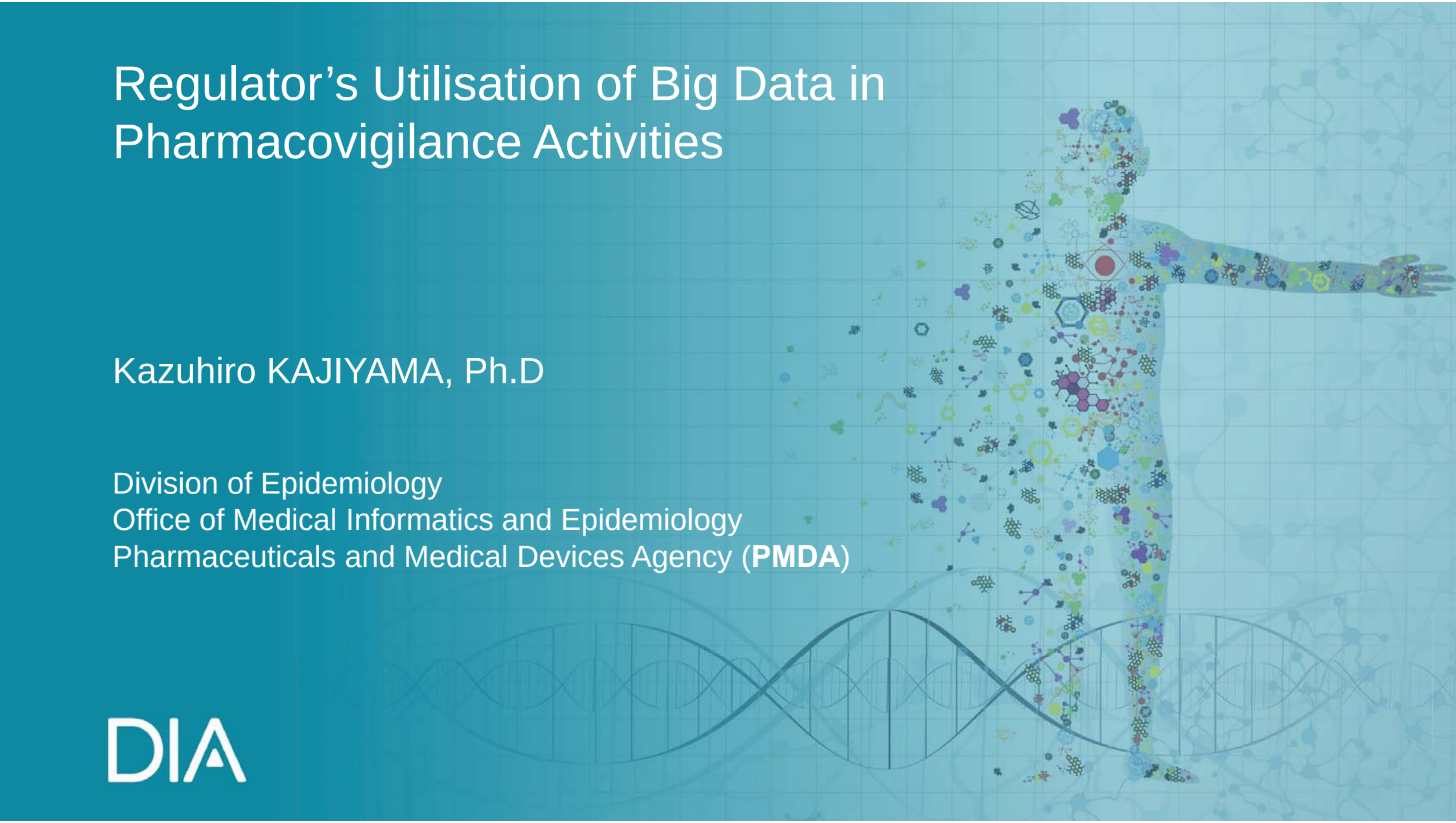
Regulator’s Utilisation of Big Data in Pharmacovigilance Activities



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Overview

- Great changes in the circumstances surrounding post-marketing drug safety measures from the end of 20th to the 21st century in japan.
- PMDA has made efforts for implementing new framework & building new infrastructure for reinforcing post-marketing drug safety measures by utilizing Big RWD
- Renovation of Good Post-Marketing Study Practice for utilizing Big RWD.
- Major future tasks for accelerating utilization of Big RWD.

