Pharmaceutical and Medical Devices Agency's (PMDA) plans for use of "Big Data" in healthcare

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Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Today's contents

- Introduction
  - About PMDA
  - PMDA Pediatric Drugs Working Group
  - Framework of post-marketing safety measures in Japan
- Current situation
  - Post-marketing data collection
  - MIHARI project
  - CDISC
- Future challenges
  - MID-NET initiative
  - Clinical Innovation Network
  - "Children and Pharmaceuticals" Data Collecting Network Development Project

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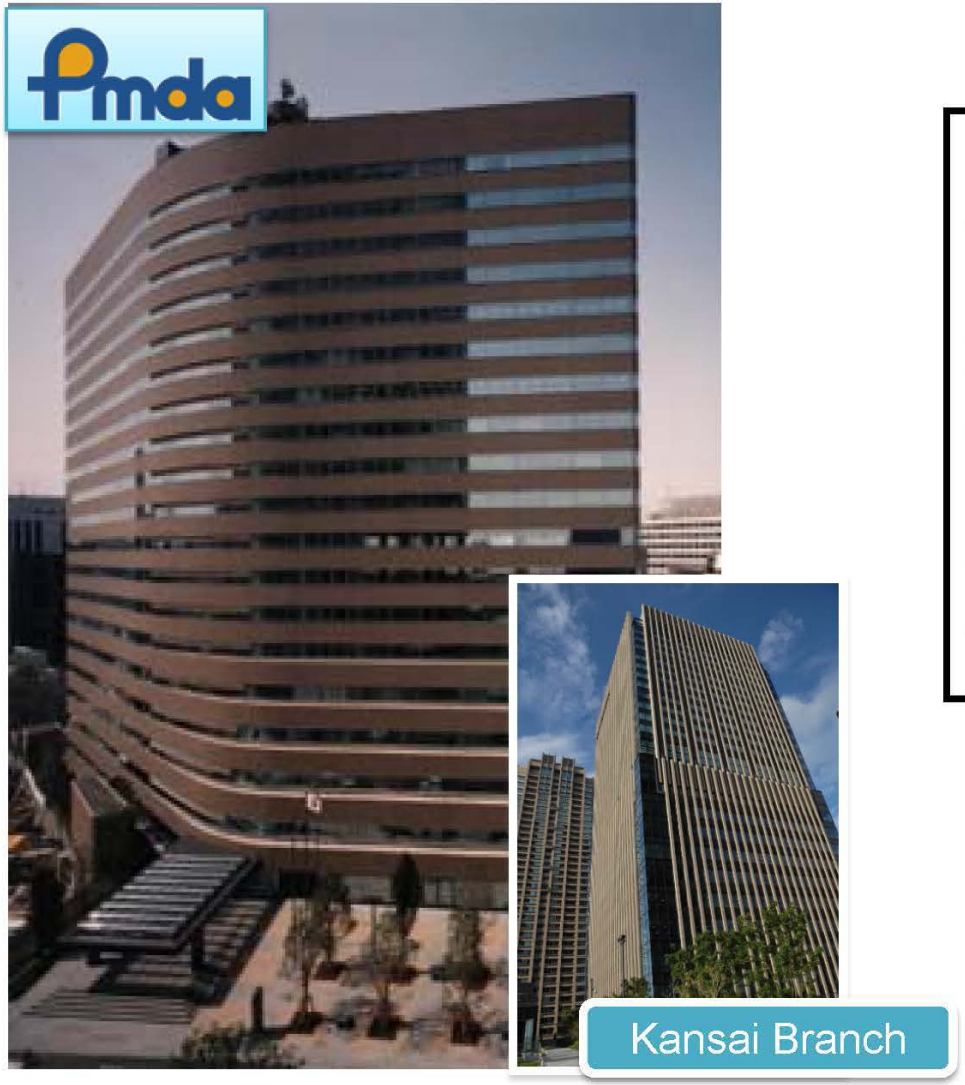
Pharmaceuticals and Medical Devices Agency



