PMDA experience with measuring the impact of pharmacovigilance

Shinobu UZU
Chief Safety Officer
Pharmaceuticals and Medical Devices Agency

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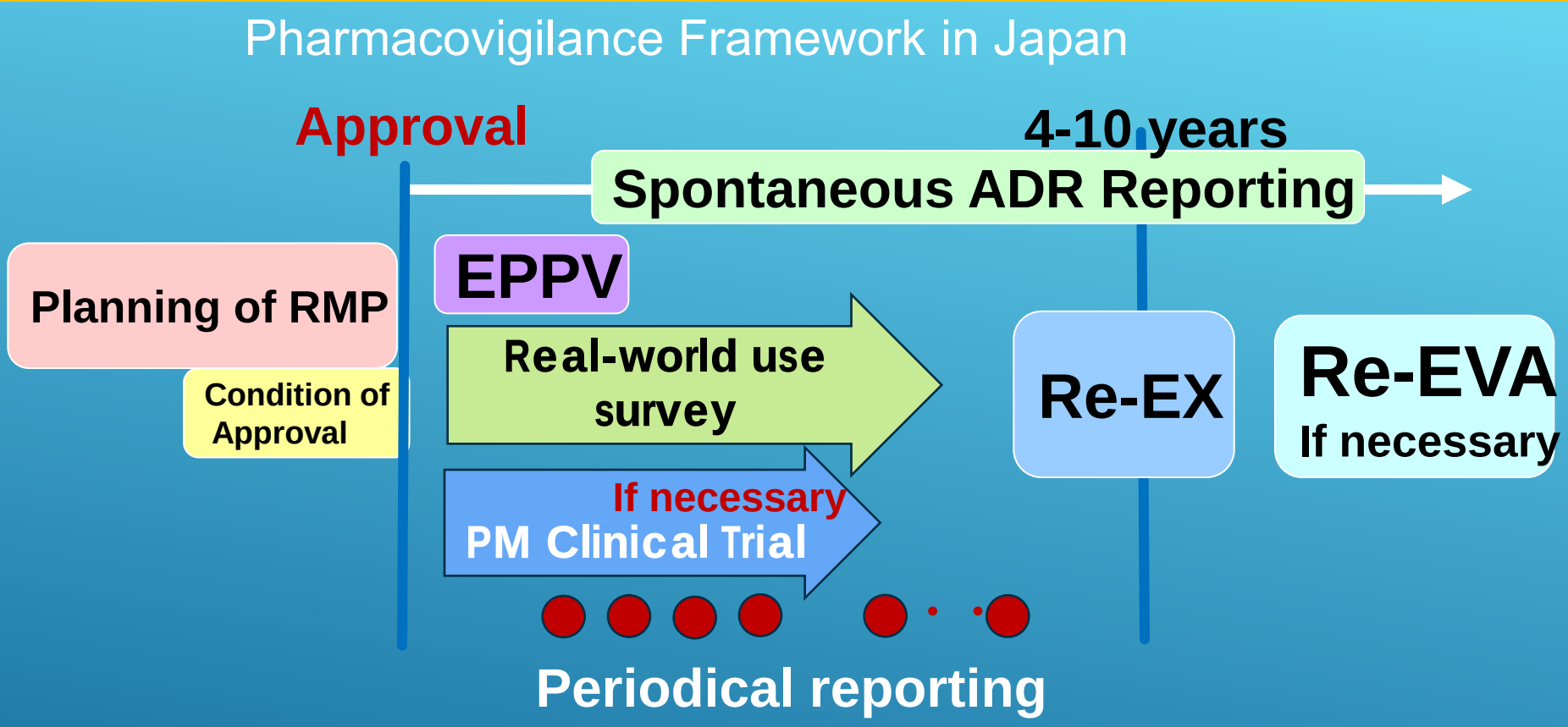
- Conventional assessment of B/R balance
  - ✓Overview of Regulatory Scheme for Post-Market
  - ✓Limitation of the conventional assessment
- New activities for evaluation of B/R balance

Overview of the regulatory schemes to assess B&R balance in Japan?