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Previously: Circumstances surrounding Post-Marketing Surveillance about a decade ago in Japan

- More than half of new drugs were approved about 1 to 3 years behind the US.

Fiscal Year	2006	2007	2008	2009	2010
Application Lag (Median-Year)	1.2	2.4	1.5	1.5	1.0
Review Time Lag (Median-Year)	1.2	1.0	0.7	0.5	0.1
Drug Lag (Total of Above)	**2.4**	**3.4**	**2.2**	**2.0**	**1.1**

Ando Y. et.al., GaBI Journal, 2013;2(1):41-4

- Safety data in clinical practices (in foreign countries) were usually available for newly approved drugs in Japan.
- Thus, a Japanese study in the post-market has been conducted for confirming there are **NO BIG Differences** in safety between Japanese and Foreign population as well as between pre- and post approval.

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Conventional approach for providing Post-Marketing Safety Measures

PMDA

Drug Safety Assessment

- Spontaneous Adverse Drug Reaction report DB
- Literatures
- Overseas regulatory actions
- etc...

Report

Ministry of Health, Labour and Welfare

Safety Measures

Medical institutions

Risk Communication

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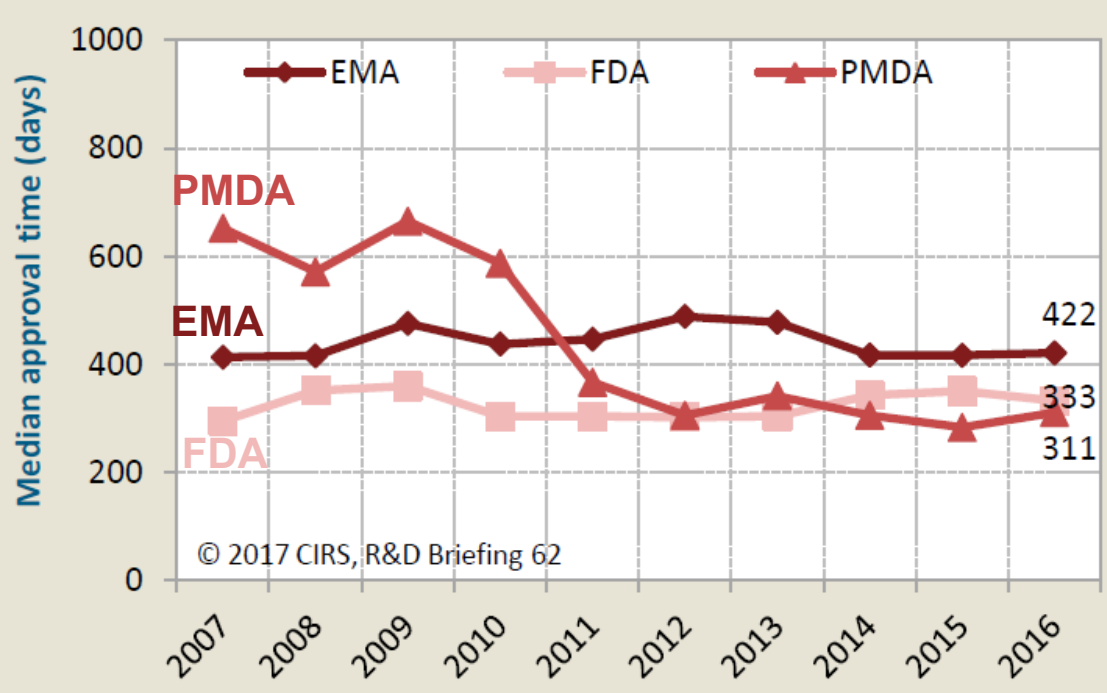
Entering an era of simultaneous approval in ICH regions

Median approval time for NASs approved by ICH agencies by approval year



Center for innovation in regulatory science(CIRS), R&D Briefing 62: "New drug approvals in ICH countries 2007 – 2016"

Review time in Japan has shortened and is similar to US and EU time

faced with new challenge...

For a new drug approved in Japan, no experiences or a limited experiences in clinical practices were available in any countries.

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Big RWD in the field of health service has been emerged

- **Health insurance claims :** 98% are computerized!

- **Electronic medical records :** 77% of hospitals with over 400beds are using!
  (Government's Goal: 90% by Mar. 2020)

PMDA had started to utilize those Big RWD as an additional data source for conducting more efficient and effective safety measures of new drugs.