Date of Establishment : April 2004

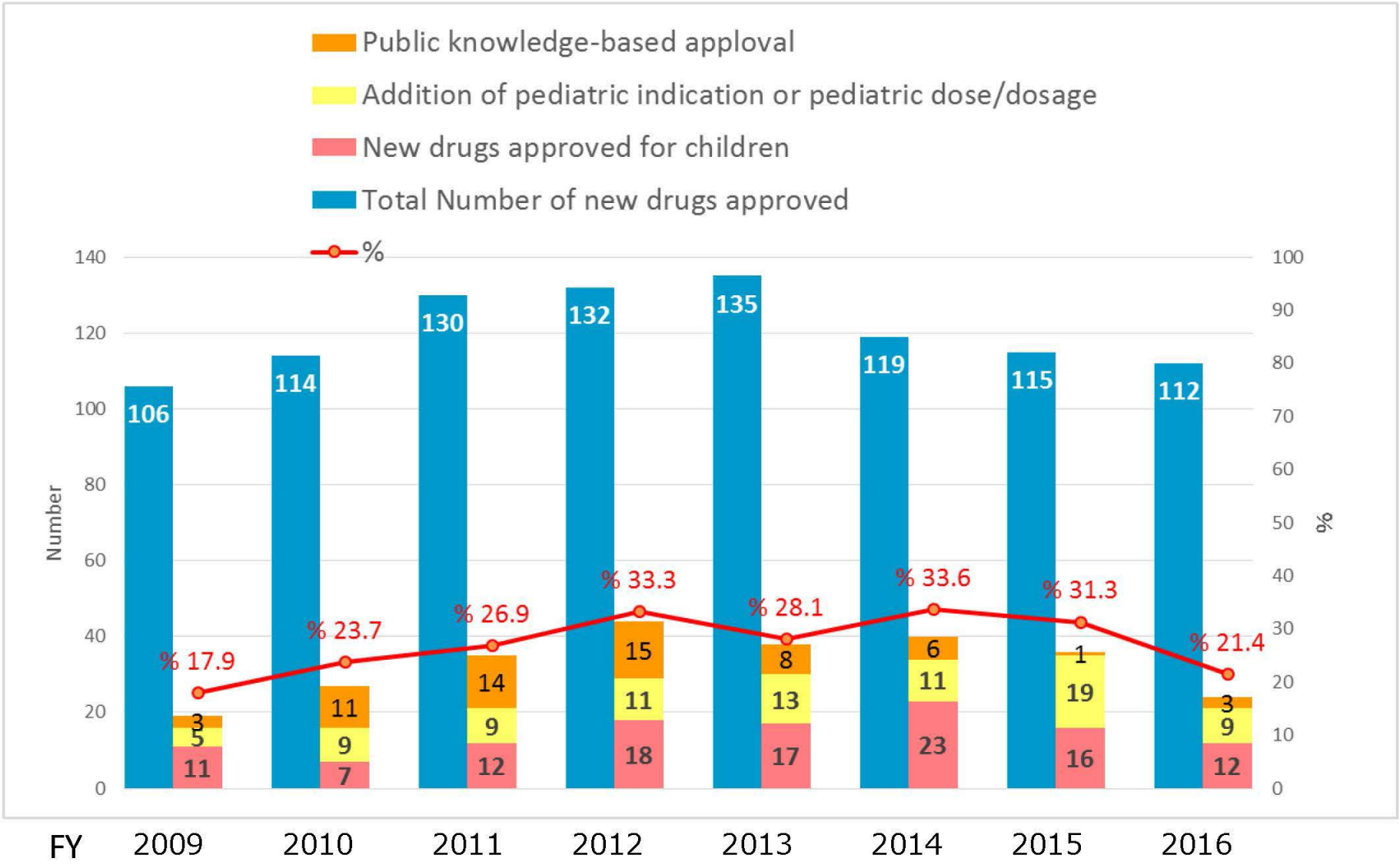
Major Responsibilities

- **Scientific Review for Drugs & Medical Devices**
- **GCP, GMP Inspection**
- **Consultation on Clinical Trials**
- **Safety Measures**
- **Relief Services**

Work in close relationship with Ministry of Health, Labor and Welfare (MHLW)

厚生労働省
Ministry of Health, Labour and Welfare

New Drug Approval



Today's contents

- Introduction
  - About PMDA
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- Current situation
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PMDA Pediatric Drugs Working Group

- One of the projects across multi-offices in PMDA
- Established in November 2011

International Collaborations

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada

TGA Health Safety Regulation

Collaboration at Pediatric Cluster

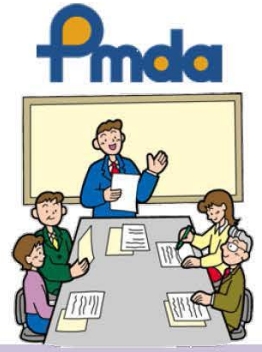
External Communications

Discuss pediatric issues with domestic stakeholders

Members from Offices of New Drug, Office of Safety, Office of Regulatory Science, *etc.*

Analyze and identify pediatric issues raised in past reviews and consultations

Analyses



Internal Communications with Review Teams

Today's contents

- Introduction
  - About PMDA
  - PMDA Pediatric Drugs Working Group
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- Current situation
  - Post-marketing data collection
  - MIHARI project
  - CDISC
- Future challenges
  - MID-NET initiative
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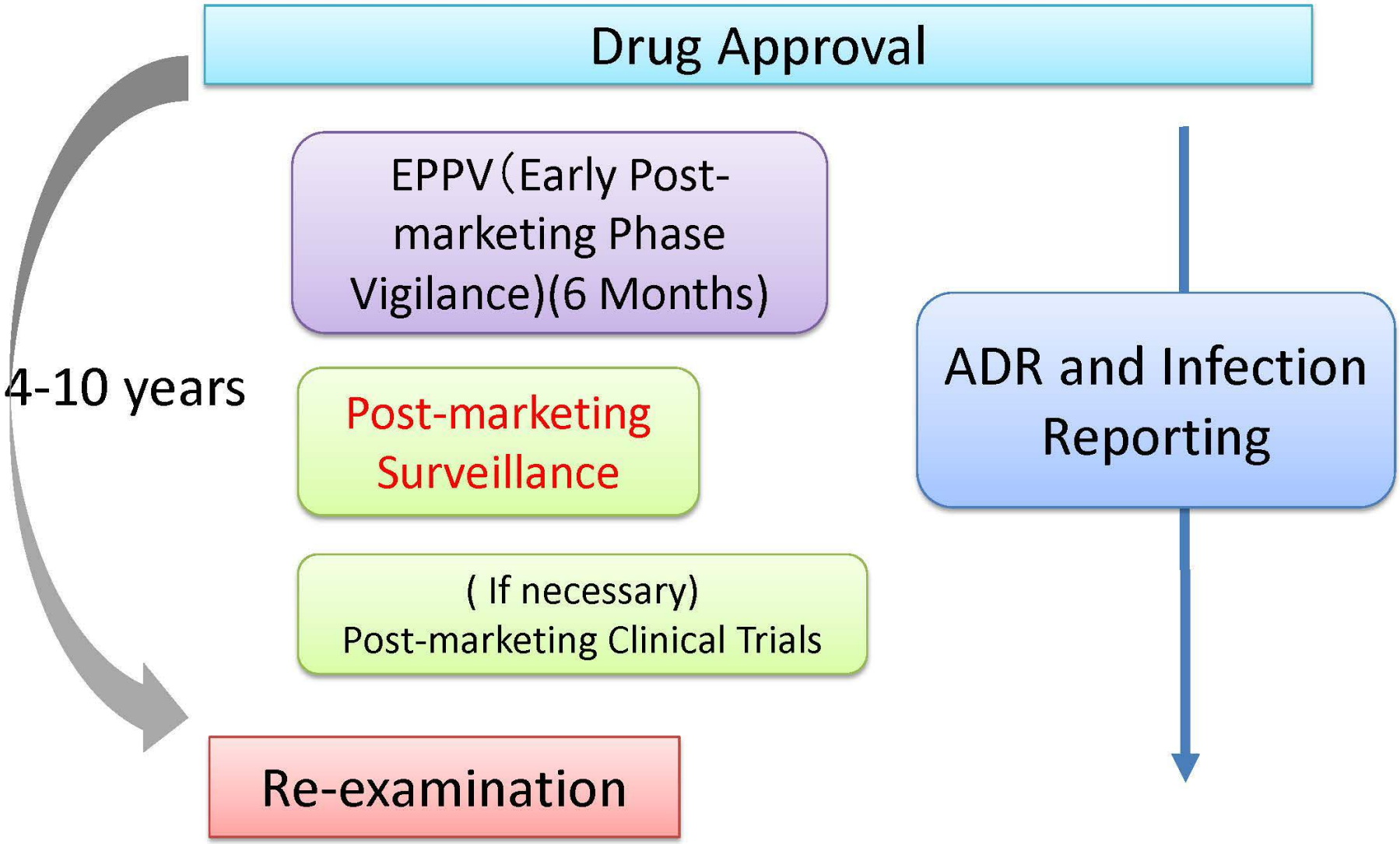
Framework of post-marketing safety measures in Japan



Re-examination (1980～)