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

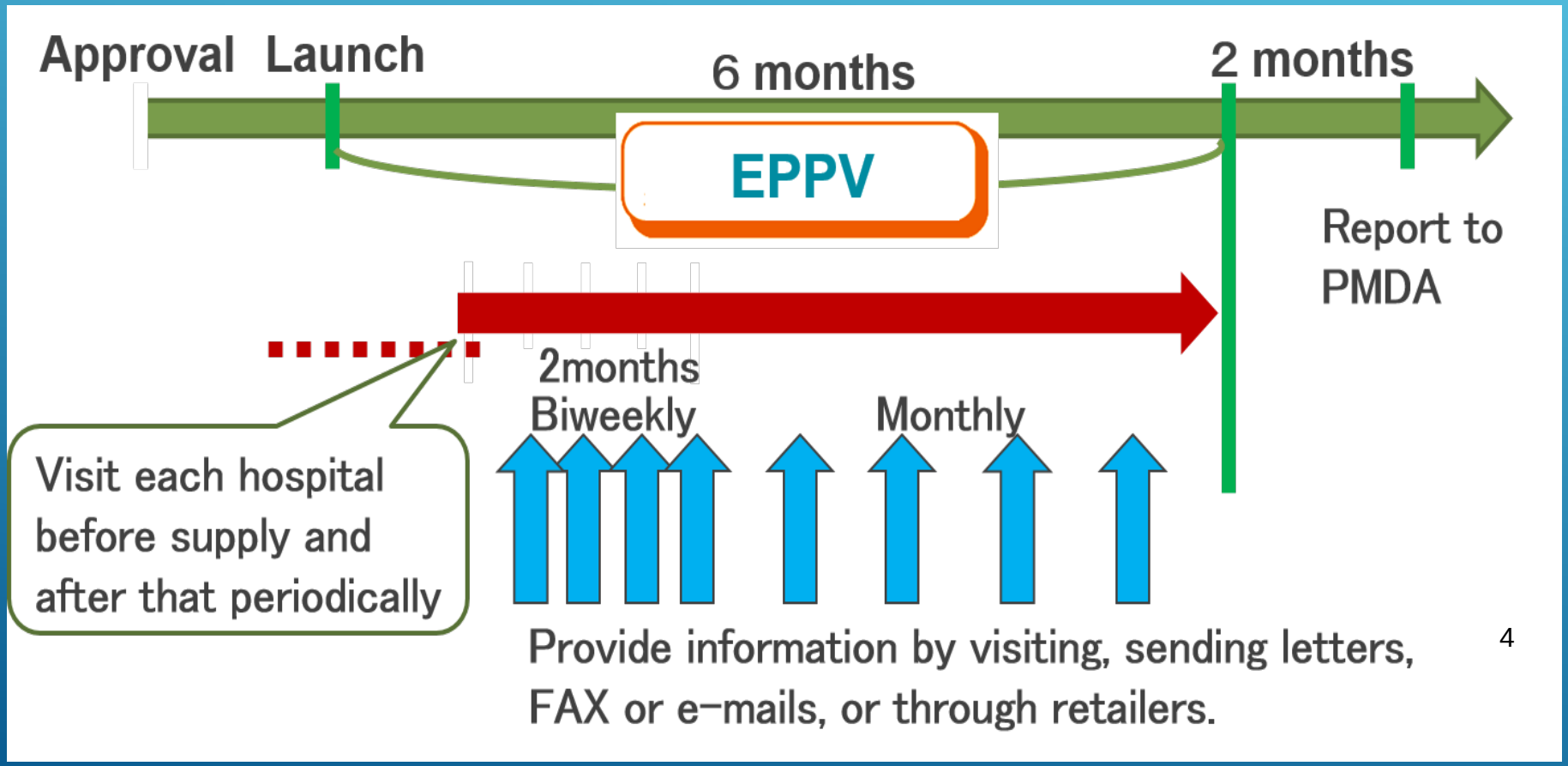
RMP : Risk Management Plan

Re-EX : Re-examination

Re-EVA: Re-evaluation

Early Post-marketing Phase Vigilance（EPPV）

- Marketing authorization holders are required to provide the safety information to health care professionals (HCP) and to collect ADR information intensively for the time frame by visiting hospitals periodically in early post-marketing phase.



Time from approvals to make precautions

Most of “Dear Healthcare Professionals Letters” were sent in a year from launching drugs.