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Efforts for utilizing Big RWD in PMDA

■ MIHARI Project

To establish a new framework for promoting implementation of safety measures on the basis of quantitative risks provided by evaluation of electronic healthcare data available in Japan.

(Pilot phase 2009 - 2013. Since 2014 fully implemented!)

MIHARI
Medical Information for Risk Assessment Initiative

■ MID-NET® Project

(MID-NET®: Medical Information Database NETwork)

To establish a new distributed database system for utilizing in safety assessment, consisted of Hospital Information System (HIS) data managed by 23 hospitals of 10 medical institutions in Japan. (Development phase 2011 - 2017. Since Apr. 2018 fully implemented!)

MID-NET®
Medical Information Database Network

DIA

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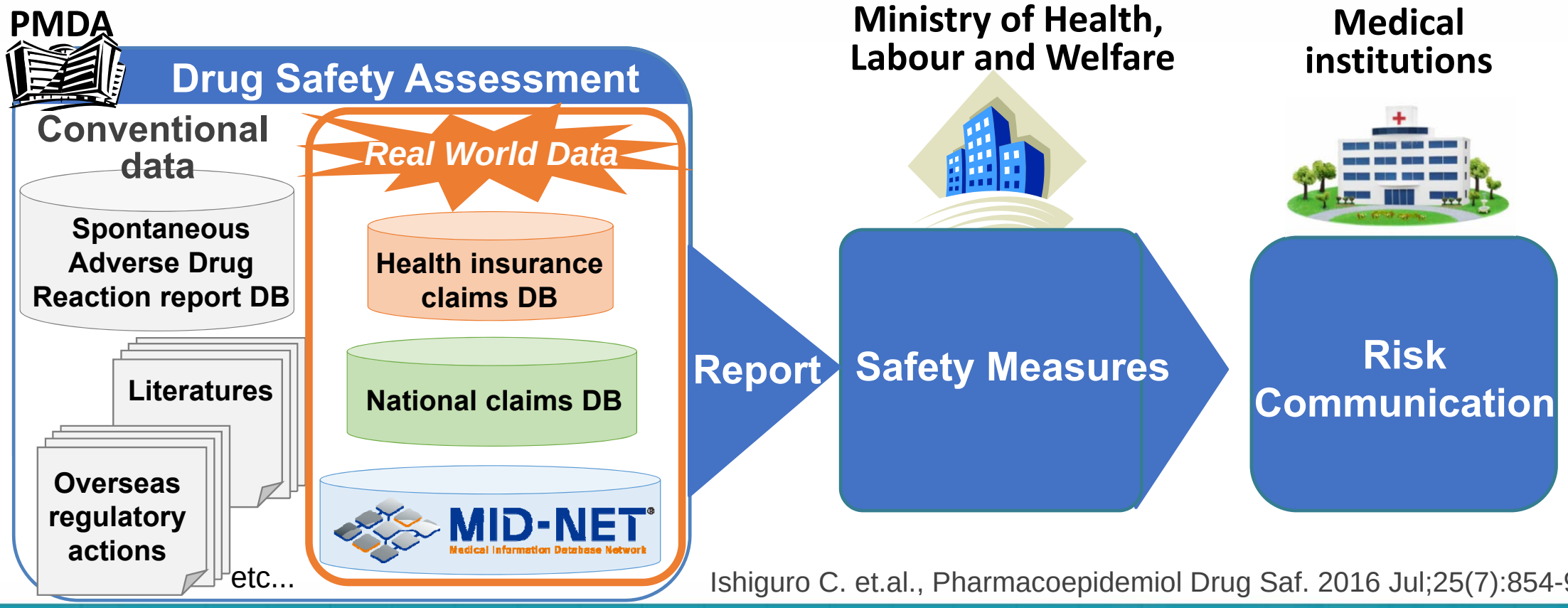
Current framework for drug safety measures using RWD implemented by MIHARI Project



Ishiguro C. et.al., Pharmacoepidemiol Drug Saf. 2016 Jul;25(7):854-9.