- The re-examination system is aimed at reconfirmation of the clinical usefulness of drugs at the end of the a predetermined period after approval (“re-examination period”), through collecting information on the effectiveness and safety of the drug during the period.
- The surveillance and studies required for re-examination applications must be performed in compliance with the GPSP, GCP or GLP depending on their objective.
- The timing when these drugs should be re-examined is designated by MHLW at the time of their approval as new drugs.
- Re-examination period of drugs containing new active ingredients: 8 years (maximum 10 years)

Re-examination Results

- Applications for re-examination are judged according to the following criteria;
  - Category 1: Regarded to be useful (w/o any change in approval)
  - Category 2: Regarded to be useful with a partial change in approval
  - Category 3: Regarded not to be useful

Today's contents

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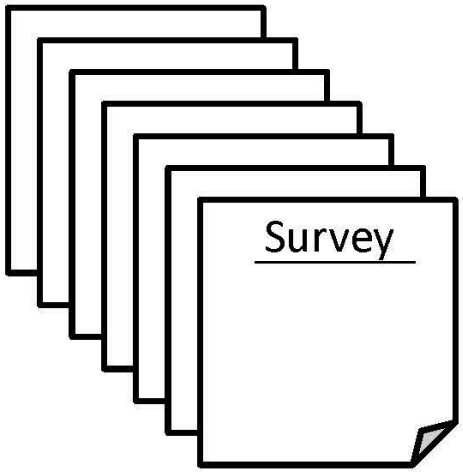
Conventional post-marketing data collection

- Conducted in almost all drugs to collect efficacy and safety information under the real clinical use
- If necessary, investigation on long-term treatment, use in children, geriatrics and patients with renal or hepatic impairment, etc.
- Confirm concern Adverse Reactions (ARs), unknown ARs, and factors considered influential to efficacy and safety of the drug
- All-case surveillance are required when limited data available at the time of approval, orphan products



Limitation of conventional post-marketing data collection

Post-marketing surveillance is beneficial

- —It allows follow-up of specific safety information in real clinical use
- —It is useful especially when pre-market data is limited; NMEs, orphan products

However,

- It is non-interventional, mostly uncontrolled
- It is difficult to collect lots of information; burdensome tasks for medical experts, a lot of costs

Other options for collecting data ?

Today's contents

- Introduction
  - About PMDA
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  - Post-marketing data collection
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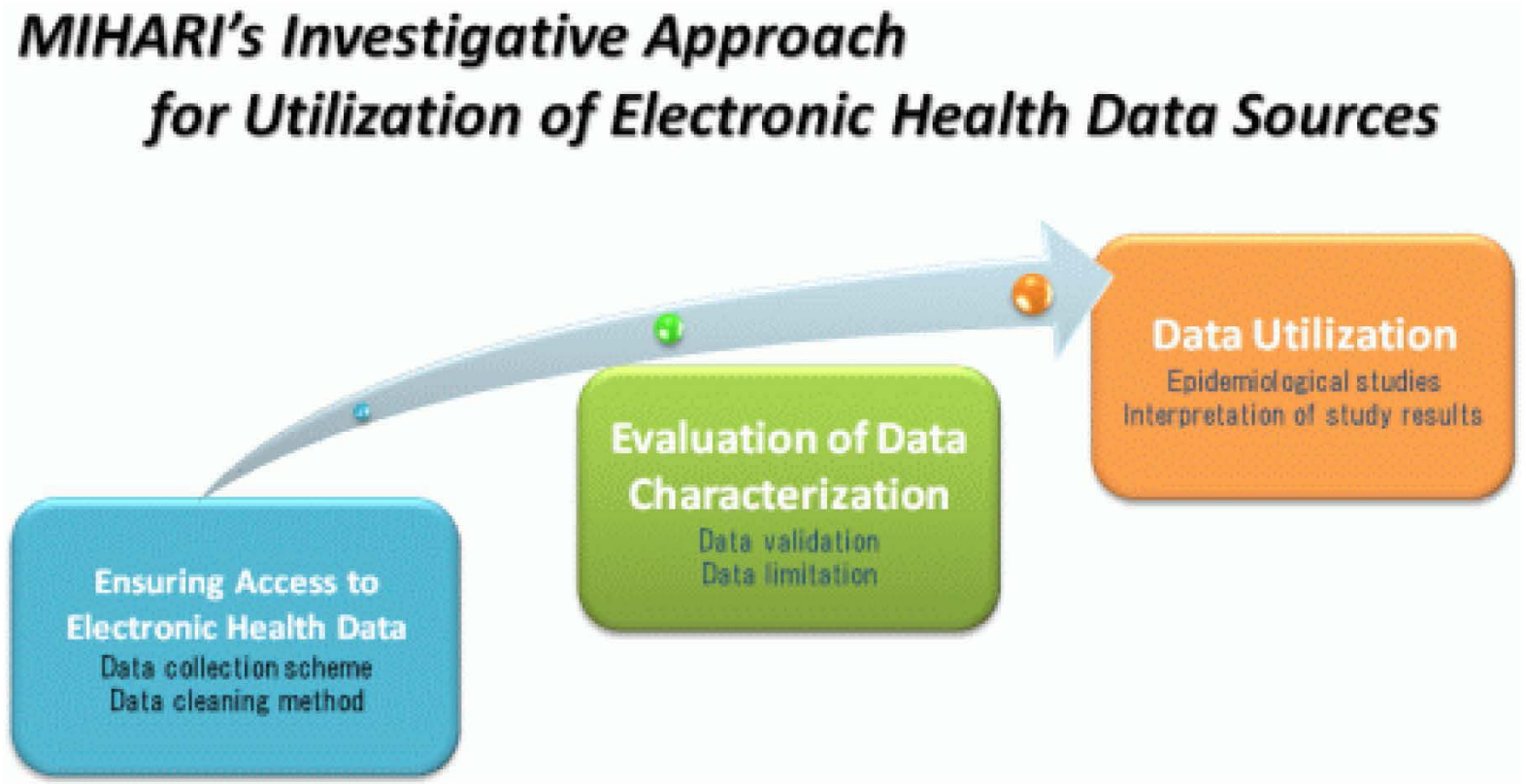
MIHARI project

