Challenges for Post-marketing Drug Safety Measures Using Electronic Healthcare Database in Japan

-MIHARI project and MID-NET project-

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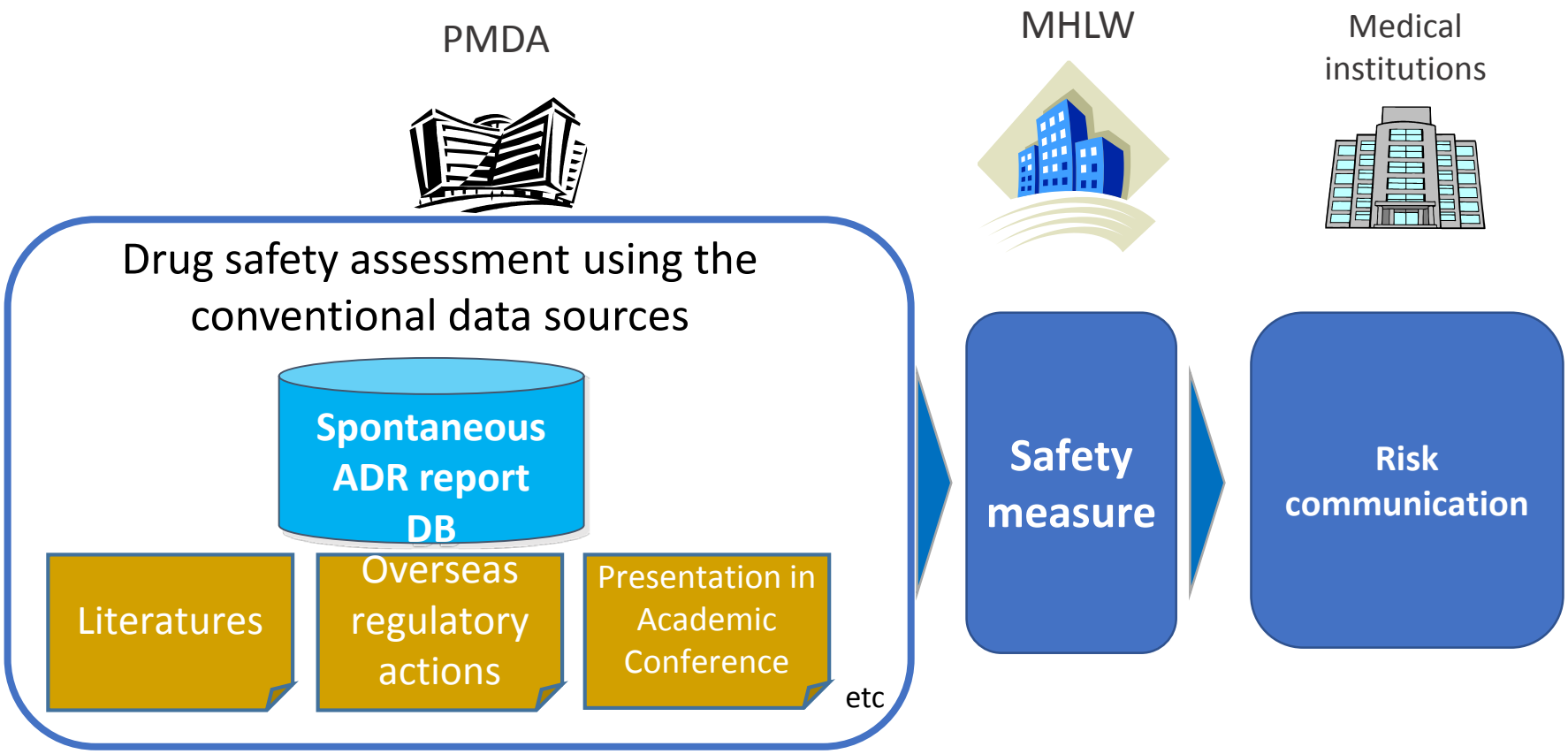
PMDA

Today's Agenda

- Limitation of Current process of the post-marketing drug safety assessment
- MIHARI Project
- MID-NET Project
- Future Perspectives

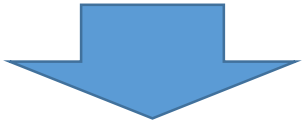
Current process of drug safety measures in Japan



MHLW: Ministry of Health, Labour and Welfare, Japan

Limitations of Current process

- 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 post-marketing studies that had no comparison group
- Sometimes difficult to distinguish ADR from events associated with underlying diseases or other factors



Other source of information and other methods are required

– To strengthen post-marketing drug safety measures and compensate for the limitations

PMDA's challenges

- Two projects to reinforce and enhance post-marketing drug safety measures in PMDA

➢ MIHARI Project (MIHARI means "monitor" in Japanese)

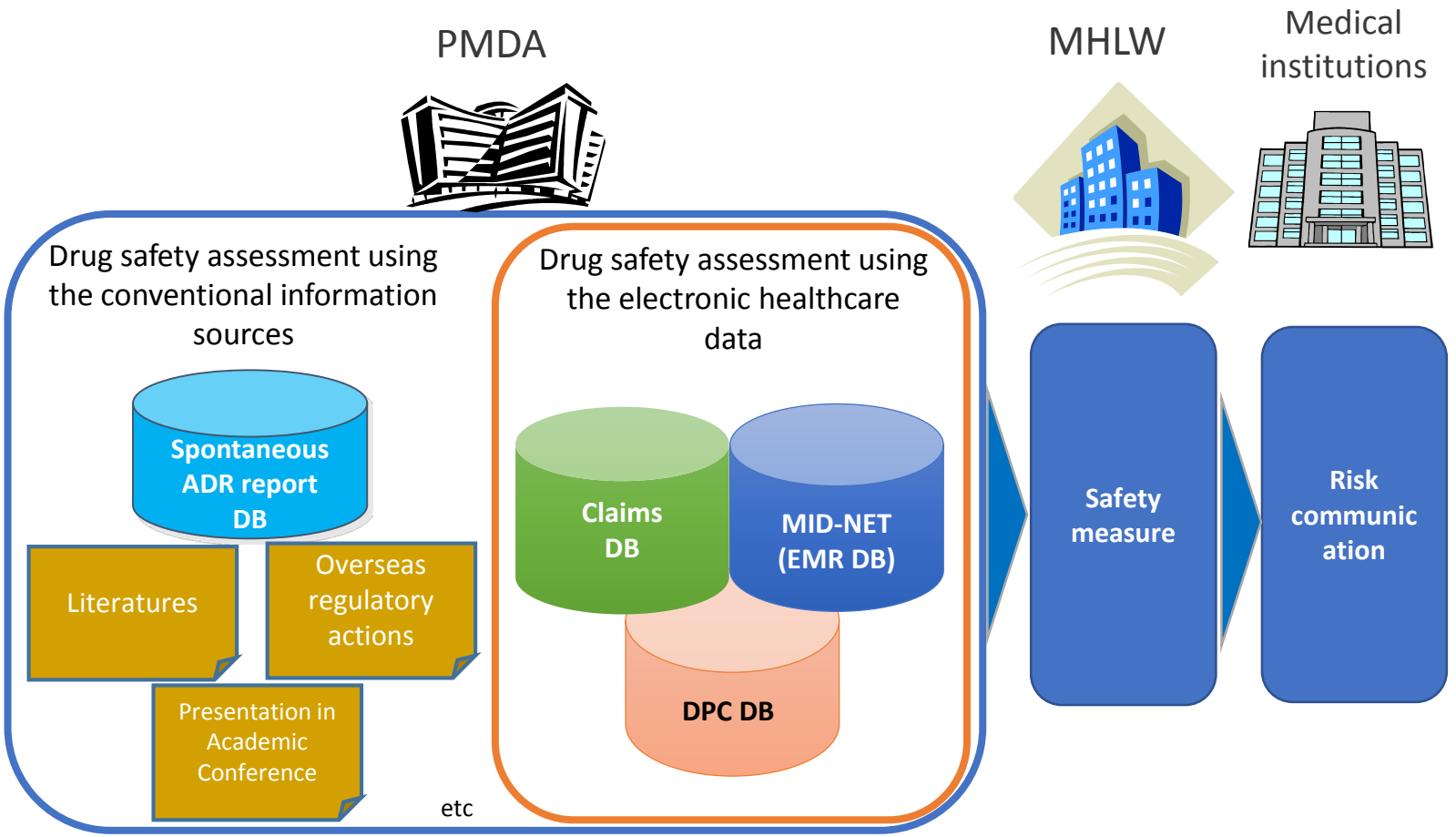
Establishment of a framework in PMDA to utilize Pharmacoepidemiological methods for safety assessment of a drug