Drug	Date to send letter	Months from launching to sending	Estimated number of Patients
Lamotrigine	4.Feb.2015	74	376,000
Simeprevir sodium	24.Oct.2014	11	18,900
Paliperidone	17.Apr.2014	6	10,900
Drospirenon Ethinylestradiol Betadex	17.Jan.2014	38	187,000
Iguratimod	17.May2013	9	2,600
Denosumab	11.Sep.2012	6	7,300
Dabigatran Etexilate	12.Aug.2011	5	64,000

What are real-world use surveys ?

MAHs conduct real world use surveys for most of new drugs, that are use-results surveys and specified use-results surveys.

- **Use-results surveys**

The purpose is to collect safety and efficacy data for real world.
The number of patients is usually three thousand.

- Specified use-results surveys

✓The purpose is to collect safety and efficacy data for special population such as elderly, renal/liver disorder patients or safety data for targeted ADR.

✓The number of patients are set according to the targets but usually from hundreds to a few thousand.

✓In case an intensive monitoring is necessary, all patients taking a drug are registered to obtain benefit and risk information for a designated period.

The experience of real-world use survey for Leflunomide

To register all patients taking Leflunomide until the number of patients reaches 3,000 to collect benefit and risk information.

Table 2 Comparison of the incidence rates of drug-induced lung disease in Japan and abroad

	Japan	Overseas
Gefitinib	3.98% (4,473 Japanese cases, AstraZeneca's cohort study)	0.3% (23,000 US cases, FDA Approval Letter)
Leflunomide	1.81% (3,867 Japanese cases)	0.017% (861,860 overseas cases)
Bleomycin	0.66% (3,772 Japanese cases)	0.01% (295,800 global cases)

The incidence rate is markedly higher in Japan than abroad for any of the causative agents.

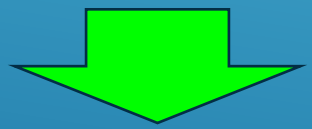
Azuma A, Japan Med Associate J, 50: 405-411, 2007

Serious cases of ILD have been reported.
5 death cases in 3 months soon after the launch.
16 ILD cases in 3412 patients enrolled in the survey

"Box Warning" in the label was revised to take more precautions against ILD

Limitations of conventional PV data

- Under-reporting of ADR (Reporting biases)
- Lack of adequate denominator information of drug utilization for estimation of risk
- Not available of the comparative incidence rates between drugs in real-world use surveys that have no reference group
- Sometimes difficult to distinguish ADR from events associated with underlying diseases or other factors



To strengthen post-marketing drug safety measures in PMDA by developing new safety assessment framework using Japanese medical information databases etc.

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- New activities for evaluation of B/R balance
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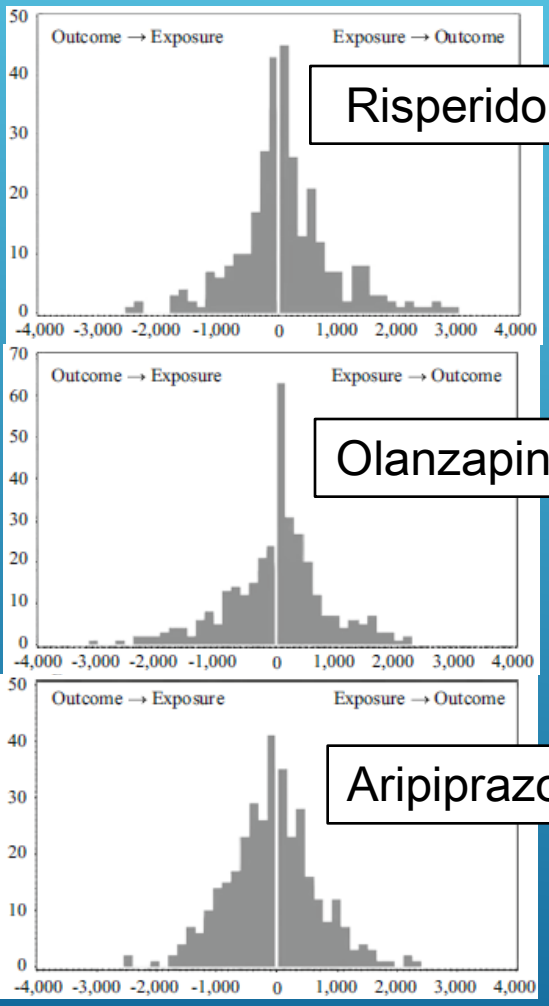
  - ✓ MID-NET
  - ✓ Project of Child and Drug Information Center
  - ✓ Registries for Medical Devices and Regenerative Medicine