MIHARI: Medical Information for Risk Assessment Initiative

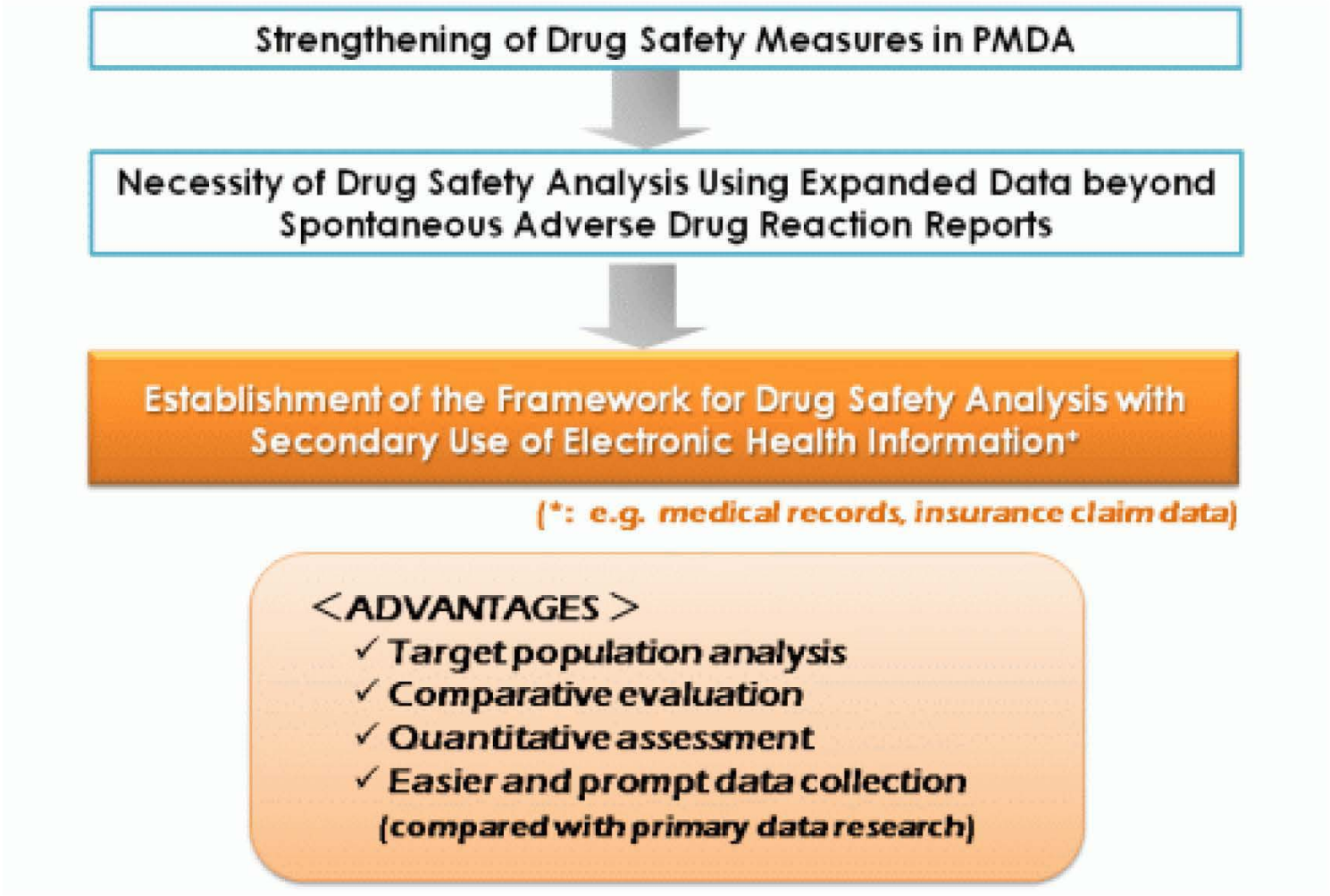
MIHARI means “monitoring” in Japanese.

What is the MIHARI project?

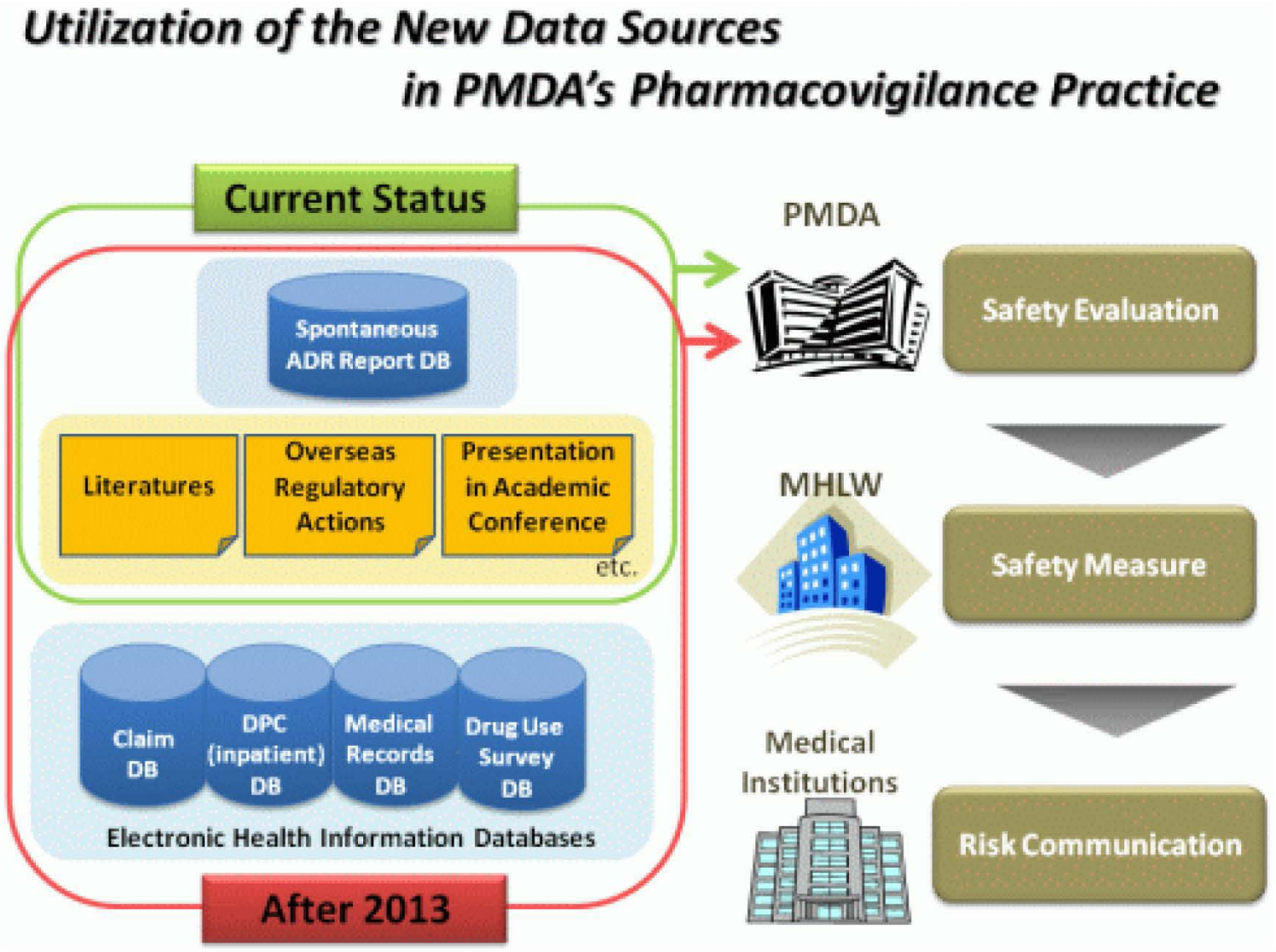


MIHARI project

Why the MIHARI project was started?