➢ MID-NET Project (Medical Information Database NETwork)

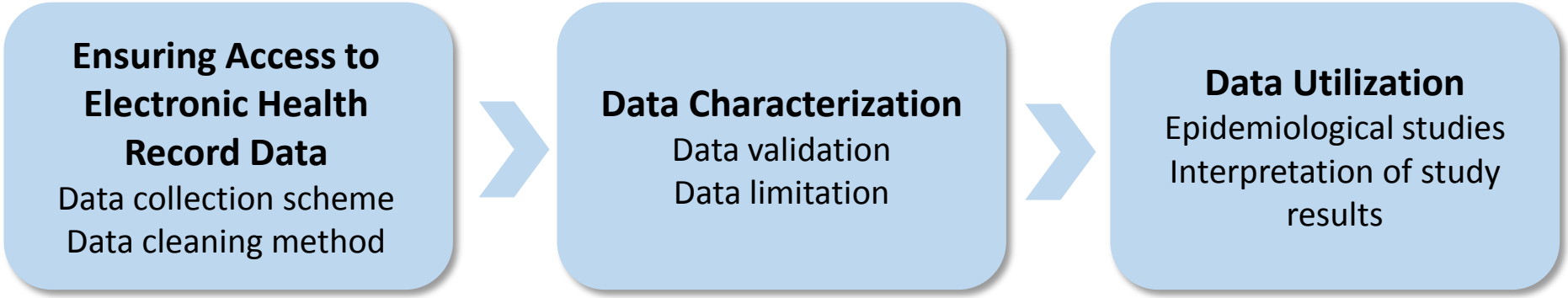
Establishment of a new medical information database in Japanese patients for safety assessment of a drug

MIHARI Project

Goal of MIHARI Project



MIHARI's Investigative Approach in the pilot phase



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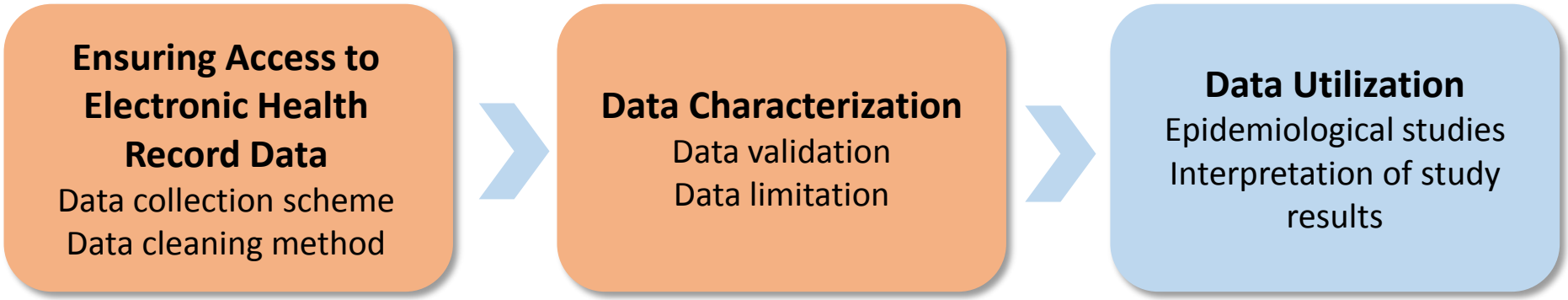


Current data sources available in Japan (1)

Claims data

- The data for the purposes of reimbursement
- Data in the standardized format is created
  - Claims data from health insurance associations
    - About 2 million patients
    - Commercially available
  - National Claims data from government
    - Almost all of patients in Japan (over 127 million patients)
    - Applicants approved through a rigorous review can use

Diagnosis and Procedure Combination (DPC) data

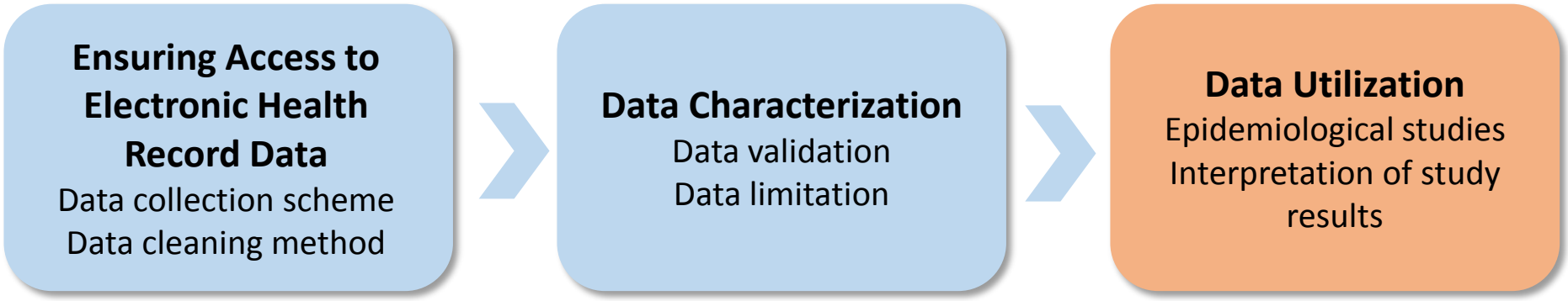
- Prospective payment system for acute inpatient medical care
- Data in the standardized format is available
  - Holders of databases perform all analysis in response to requests