What is MIHARI Project?
Medical Information for Risk Assessment Initiative

- "MIHARI" means a guard or a watch in Japanese.
- MIHARI Project is:
  - To utilize electronic healthcare records (EHR: health insurance claim data, medical records, etc) in order to evaluate possible Safety issues more quickly and more securely.
- In 2009-2013, more than 40 pilot studies were conducted to characterize the existing EHR databases and to develop phamacoepidemiological methodology to utilize EHR for quantitative risk evaluation of drugs.
- In 2014, MIHARI project was formally launched as a regular safety assessment process of drugs.

Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia of MIHARI project

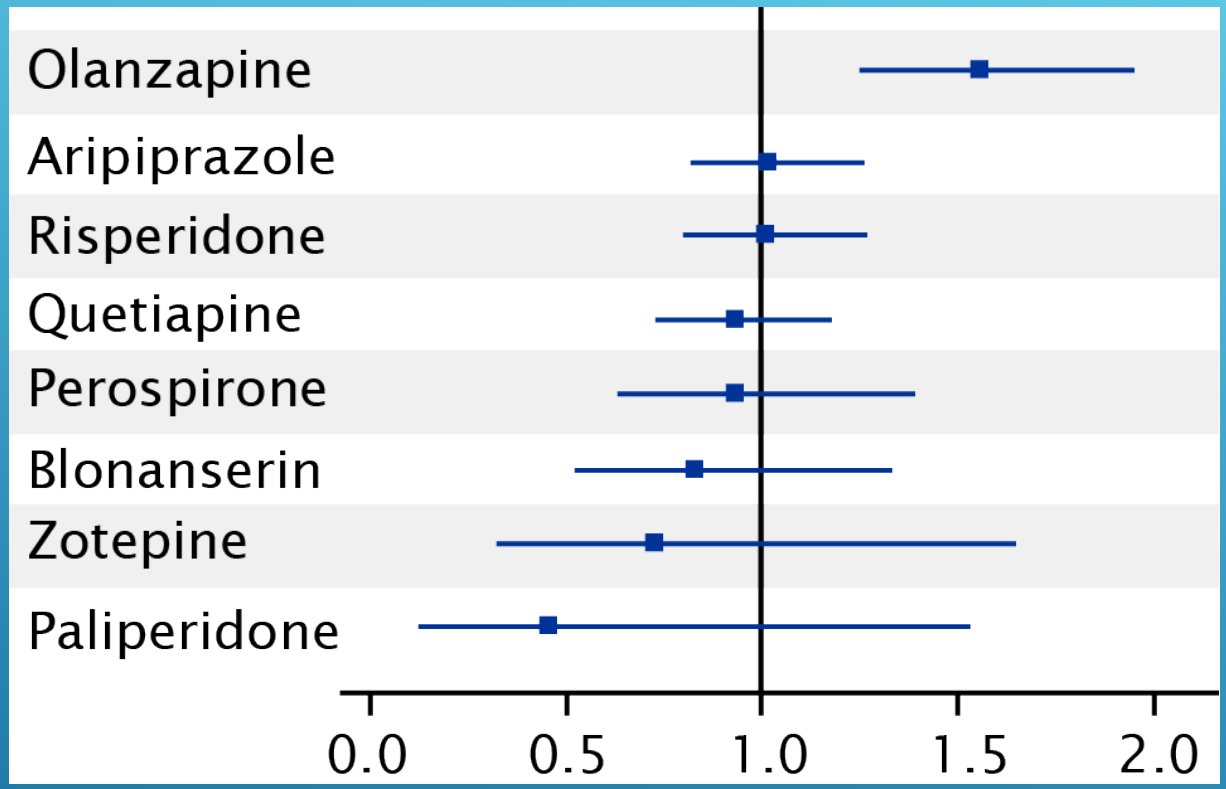


Risperidone

Olanzapine

Aripiprazole

Number of days since an initial administration of AAP



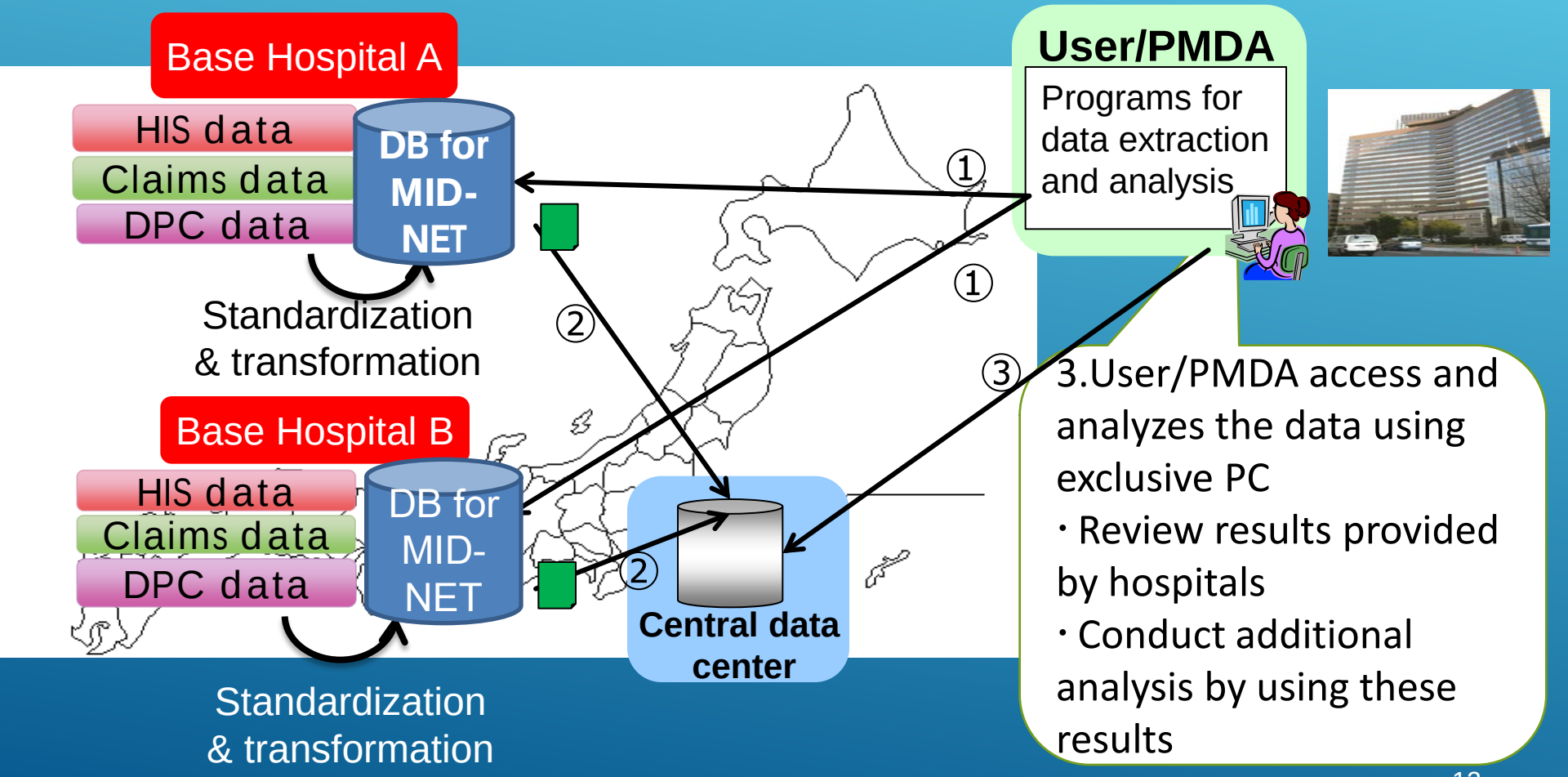
Adjusted sequence ratio (95 % CI)