MIHARI project



MIHARI Communication

- The study results of the MIHARI Project have been updated on the PMDA website timely.

No	Title
1	Drug utilization assessment of biguanides antidiabetic agent
2	Interferon products and the risk of depressive symptoms
3	Olanzapine and the risk of hyperlipidemia
4	Nonsteroidal anti-inflammatory drugs and the risk of acute asthmatic attack
5	Drug utilization assessment of antimicrobial agents during the perioperative period in children
6	Drug utilization assessment of doxorubicin
7	Validity of the definition to identify the new incidence of diabetes mellitus, hyperlipidemia, and hyperthyroidism using electronic medical records
8	Validity of the definition to identify the new incidence of acute renal failure using electronic medical records
9	Antipsychotics and the risk of glucose metabolism disorder
10	Antipsychotics and the risk of parkinsonism

(as of March 16, 2015)

http://www.pmda.go.jp/files/000205168.pdf#page=20

Today's contents

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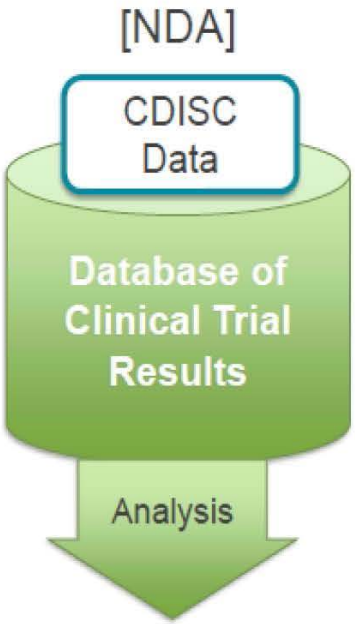
Review/consultation framework using an innovative assessment techniques

CDISC Data Submission [NDA]



NDA Review → **More effective & High level review**

- B/R evaluation with raw data analysis

Scientific Consultation → **More efficient & Successful development**

- Scientific advices based on the information obtained from analyses including M&S

Cross-Products Analysis → **More evidences & Advancing Regulatory Science**

- Establish disease models
- Identifying common risk factors among different drugs

Modeling & Simulation: Concentration-Response
Model PBPK: Physiologically-based Pharmacokinetic Model, etc.

22

DIA

https://www.pmda.go.jp/files/000217799.pdf

Today's contents

- Introduction
  - About PMDA
  - PMDA Pediatric Drugs Working Group
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- Current situation
  - Post-marketing data collection
  - MIHARI project
  - CDISC
- Future challenges
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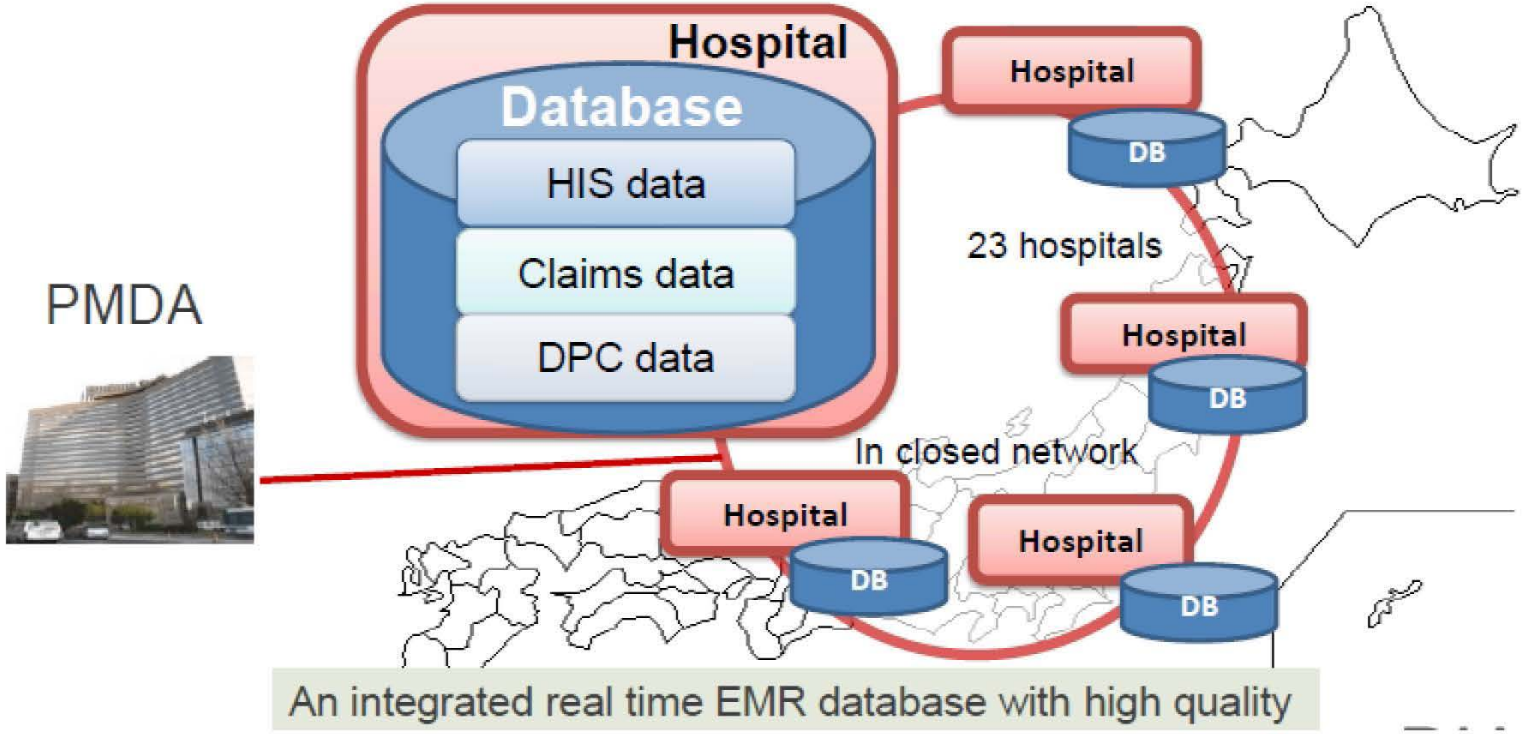
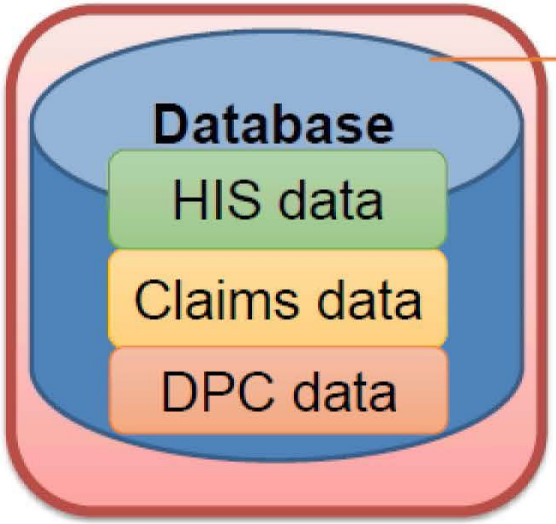
MID-NET initiative

