for patients

Package Inserts for OTC Drugs

The screenshot shows the PMDA website homepage with the following callouts:

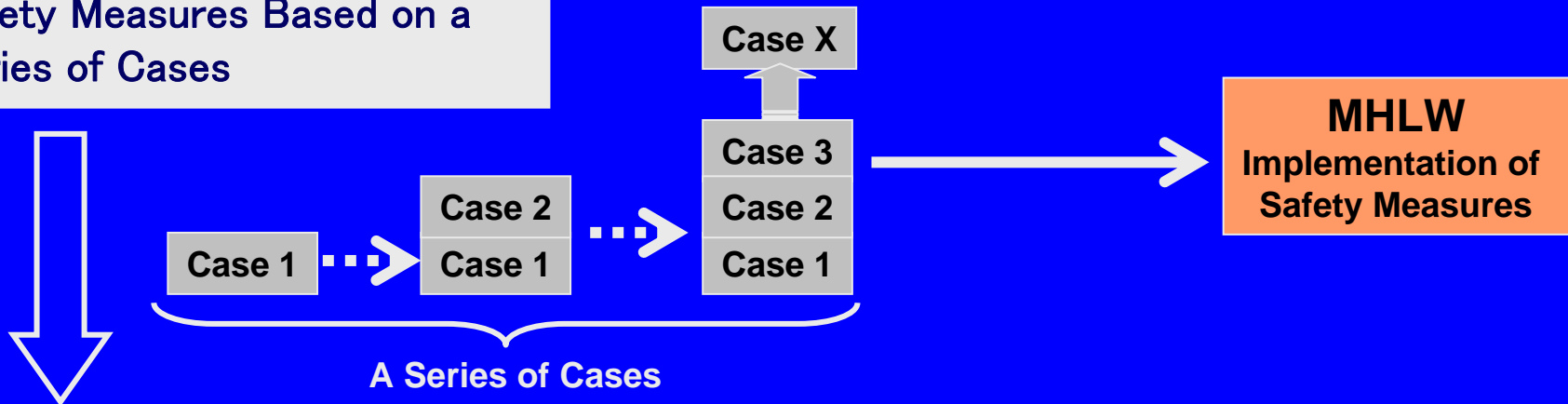
- 緊急安全性情報(ドクターレター)等 発出のお知らせ**: Emergency safety information (doctor letters) etc. issued notice. Includes links for "厚生労働省より、リン酸オセルタミビルについて緊急安全性情報等が発出されました" and "厚生労働省発表資料・使用上の注意改訂情報".
- 新着情報**: New information. Includes links for "平成19年3月23日" (March 23, 2017) and "平成19年3月22日" (March 22, 2017) regarding safety information and doctor letters.
- お知らせ**: Notice. Includes links for "平成19年3月23日" (March 23, 2017) regarding website updates and "平成19年2月18日" (February 18, 2017) regarding doctor letters.
- Information for the general public**: Includes sections for "重要副作用疾患別対応マニュアル" (Manual for important side effects by disease), "おくすりQ&A" (Medicine Q&A), "おくすりの説明書検索" (Medicine instruction book search), "おくすり相談・医療機器相談窓口のご案内" (Medicine/medical device consultation window), and "患者向医薬品ガイド" (Patient-oriented medicine guide).
- Information for the Health Care Professionals**: Includes a list of links such as "添付文書情報(医療用医薬品)", "副作用が疑われる症例報告に関する情報", "緊急安全性情報(ドクターレター)", "医薬品・医療機器等安全性情報(厚生労働省発行)", "医薬品安全対策通知", "使用上の注意の改訂情報", "厚生労働省発表資料(医薬品等関連)", "DSU(医薬品安全対策情報)", "患者向医薬品ガイド", "重要副作用疾患別対応マニュアル", "承認情報(医薬品)", "医療用医薬品 品質情報", "回収情報", "医療安全情報", and "安全対策の取り組み".
- For Patients and the general public**: Includes "Q & A on Pharmaceutical", "Consultation on Drugs / Devices", and "Measures against the Serious Adverse Events".
- For Health Care Professionals**: Includes "Reports of suspected adverse events or suspected Defects" and "Doctor letters and Safety Information".
- Other callouts**: "Package Inserts for Pharmaceuticals or Medical Devices", "Information on approvals of Drugs/Devices", "Recalls", "Information about the free mail system provided by", "Pharmaceutical Guidance for patients", and "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.