Takeuchi Y et al, *Drug Saf* (2015)38: 641-650

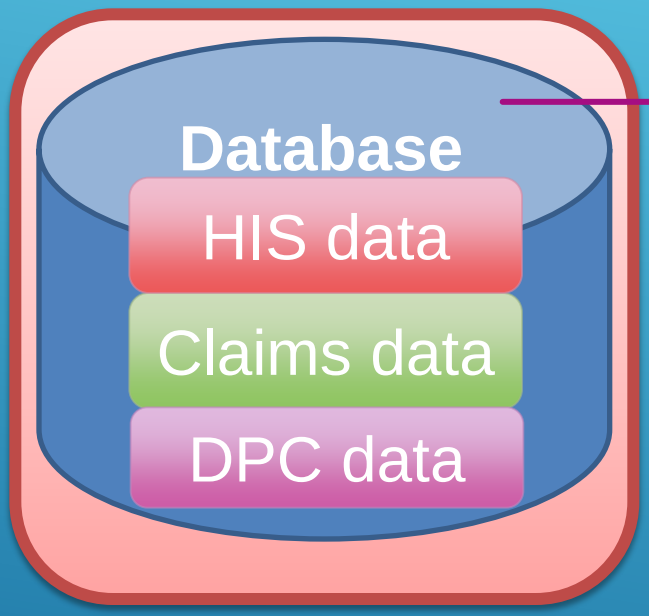
Overview of MID-NET System

Network of 10 base hospital database of 23 hospitals

1.User/PMDA sends query programs for data extraction to 10 base hospitals, consisting of 7 university hospitals and 3 hospital groups.
2.Each hospital approves queries and sends a result of analysis to data center.



Data categories in the MID-NET system



HIS data

- Patient identifying data
- Medical examination history data (including admission , discharge data)
- Disease order data
- Discharge summary data
- Prescription order/compiled data
- Injection order/compiled data

Outcome data

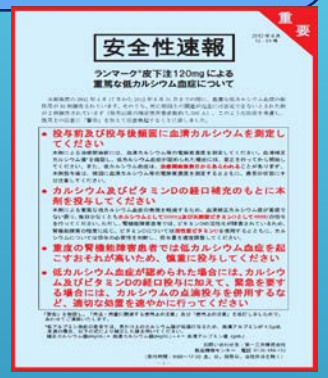
- Laboratory test data
- Radiographic inspection data
- Physiological laboratory data
- Therapeutic drug monitoring data
- Bacteriological test data

MID-NET will contribute to regulatory action
(Trial analysis: Denosumab for Hypocalcemia)

Launched
(2012.4.17)

Spontaneous ADR reports
(～2012.8.31)
・serious Hypocalcemia:
32 cases
・death:2 cases

Dear healthcare professionals letter
(2012.9.12)

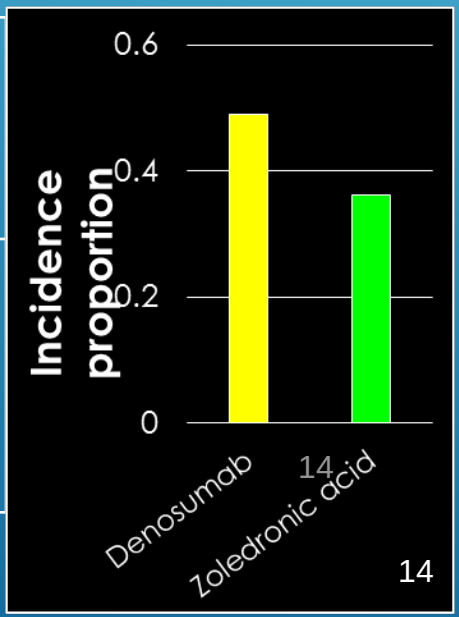


In near future

・Quantitative risk assessment compared with control

	Number of patients	Number of patient with Hypocalcemia	Incidence proportion	Relative risk
Denosumab	190	93	0.489	1.35
Zoledronic acid	245	89	0.363	

Data from 3 hospitals（2013/7～12）



Full-scale utilization will start from FY2018

- Scope of the utilization of MID-NET
  Researches for drug safety, including B/R balance assessment, or receiving grants from the Gov.

- Users
  Regulators, Academia, Pharmaceutical companies and etc.

- Operational cost and user fee
  The user fee and procedures for utilization are discussed in the committee of MHLW.