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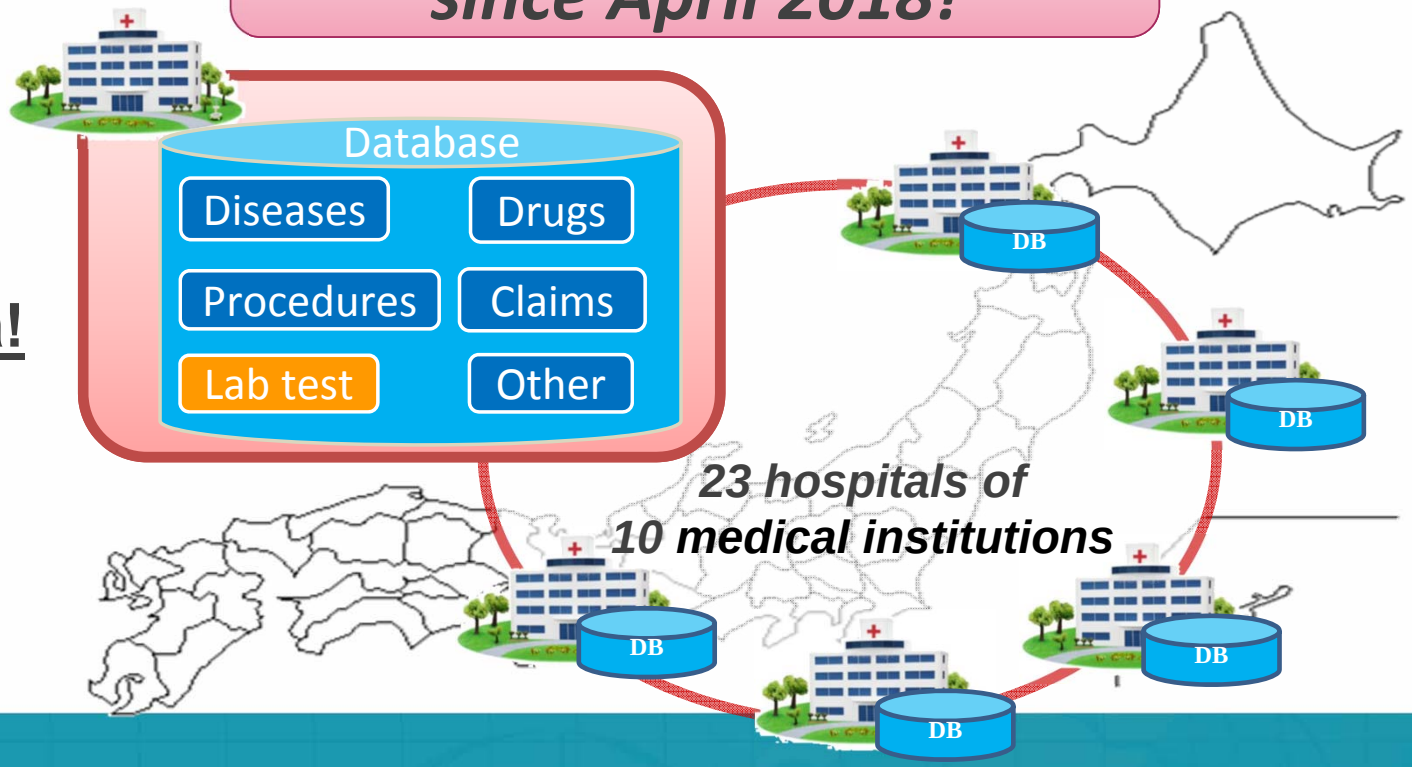
MID-NET®: Medical Information Database NETwork

NOW, We can use...

- Detailed
- Real Time
- Quality Managed

Medical Information Data!

Started full-scale operation since April 2018!



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MID-NET®: Medical Information Database NETwork

NOW, We can use...

- Detailed
- Real Time
- Quality Managed

Medical Information Data!

Database in each hospital are converted to Common Data Model!

Various HIS data are available !

- **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**

Approximately 200 lab test results are available!