Current data sources available in Japan (2)

Electrical Medical Record (EMR)

- EMR includes detailed information on medical practices within medical institution
  - EMR includes data from HIS (Hospital Information System)
  - One is the key features is that the data includes the laboratory test results
- HIS data is created by customized system according to each hospital's need
  - HIS data needs to be transformed into a standardized format
- EMR available in Japan
  - MID-NET (described below)
  - Some researchers may use the standardized EMR by collaborating with some medical institutions

MIHARI's Investigative Approach in the pilot phase



Pilot studies in the pilot phase (2009-2013)

- More than 40 pilot studies were conducted
  - To assess the feasibility of applying the well-known pharmacoepidemiological design/methods to drug safety assessment with Japanese electronic healthcare data
  - In pilot studies, already well-known safety issues were evaluated

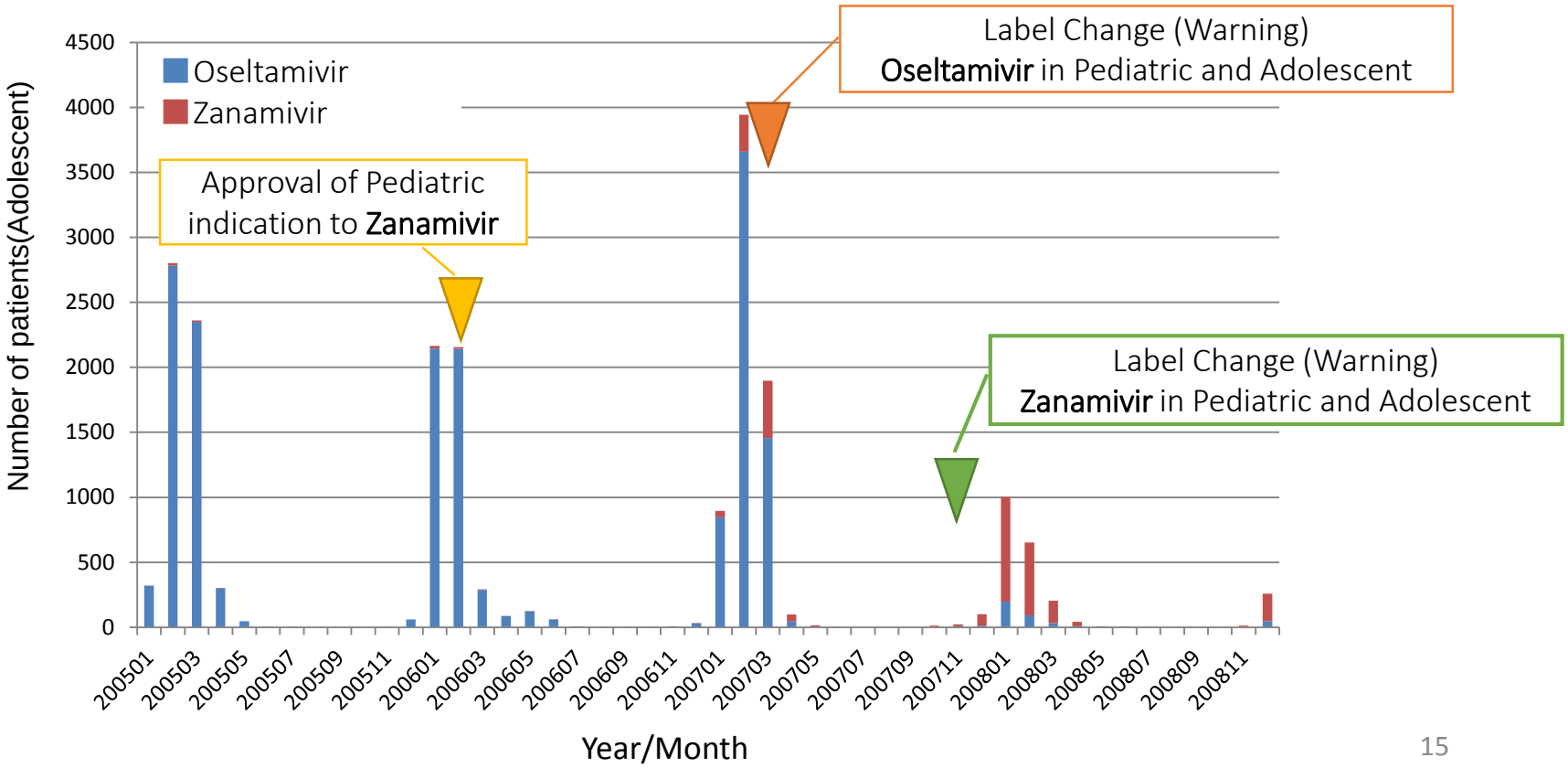
The design/methods used

- Design
  - Cohort design
  - Nested case control design
  - Sequence Symmetry Analysis
  - Self-controlled case series
  - Validation study
- Methods
  - Segment regression analysis
  - Propensity score (PS) methods for control confounding

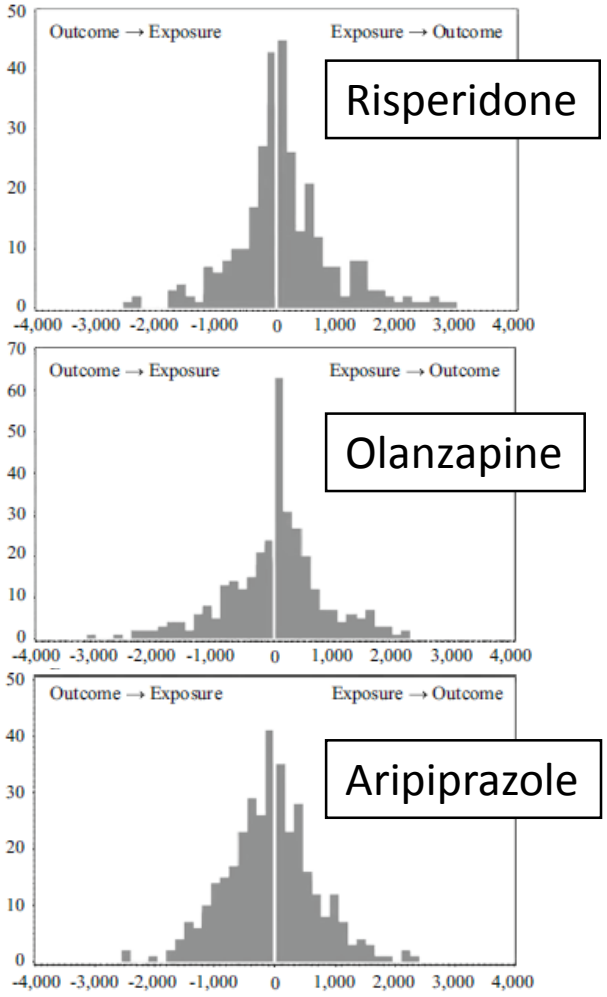
Example: Impacts of regulatory action (anti-Influenza drug)