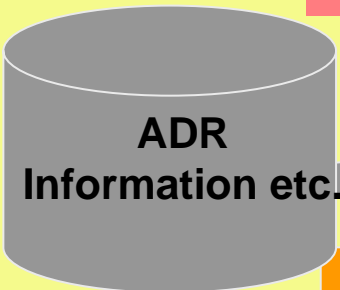
Improvement of Safety Measures

Safety Measures Based on a Series of Cases



Prospective/ Preventive Safety Measures

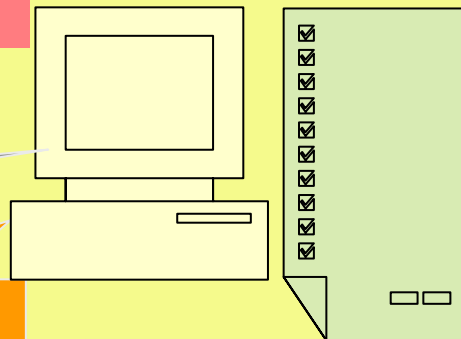
PMDA



Data Mining Technique

Sentinel Medical Institution Network (In Specific Area)

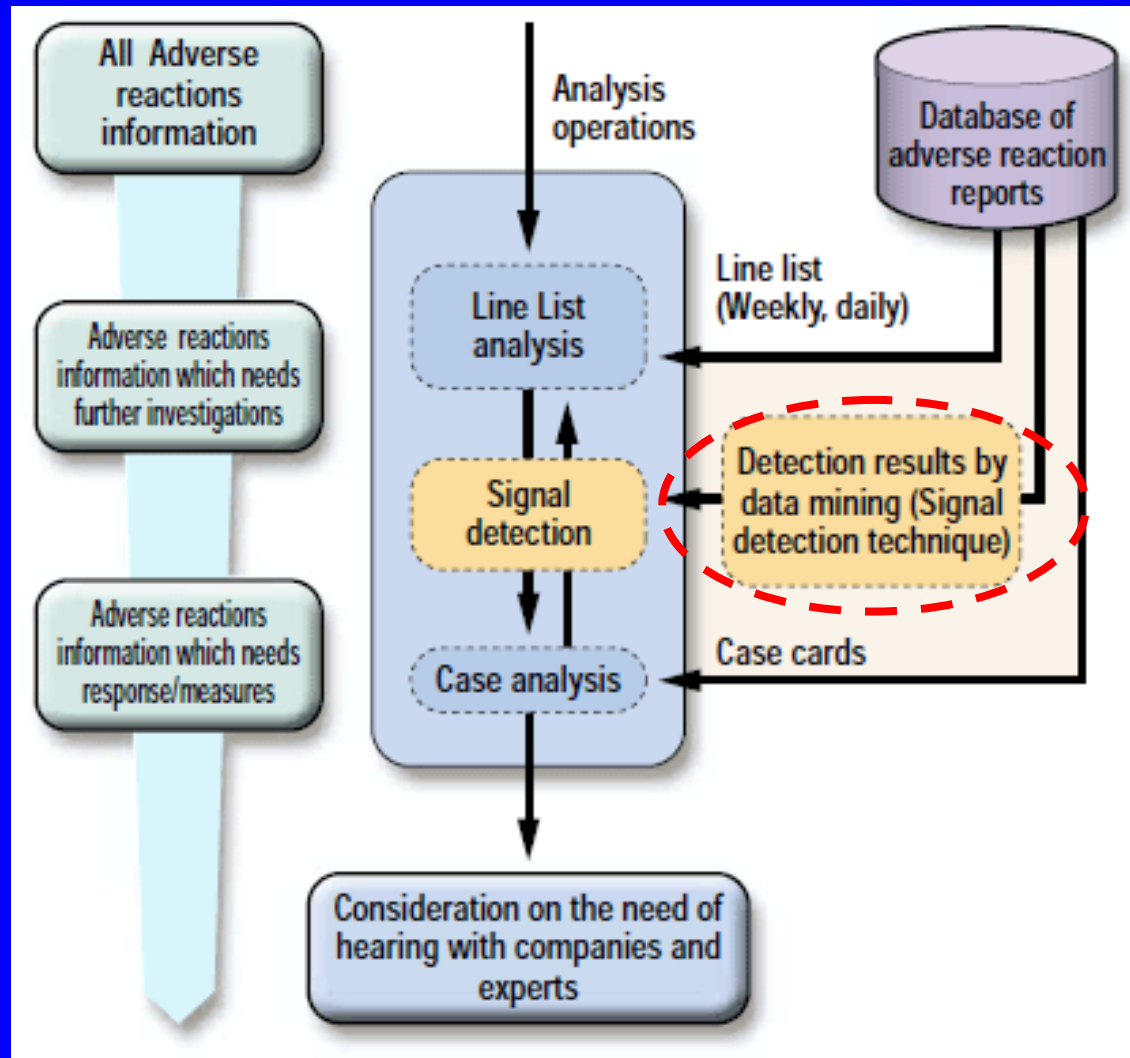
Risk Extraction



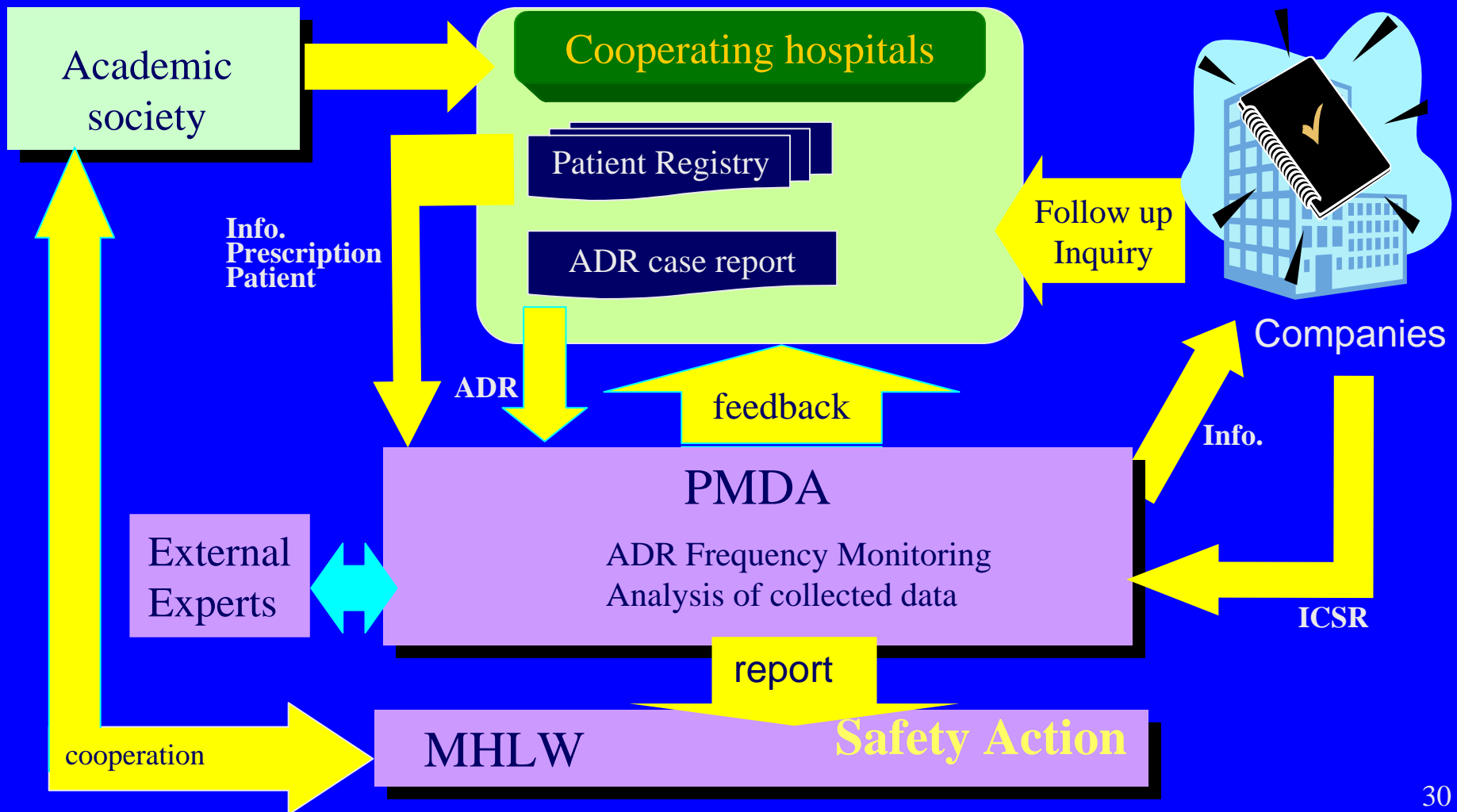
Scientific Analysis/Evaluation

MHLW Implementation of Safety Measures