- The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients)



https://www.pmda.go.jp/files/000216750.pdf

Data categories in the MID-NET system



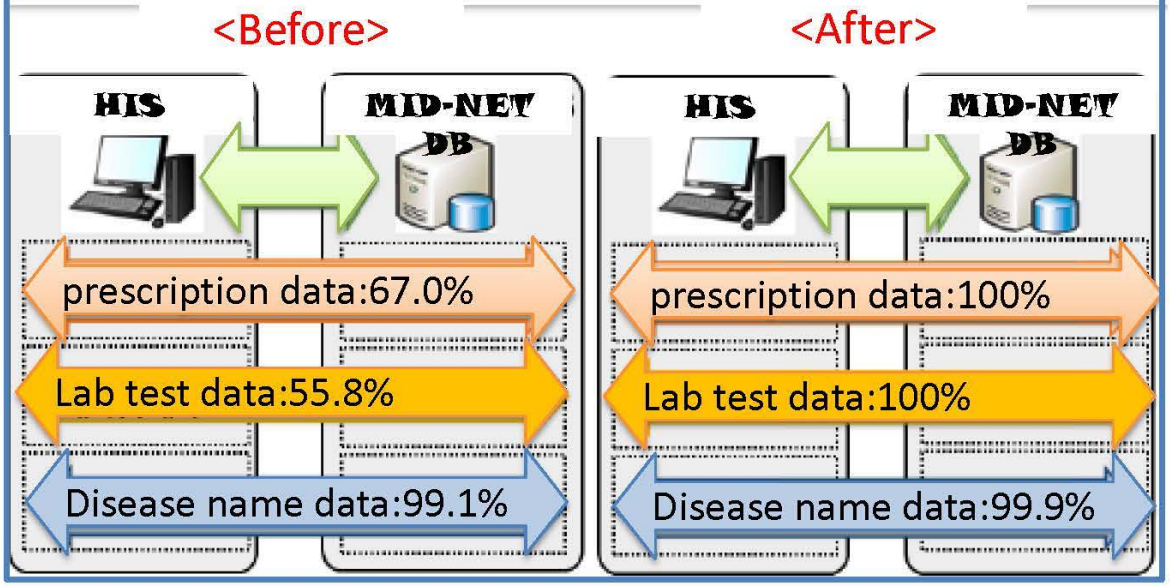
HIS data

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

https://www.pmda.go.jp/files/000216750.pdf

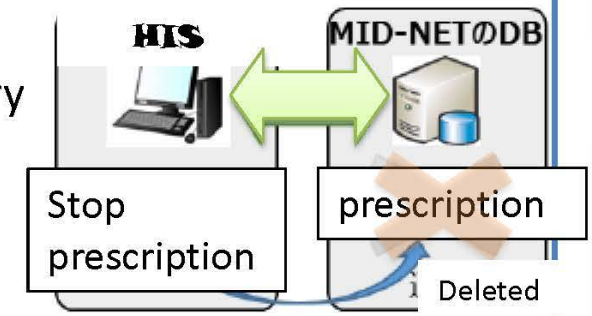
Quality maintenance of MID-NET data

1. Quality control survey of existing data



2. Quality control survey of real time data

Data transferred to DB are updated daily. So it is necessary that data are updated appropriately. Currently, real time data quality control are being performed.



Introduction period (Before quality control)

- Check sampling data (resulted in not adequate)

Current (After quality control)

- Operate quality control hospital by hospital (Compare actual data of a hospital information system (HIS) and number of data items & contents. Confirm if the data transferred to database accurately.)

Database which verified high quality reliability and the most advanced database in Japan.

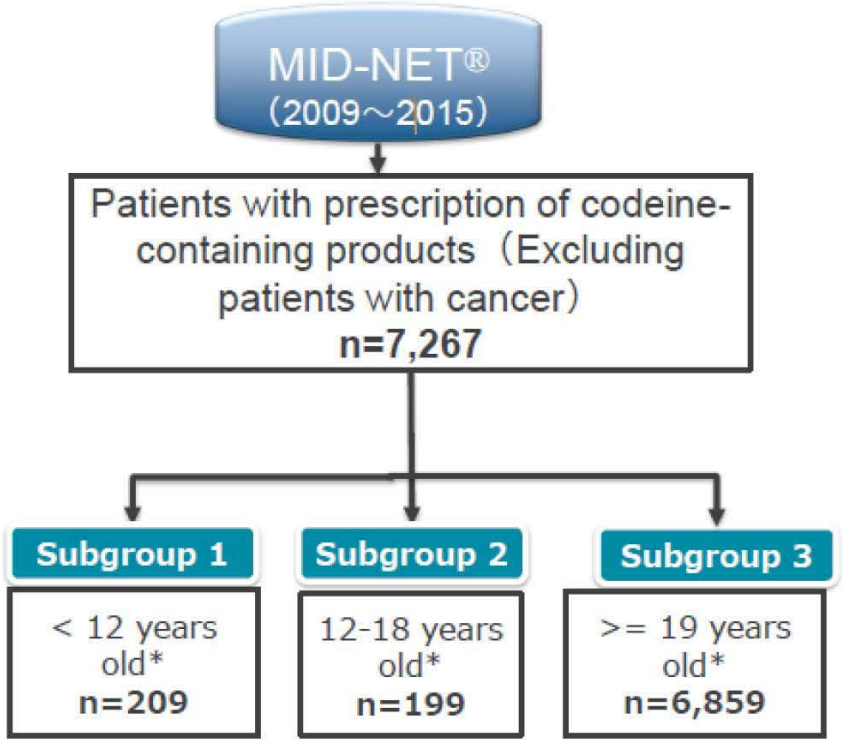
http://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000169582.pdf

Example:

- Codeine (Morphine-like agent) is used for pain relief and cough suppression.
- There are possibilities that codeine induces rare but serious side effects such as breathing problems.
- PMDA, US FDA and EMA had issued recommendation to restrict use of codeine-containing medicine as pain relief and cough suppression for children under 12.