Objectives:

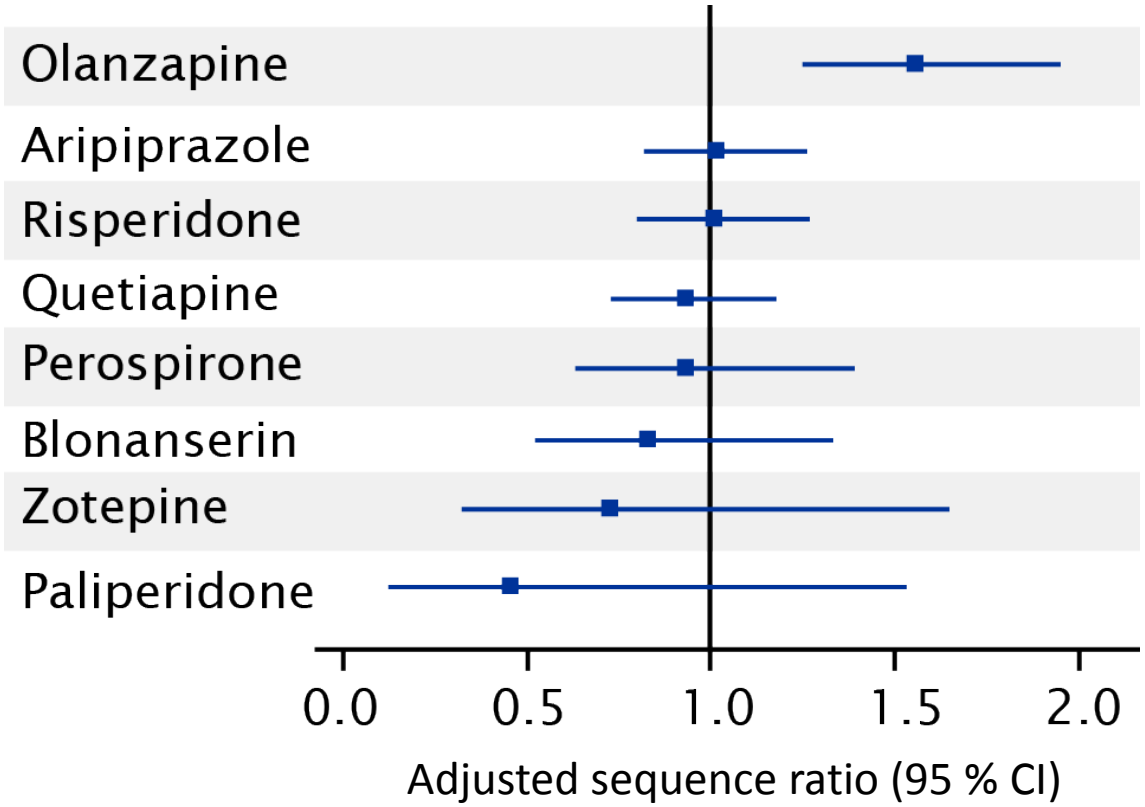
To assess impacts of regulatory safety measure for an individual products using the Japanese claims data



Example: Risk evaluation of Atypical Antipsychotics (AAP) for Hyperlipidemia



Number of days since an initial administration of AAP



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

Other activities: Cooperation with other office

PMDA

Office of Medical Informatics and Epidemiology

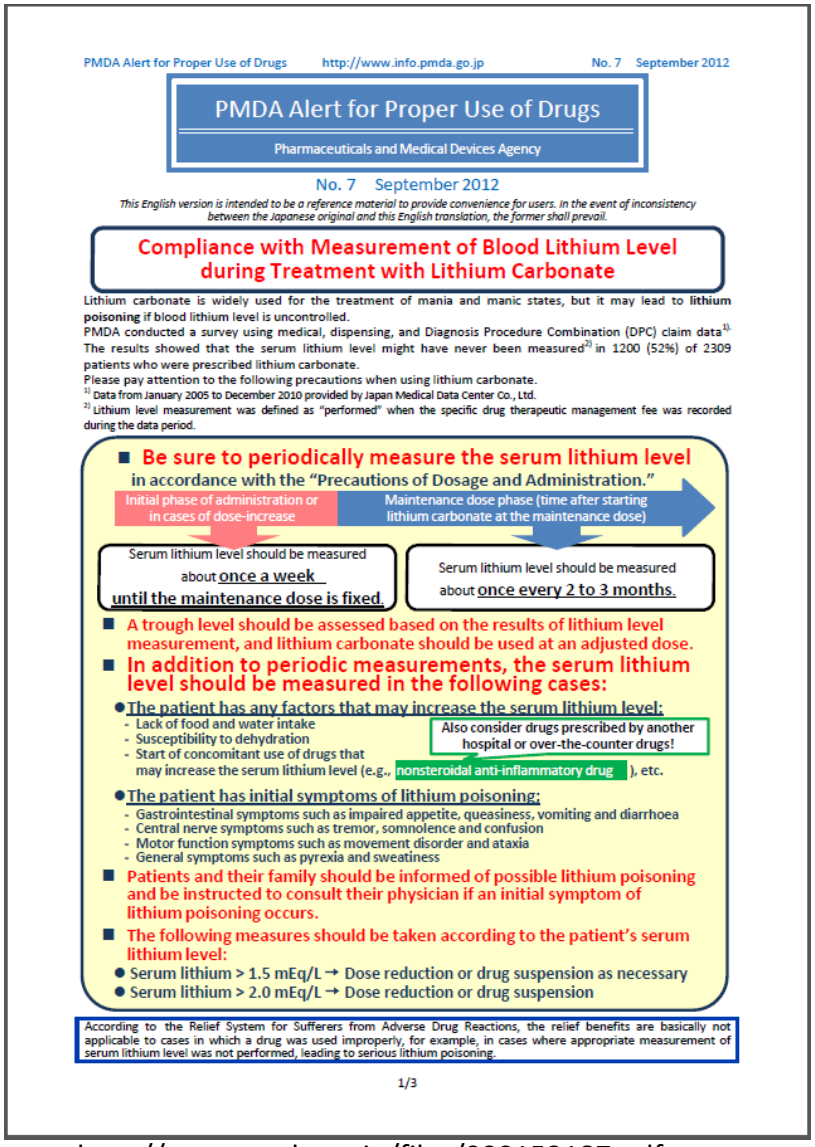
Office of Safety II

Requests from other office

- ✓ Literature review
- ✓ Pharmacoepidemiological studies using electronic healthcare database

PMDA alert based on survey using claims data

- Targeted drug : Lithium Carbonate
  - Drug for treatment of mania and mania status
  - It can cause lithium poisoning if blood lithium level is uncontrolled
- PMDA conducted a survey using claims data[1].
- The serum lithium level might have never been measured[2] in 1,200 of 2,309 patients (52%) who were prescribed lithium carbonate



PMDA Alert for Proper Use of Drugs http://www.info.pmda.go.jp No. 7 September 2012

PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 7 September 2012

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Compliance with Measurement of Blood Lithium Level during Treatment with Lithium Carbonate

Lithium carbonate is widely used for the treatment of mania and manic states, but it may lead to **lithium poisoning** if blood lithium level is uncontrolled.
PMDA conducted a survey using medical, dispensing, and Diagnosis Procedure Combination (DPC) claim data[1]. The results showed that the serum lithium level might have never been measured[2] in 1200 (52%) of 2309 patients who were prescribed lithium carbonate.
Please pay attention to the following precautions when using lithium carbonate.