Application of Data Mining Method to Post-marketing Safety Operations

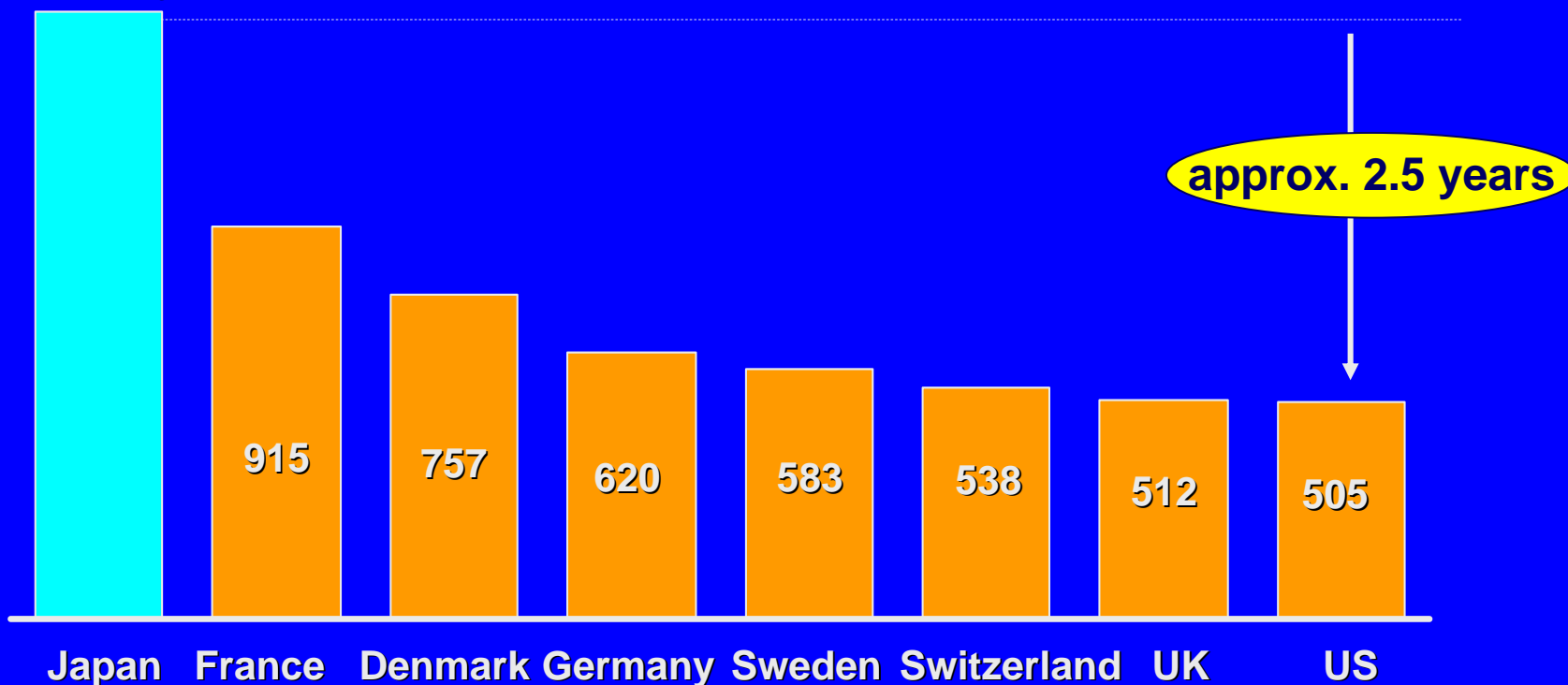


Sentinel Medical Institution Network for Oncology Combination Therapy Surveillance



Present situation of “Drug Lag”

1,417 days (approx. 4 years)



* 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**

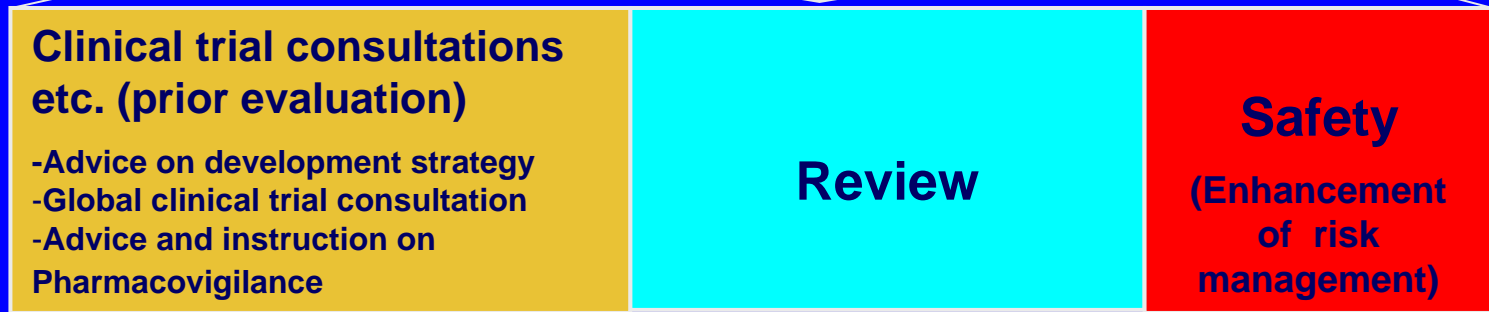
To reduce a total of **2.5 years**

Total risk management system for Consultation, Review and Safety

Present



Future



(Application with inadequate documents will be rejected)

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)

Offices of New Drugs

Office of Safety

New drug application

Initial Interview

expert discussions
on review

Meeting on items
for the council

Council (committee / executive session)

Approval

Reexamination

Collection of safety issues

Consideration of the need and issues for
early post-marketing phase vigilance
Consideration of the draft package insert

Consideration of the draft package insert

Use-results surveillance, Special use-results surveillance and
Protocol of Post-market clinical trial

Safety update

Report of the result of
early phase post-
marketing phase
vigilance

Consideration of need for
package insert revision

Reports of use-results surveillance, Special use-results,
surveillance and the Post-marketing clinical trial

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