Modified from http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000171831.pdf

MID-NET® Pilot study: Example 1: Risk of respiratory depression associated with Codeine



	Number of patients (n)	%	% to source population
Total	7,267	100	0.7
Subgroup 1 < 12 years old*	209	2.9	0.2
Subgroup 2 12-18 years old*	199	2.7	0.5
Subgroup 3 >=19 years old*	6,859	94.4	0.8

*Age at first prescription

https://www.pmda.go.jp/files/000218744.pdf

MID-NET® Pilot study: Example 1: Risk of respiratory depression associated with Codeine

Possible cases causing respiratory depression during administration of codeine-containing products

	Case (n)	Patients in the cohort (n)	%	95%CI
Total	24	7,267	0.3	0.2-0.4
Subgroup 1 < 12 years old	-*2	209	-*2	0.0-1.0
Subgroup 2 12-18 years old	0	199	0	0.0-0.0
Subgroup 3 >=19 years old	-*2	6,859	-*2	0.2-0.5

※1 Definition of respiratory depression
① Prescription of drugs for respiratory depression (i.e.; levallorphan, naloxon)
② Diagnosis with disease relating to respiratory depression (i.e.; dyspnea, acute respiratory failure, respiratory failure) and use of oxygen inhalation

※2 masked due to small sample size

10

DIA driving insights to action!

https://www.pmda.go.jp/files/000218744.pdf

Today's contents

- Introduction
  - About PMDA
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  - Framework of post-marketing safety measures in Japan
- Current situation
  - Post-marketing data collection
  - MIHARI project
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  - "Children and Pharmaceuticals" Data Collecting Network Development Project

Clinical Innovation Network (CIN)
(Improvement of Infrastructure for Clinical Study with Disease Registry)

【Background】
・Cost of developing a new drug or other medical products is rising over the world, especially in Japan compared to other countries.
・Recently, new approaches for clinical study with disease registry has been highly interesting.

【Brief overview of CIN】
・ The clinical study infrastructure in Japan is improved so that cost effective clinical studies are performed with disease registries, based on Regulatory Science. The improvement will accelerate clinical studies in Japan by entities in the world, which would results in the contribution to healthy life expectancy for people.
・CIN will also support for marketing in Asia of medial products developed in Japan.

National institute of Biomedical Innovation, Health and Nutrition
Hospitals in networks in Japan
Hospitals in Asia

・Acceleration of global clinical trials
・Asian Regulatory Training center
・Development of registries for patients with intractable diseases
・Rare diseases drug development Gateway

National Center, Clinical Research Core Hospital

・Development of disease registries
・Foundation of a clinical trial consortium, acceleration of clinical studies
・Advancement of regenerative medicine clinical studies
・Establishment of a Clinical Trial Cooperation Office

Participation in the consortium
Data provision (With consideration to personal information)

Industry

・Utilizes data in clinical studies
・Performs clinical studies quickly and cost-effectively

Activation of clinical studies in Japan by entities in the world

・Personnel exchanges
・Post marketing safety measures

・Support for R&D
・human resource cultivation in the clinical research and trial field

・Research for method to utilize disease registry in clinical study (Regulatory Science)

PMDA
Jurisdiction : MHLW

AMED
Jurisdiction : CAO, MEXT, MHLW, METI

CIN Promotion Conference
Composed of stakeholders , including National Centers, Industries and Japanese Government; and promotes the CIN project.

21

http://pari.u-tokyo.ac.jp/eng/event/smp150818_mori.pdf

Project for promoting Clinical Innovation Network (FY2017)

- Background
  - Japan Revitalization Strategy 2016
  - Promotion of innovation through development of clinical innovation networks

The Government will promote development of "Clinical Innovation Networks," creating a network of disease registration systems developed by the National Research Center for Advanced and Specialized Medical Care (NC) and academic societies, thereby improving environment for efficient clinical development.

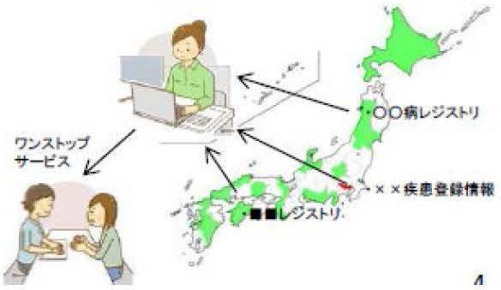
http://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000169583.pdf
http://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/zentaihombun_160602_en.pdf

Project for promoting Clinical Innovation Network (FY2017) cont

- Current situation and issues
  - Disease registries have developed for a variety of purpose such as tracking patients, entry to clinical trial, post-marketing data collection.
    - These registries does not necessarily collect enough information to suit those purpose
    - It is difficult to find out where and what kind of registries exist because a variety of institutes (e.g. university, NC, academic society) manage registries by themselves.
- Actions
  - To accelerate the use of disease registries and CIN framework,

offer one–stop service such as

- Coordinate registry information based on the purpose
- Coordinate clinical trial