[1] Data from January 2005 to December 2010 provided by Japan Medical Data Center Co., Ltd.
[2] Lithium level measurement was defined as "performed" when the specific drug therapeutic management fee was recorded during the data period.

■ **Be sure to periodically measure the serum lithium level in accordance with the "Precautions of Dosage and Administration."**

Initial phase of administration or in cases of dose-increase	Maintenance dose phase (time after starting lithium carbonate at the maintenance dose)
Serum lithium level should be measured about **once a week until the maintenance dose is fixed.**	Serum lithium level should be measured about **once every 2 to 3 months.**

■ A trough level should be assessed based on the results of lithium level measurement, and lithium carbonate should be used at an adjusted dose.

■ **In addition to periodic measurements, the serum lithium level should be measured in the following cases:**

- **The patient has any factors that may increase the serum lithium level:**
  - Lack of food and water intake
  - Susceptibility to dehydration
  - Start of concomitant use of drugs that may increase the serum lithium level (e.g., nonsteroidal anti-inflammatory drug), etc.

  Also consider drugs prescribed by another hospital or over-the-counter drugs!
- **The patient has initial symptoms of lithium poisoning:**
  - Gastrointestinal symptoms such as impaired appetite, queasiness, vomiting and diarrhoea
  - Central nerve symptoms such as tremor, somnolence and confusion
  - Motor function symptoms such as movement disorder and ataxia
  - General symptoms such as pyrexia and sweatiness

■ Patients and their family should be informed of possible lithium poisoning and be instructed to consult their physician if an initial symptom of lithium poisoning occurs.

■ The following measures should be taken according to the patient's serum lithium level:

- Serum lithium > 1.5 mEq/L → Dose reduction or drug suspension as necessary
- Serum lithium > 2.0 mEq/L → Dose reduction or drug suspension

According to the Relief System for Sufferers from Adverse Drug Reactions, the relief benefits are basically not applicable to cases in which a drug was used improperly, for example, in cases where appropriate measurement of serum lithium level was not performed, leading to serious lithium poisoning.

1/3

http://www.pmda.go.jp/files/000153187.pdf

[1] Data from January 2005 to December 2010 provided by Japan Medical Data Center Co., Ltd.
[2] Lithium level measurement was defined as "performed" when the specific drug therapeutic management fee was recorded during the data period.

Future direction of MIHARI Project

Pilot Phase (2009-2013):

- ✓ Developed framework for access to electronic healthcare database
- ✓ Assessed the feasibility of applying the well-known pharmacoepidemiological methods to drug safety assessment with Japanese electronic healthcare data

Operational Phase (2014-2018):

- To apply the framework into the current risk management process of drug safety
  - ✓ Strengthening cooperation with the office of review and the office of post-marketing safety in PMDA
- To establish an access to another database and additional pharmacoepidemiological methods using electronic healthcare data
  - ✓ Continuing to assess the feasibility of applying more advanced methods to drug safety assessment

Strengthening cooperation with other office

PMDA

Office of Medical Informatics and Epidemiology

Office of Safety II

Office of New drug

Office of Cellular and Tissue-based Products

Office of Vaccine and Blood Products

New

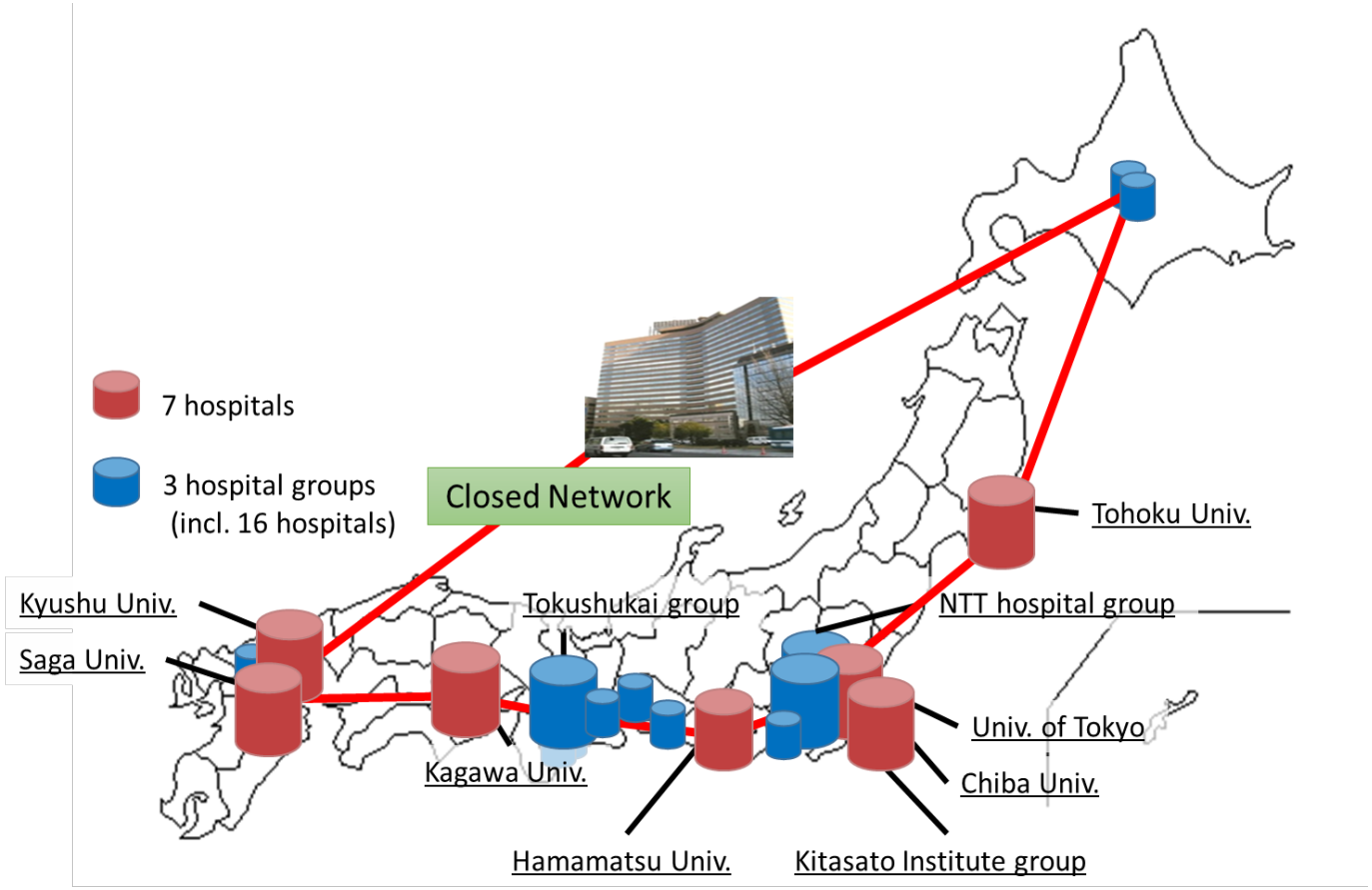
Enhancement

- *Assignment to team in charge of epidemiology*
- *Requests from other offices have been increasing*