Talking with a Japanese office about using MID-NET from 2018

MAHs can use MID-NET as one of the tools for the post-market surveillance. It is expected that a survey may become more scientific and results will be updated in each PBRER.

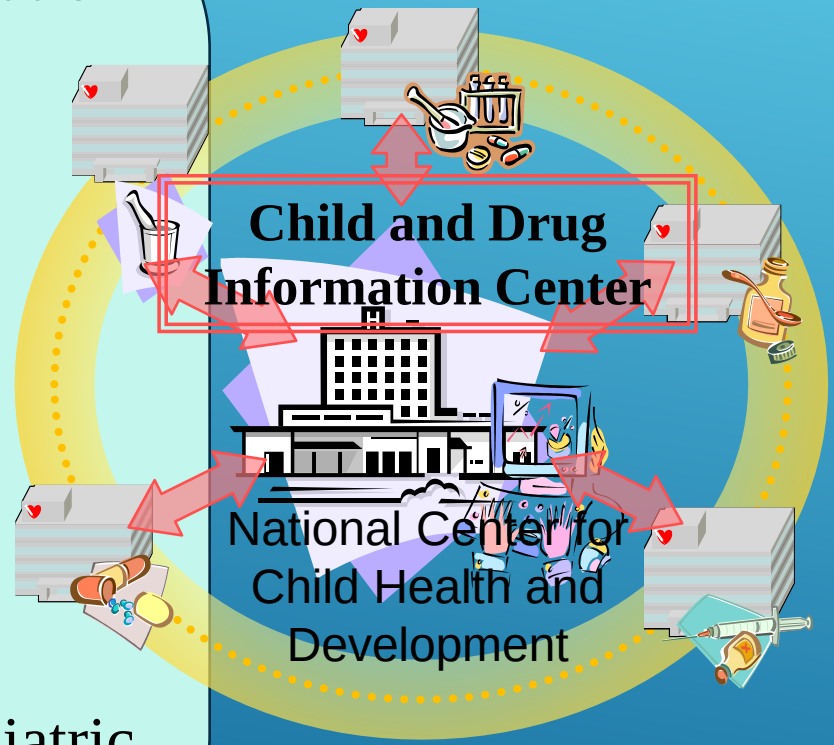
Project of Child and Drug Information Center

Purpose : Enabling to form safety measures through collecting, analyzing and evaluating information on drug use for children

★To establish Child and Drug Information Center to collect information such as

- ✓ administration, dosage for child
- ✓ adverse drug reactions

leveraging the network of pediatric medical institutions, and to build a database for analysis and evaluation