Fe	FT3	KL-6	CK-MB
K	FT4	LAP	CRP
Ca	GOT(AST)	PIV-KA-Ⅱ	CYFRA
Na	GPT(ALT)	PRP	EPO
Mg	HBs (+/-)	T3	FSH
HbA1c	HBs (IU/ml)	T4	thrombocyte
GLU	HBs (CIO)	TPHA	monocyte
ALP	HB virus	TSH	lymphocyte
AMY	HC virus	TTT	acidocyte
ALB	hCG	ZTT	basocyte
HDL	hCG-β	γ-GTP	neutrophil
LDH	IgA	myoglobin	hematocrit
LDL	IgE	vitaminB_{12}	pH(blood)
TG	IgG	rheumatoid	pCO2
Creatinine	IgM	folate	pO2
	⋮		etc

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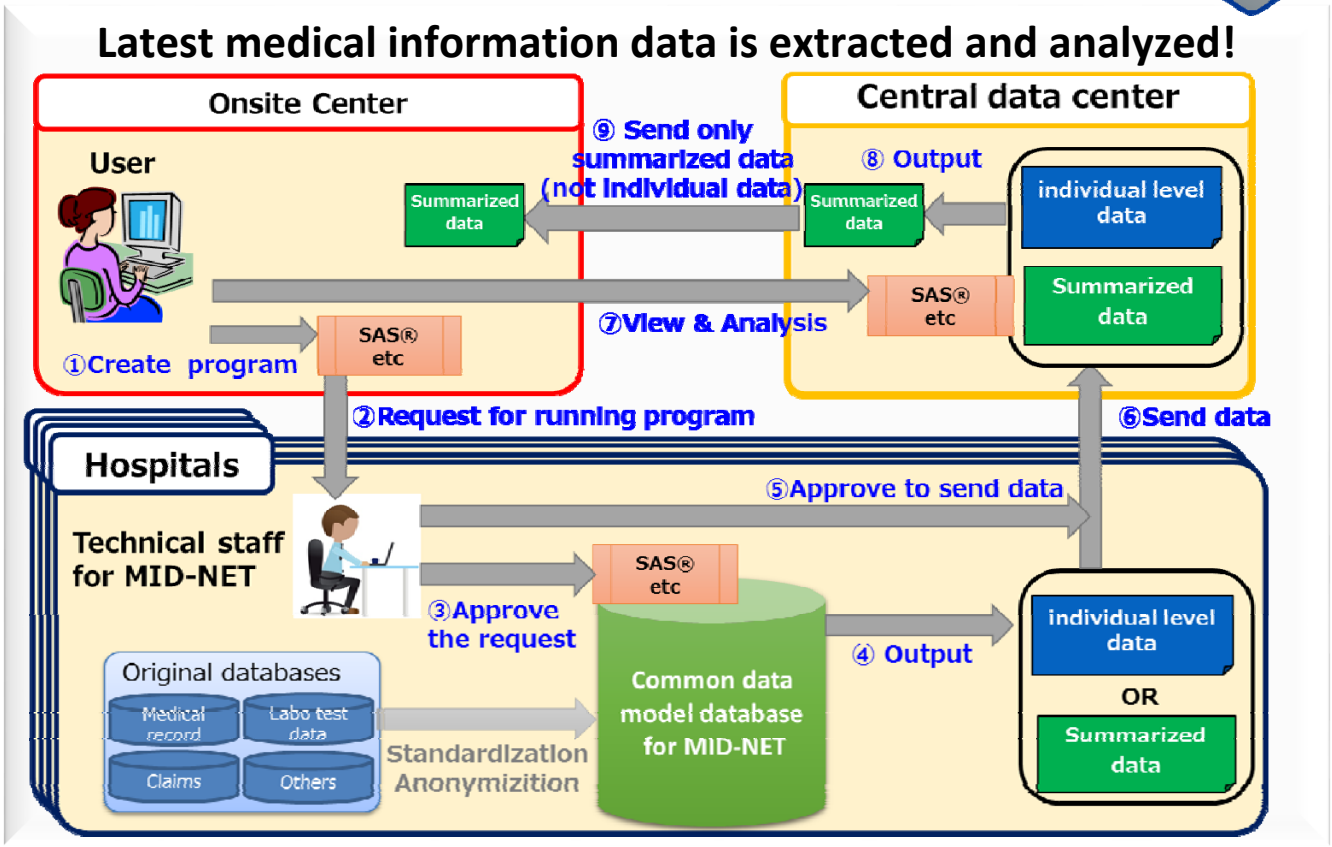