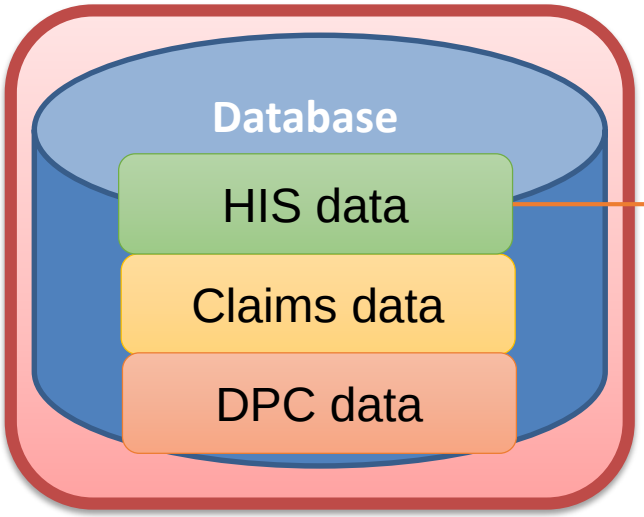
MID-NET Project

Overview of MID-NET Project

- MID-NET is project initiated by MHLW / PMDA to establish the EMR DB network for post-marketing drug safety measures using electronic healthcare data