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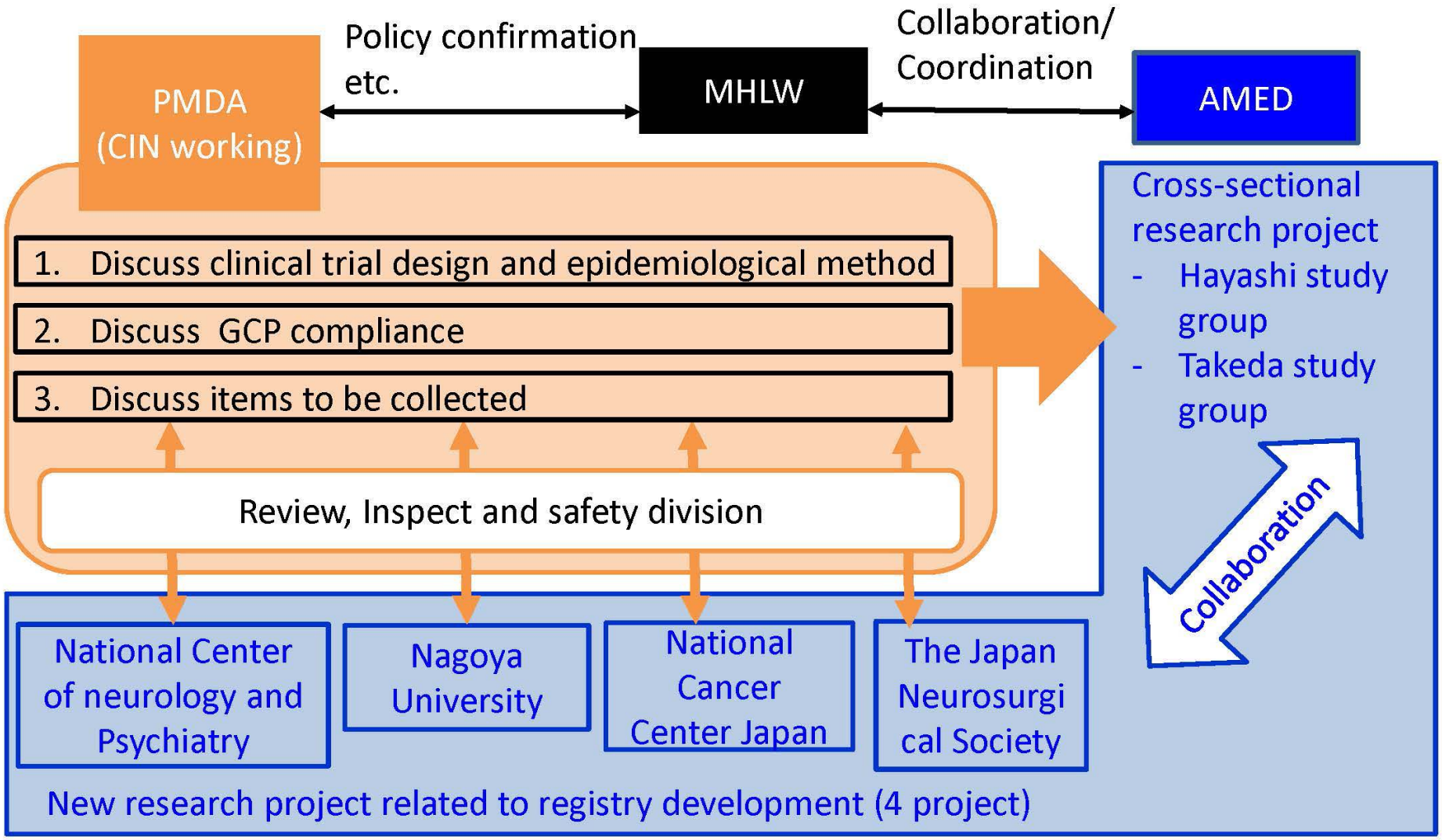
Study framework to promote CIN



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Use of disease registries for drug development

- ✓ Market research
- ✓ Feasibility research for clinical trial
- ✓ Recruiting study subjects
- ✓ Planning clinical trial

Most of conventional registries

- ✓ Use as a control in clinical trials
  - ➢ An evaluation data for drug approval
- ✓ Use as post marketing surveillance and evidence for safety measure
  - ➢ An evaluation data for re-examination

In the fields of having difficulties for doing standard clinical trial etc.

What new registries aim at

Dealing with a high development cost of pharmaceuticals and medical devices etc.
Dealing with an unmet needs

Further use of registries for development and post-marketing information collection of are expected.

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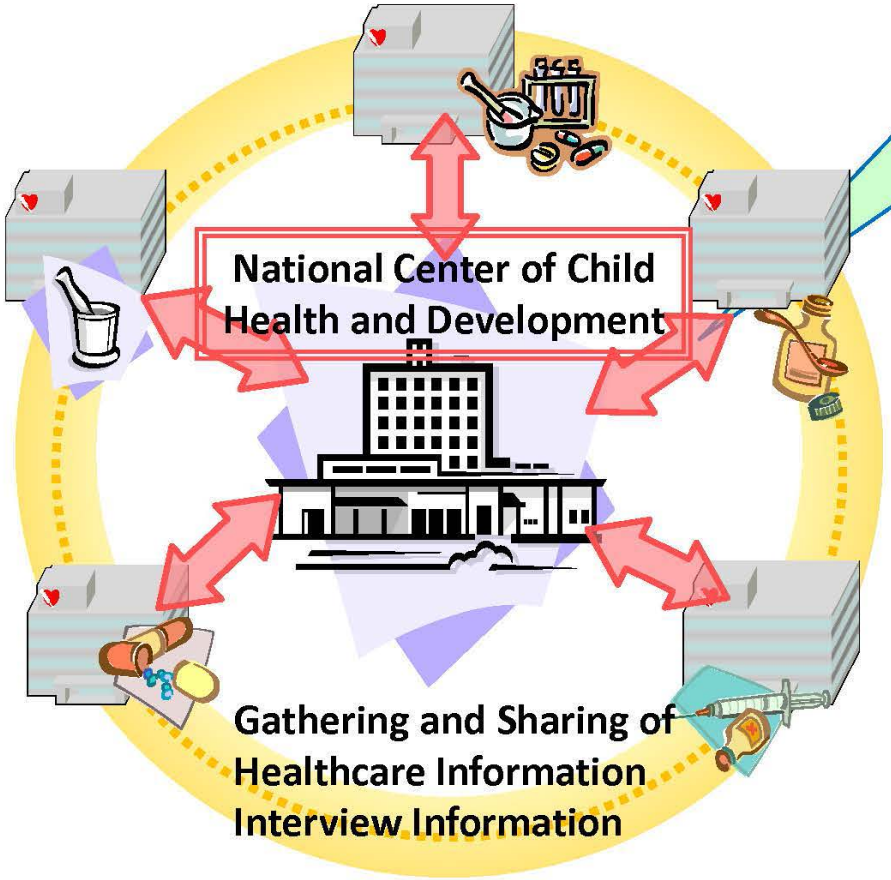
Pediatric medical information gathering system

Pediatric medical information gathering system



Development of database for collecting, evaluating and analyzing the following information in children

- Dosage of drug
- Administration of drug
- Adverse reactions

◆Development of new drugs
◆Safety measures

Better medicine for children

MHLW press release http://www.mhlw.go.jp/stf/houdou/0000116368.html (Japanese only)

Pharmaceuticals and Medical Devices Safety Information No. 331 (https://www.pmda.go.jp/files/000211141.pdf)

Conclusion

- In Japan, long-term safety in post-market is mainly evaluated by post-marketing surveillance
- Post-marketing surveillance allows follow-up of safety information in real clinical use, however, non-interventional and resources are limited
- Recent effort on building/utilizing patient registries, electronic healthcare data and pediatric medical information gathering system are expected to expand the measure of long-term safety evaluation.

Effort will be continued to develop framework and utilize surveillance/study for an enhanced safety data collection and evaluation

Thank you for your kind attention.