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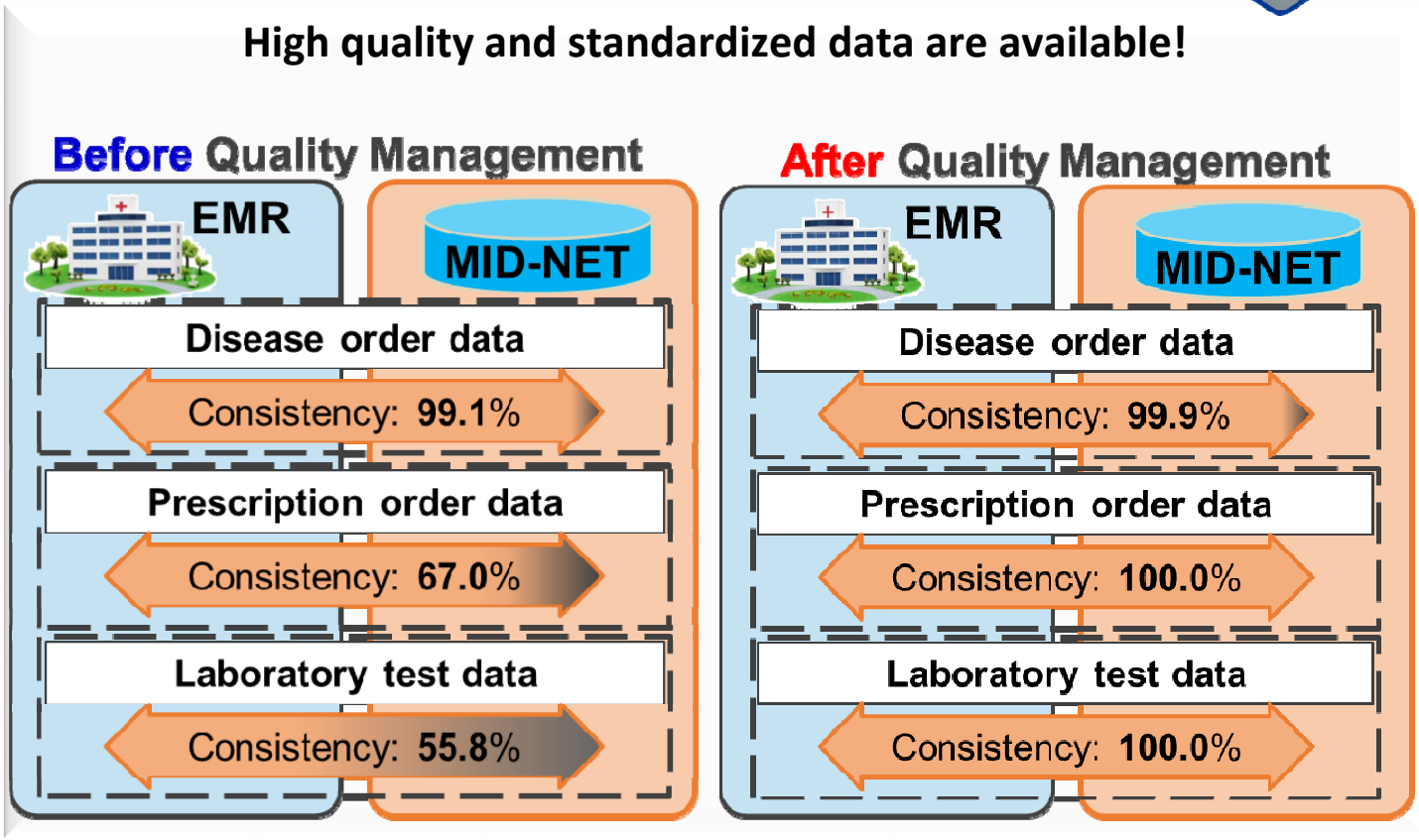

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MID-NET® can be utilized for various Post-Marketing Studies

Drug utilization study

Investigate volume of prescriptions, days of prescriptions and interval of prescriptions

Cohort study

Single Cohort (investigation of event occurrence and patient background)
Double Cohort (Adjust covariates and investigate the relationship between risks and exposures)

Interrupted time series

Investigate transitions before and after safety measures to evaluate impacts of the measures

Nested case control study

Focusing on a specific outcome, investigate the risk by the presence or absence of risk factors