Data categories in the MID-NET system



Claims data

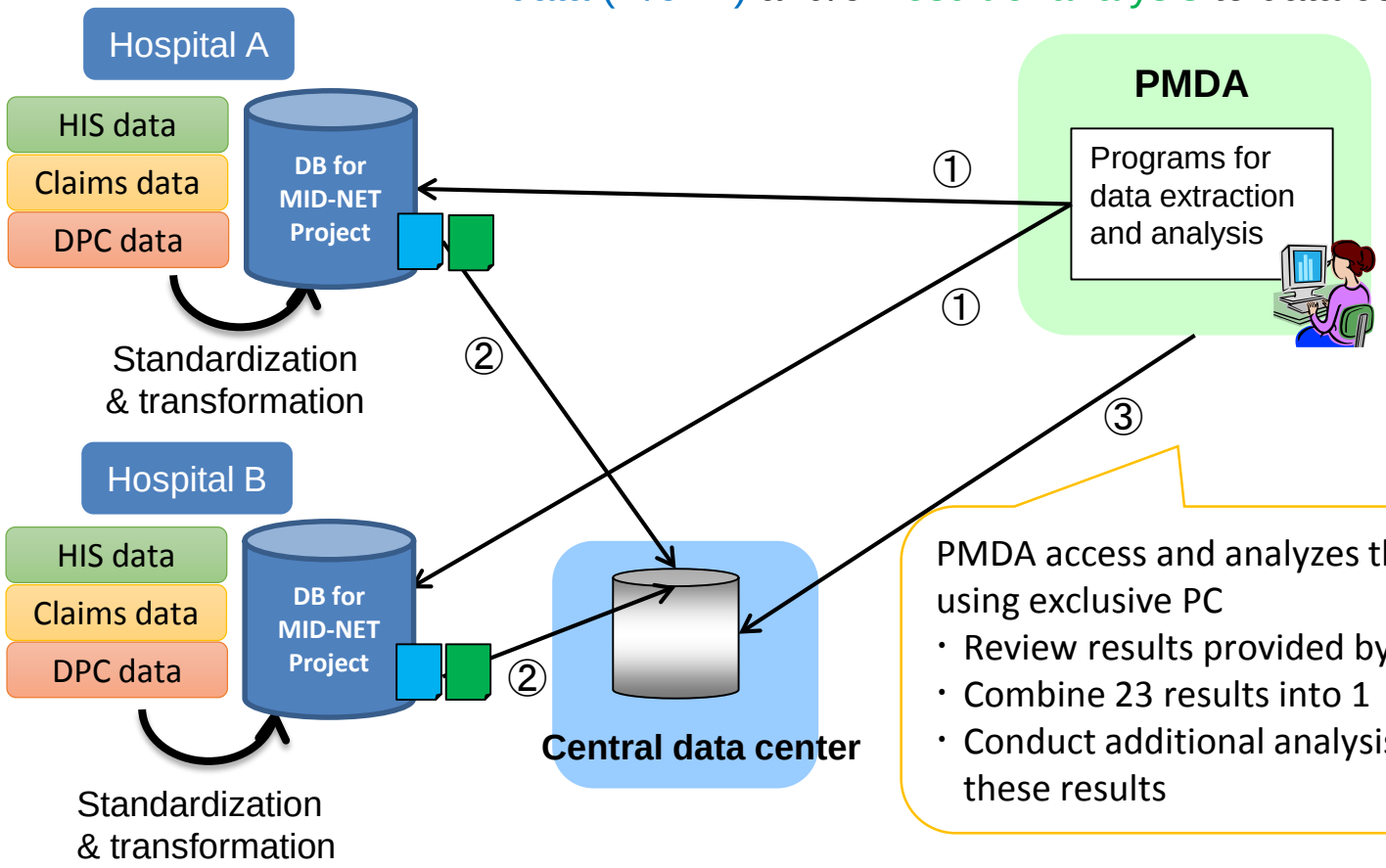
DPC data

HIS data

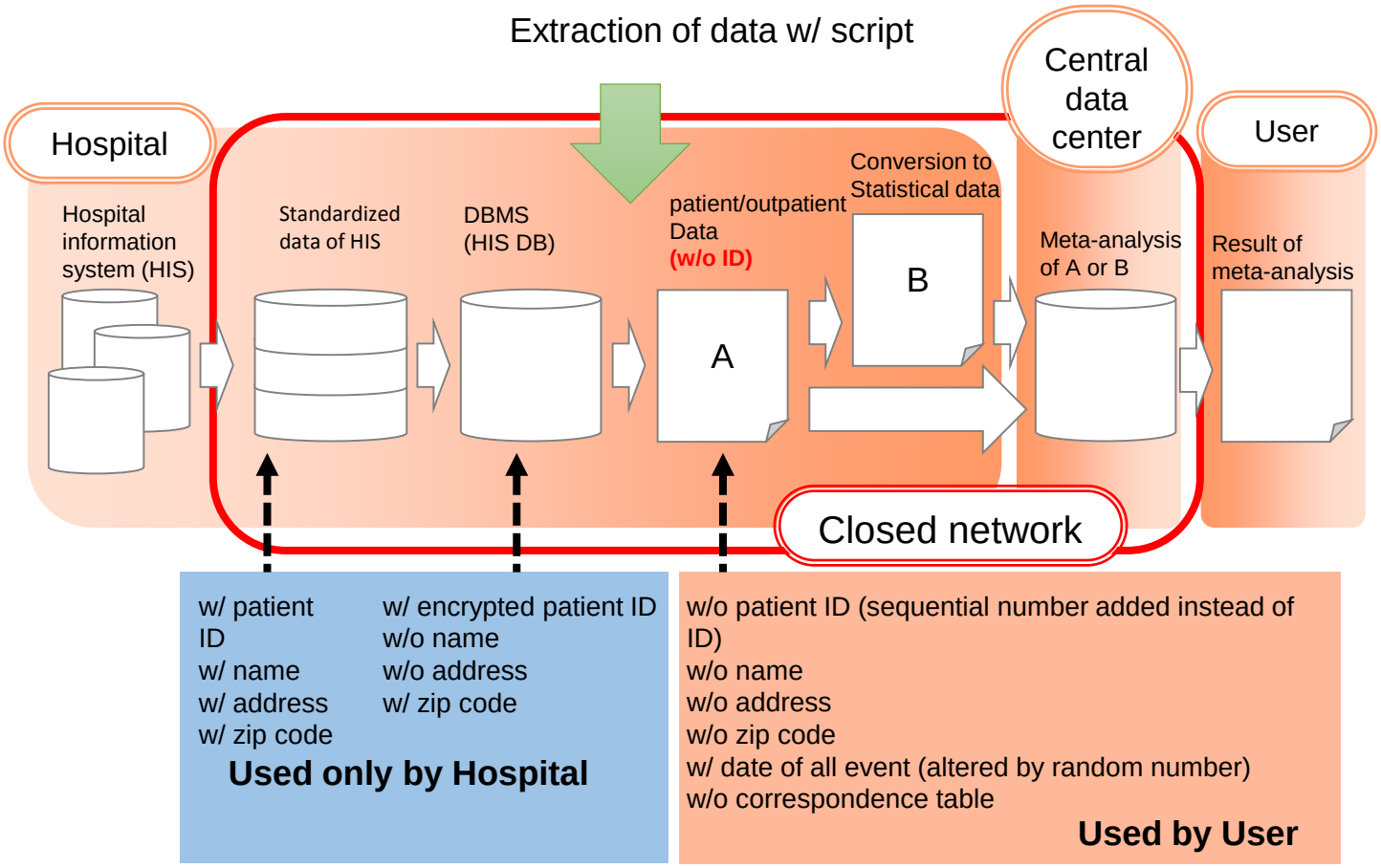
- Patient identifying data
- Medical examination history data (including admission , discharge data)
- Disease order data
- Discharge summary data
- Prescription order/compiled data
- Injection order/compiled data
- Laboratory test data
- Radiographic inspection data
- Physiological laboratory data
- Therapeutic drug monitoring data
- Bacteriological test data

Data integration method from 23 hospitals

①PMDA sends programs to 23 hospitals
②Each hospital sends anonymized individual level data (w/o ID) and/or result of analysis to data center.



Personal data flow in MID-NET



The features of MID-NET

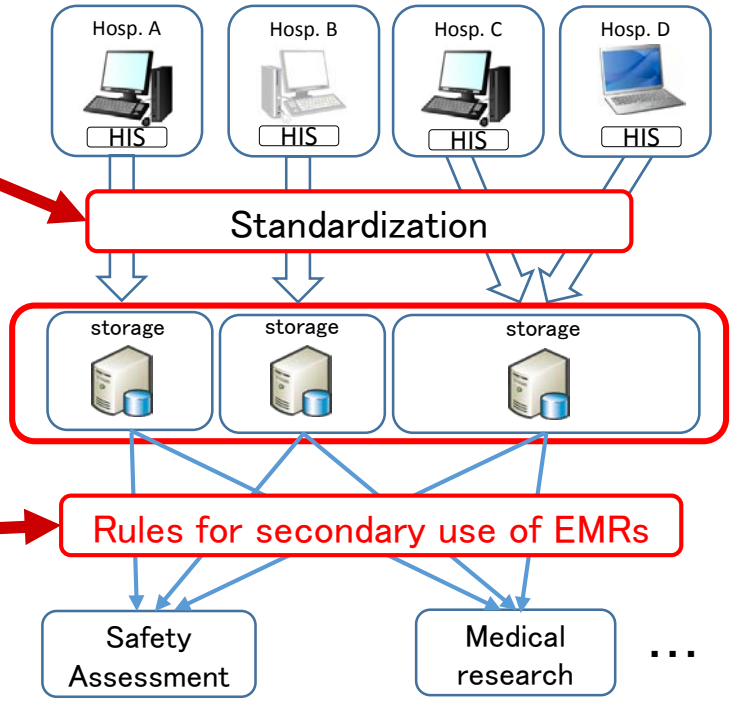
- Strengths
  - Available of various types of data (HIS data, Claims data and DPC data)
    - Including laboratory test results
  - Real time synchronization to medical record in the hospital
- Limitations
  - Number of hospitals participating in the MID-NET is currently limited (only 23 hospitals)
  - No link of data from different hospitals for a patient