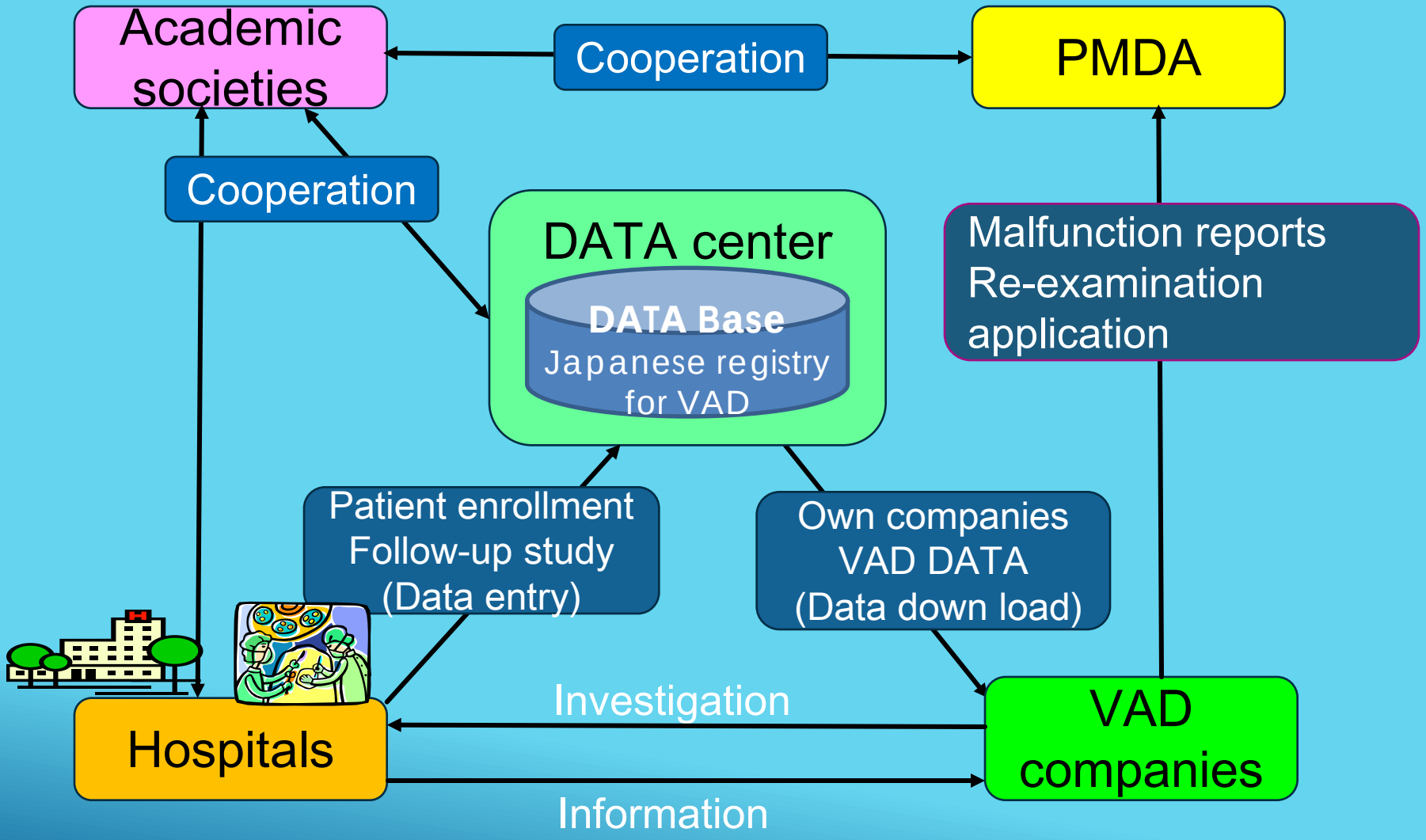


★safety measures of pediatric drugs (Revising labeling, etc.)

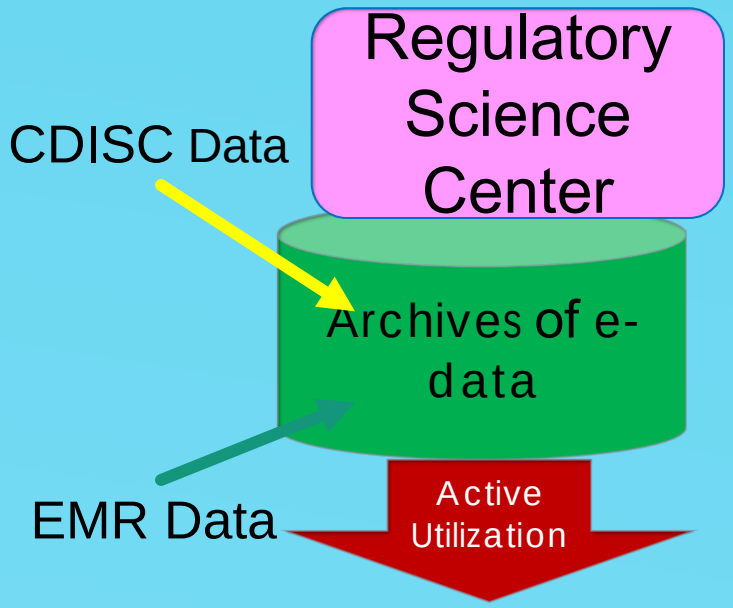
★ contribution to development of pediatric drugs

Registries for Medical Device and Regenerative Medicine

Japanese Registry for Mechanically Assisted Circulatory Support



PMDA Regulatory Science Center
(planned in 2018)



"BIG DATA"-utilized Assessment & Regulation

Utilization of e-data for better regulatory decision in

- Development
- Pre-Approval
- Pharmacovigilance

Thank you for your attention

E-mail: uzu-shinobu@pmda.go.jp
HP: https://www.pmda.go.jp/englis