Challenges for implementing MID-NET

Data standardization on medical information and quality check

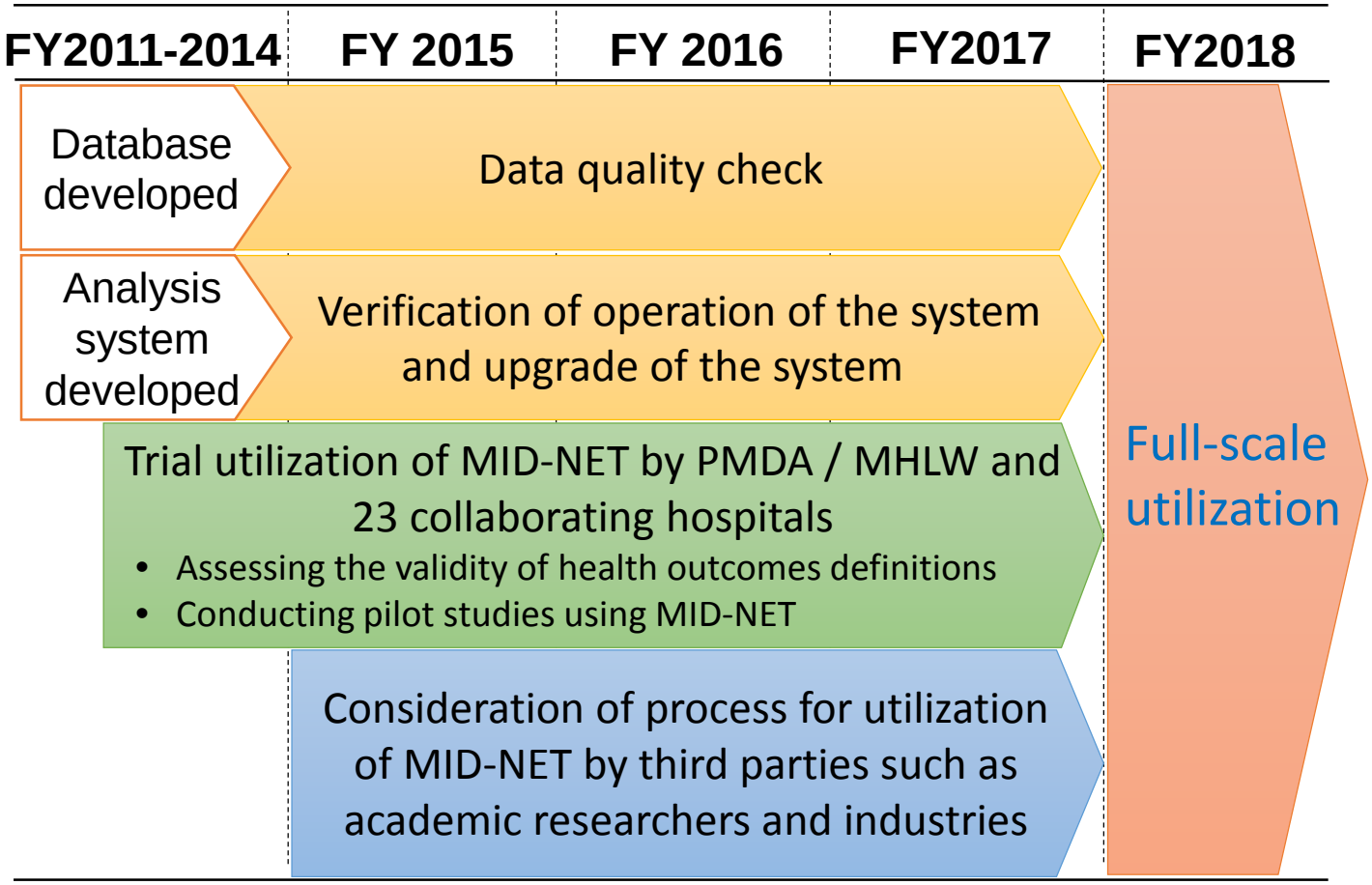
Using localized Health Level Seven (HL-7) standard, but many ambiguous points

Clear rules for secondary use of EMRs with public understanding



PMDA will actively contribute to utilization of EMRs for public health promotion

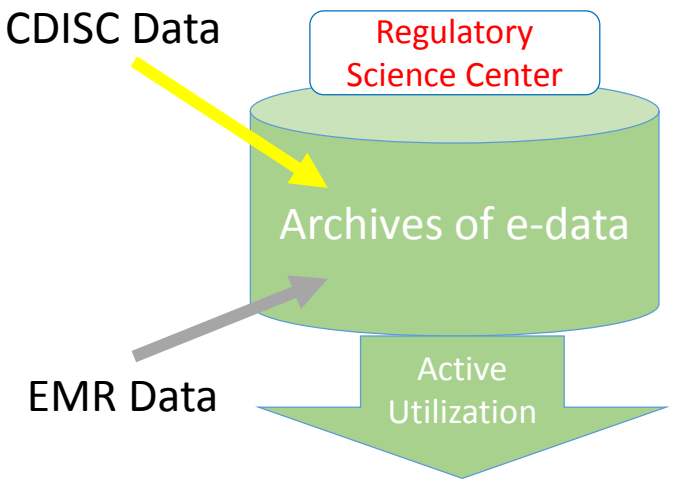
Plans for full-scale utilization



Next steps

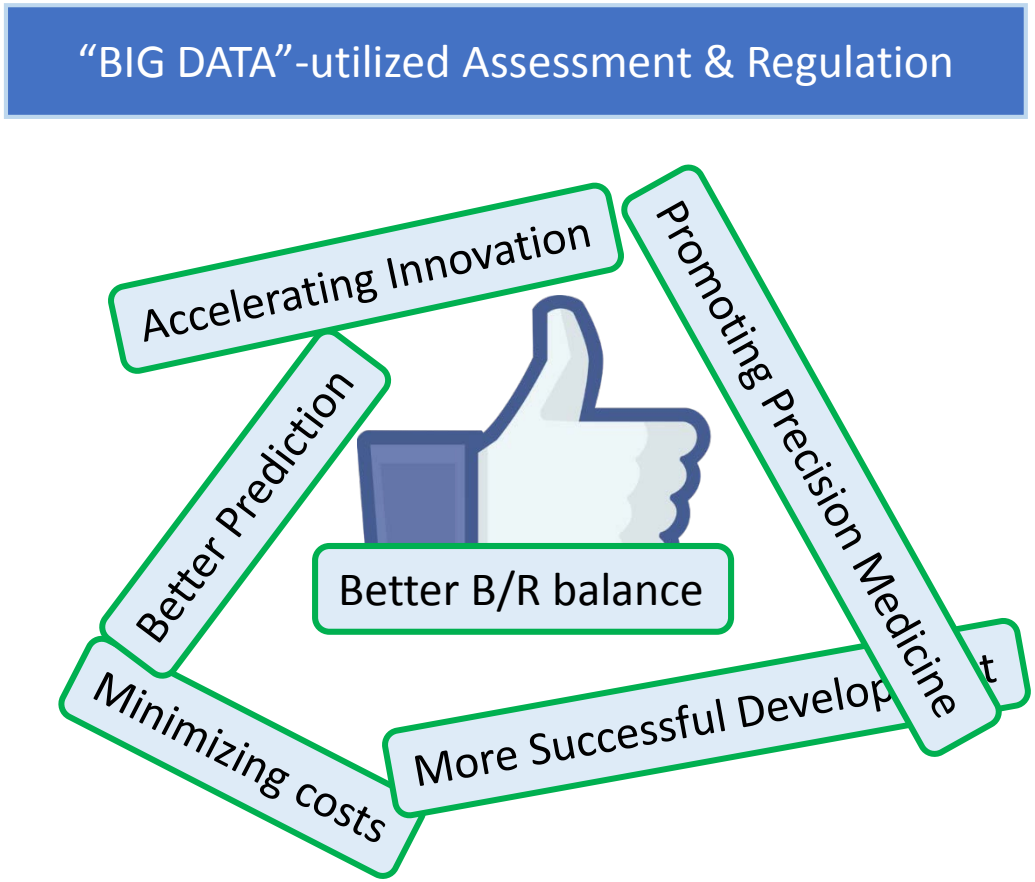
- Accumulating more regulatory experiences on pharmacoepidemiological analysis
  - More PEpi study for a individual product
  - Implementation of MID-NET
- Promotion of PEpi analysis for safety assessment by industries
  - More guideline on Pepi
  - Scientific consultation on PEpi data
- Nurturing more pharmacoepidemiologist
- Collaboration with other regulatory agencies

PMDA Regulatory Science Center (planned in 2018)



Utilization of e-data for better regulatory decision in

- Development
- Pre-Approval
- Pharmacovigilance



Thank you for attention !