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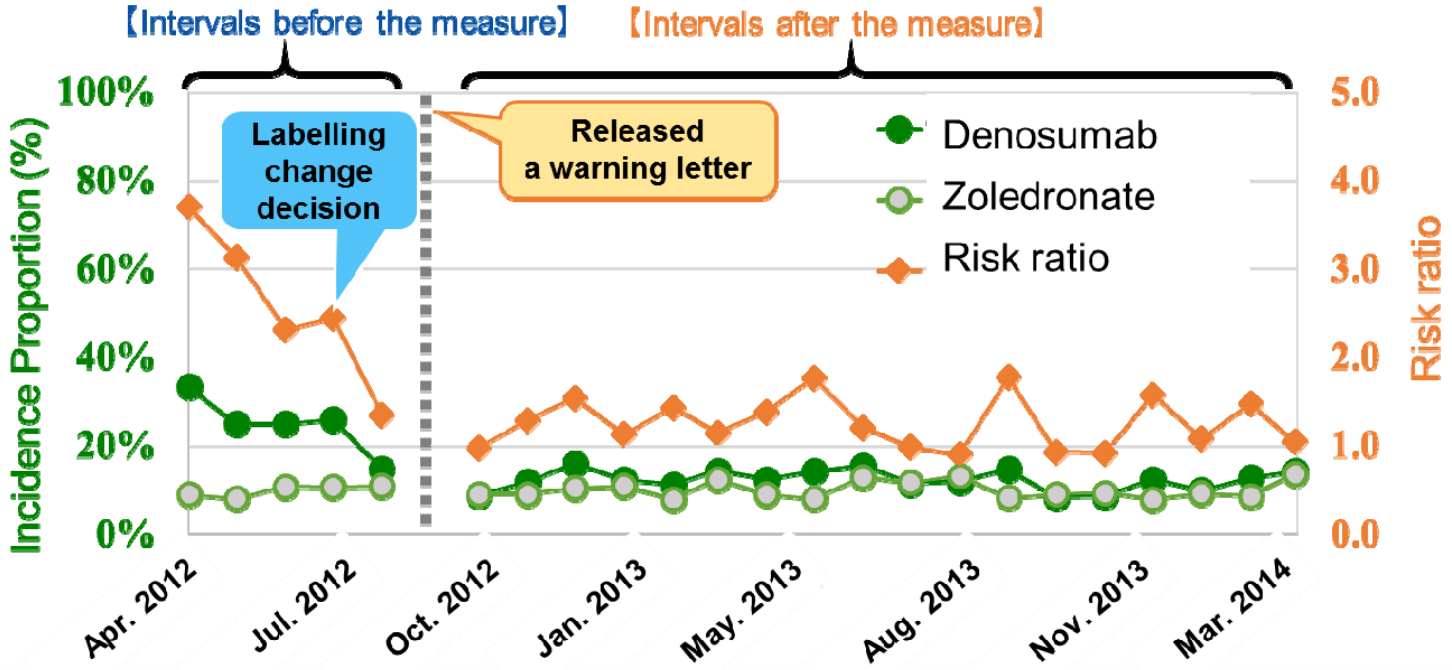
Example for interrupted time series analysis

- **Objective:**
  - To evaluate the risk of severe hypocalcemia and the effect of the regulatory action.



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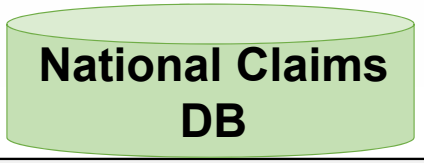
Proper selection of data source is essential for scientific safety assessment



Data Type	Electronic Medical Records	Health Insurance Claims
Data Provider	10 Medical institutions	All health insurers in Japan
Covered patients	People provided medical service by each institution (~**4 Million**)	Entire Japanese population (**120 Million**)
Obtainable Health Information	**Detailed information in medical practices** by each institution	**Standardized information relevant to reimbursement**
Diagnosis	YES	YES
Medical procedure	YES	YES
Pharmacy Dispensing	YES (on-site pharmacy)	YES
Laboratory test result	**YES**	NO
OTC Drug	NO	NO

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Role of Pharmaco-Epidemiologist in PMDA

PMDA

- **Center for Regulatory Science**
  - **Office of Medical Informatics and Epidemiology**
    - **Division of Epidemiology**

Work Together

- **Center for Product Evaluation**
  - **Offices of New Drugs**
  - **Office of Cellular and Tissue-based Products**
  - **Office of Vaccine and Blood Products**
- **Chief Safety Officer**
  - **Offices of Safety II**

<pre-approval>

- Review the Risk Management Plan of the new drug
- Propose appropriate post-marketing studies

<post-approval>

- Conduct pharmaco-epidemiological studies by utilizing Big RWD
- Review observational studies / reports submitted by MAHs

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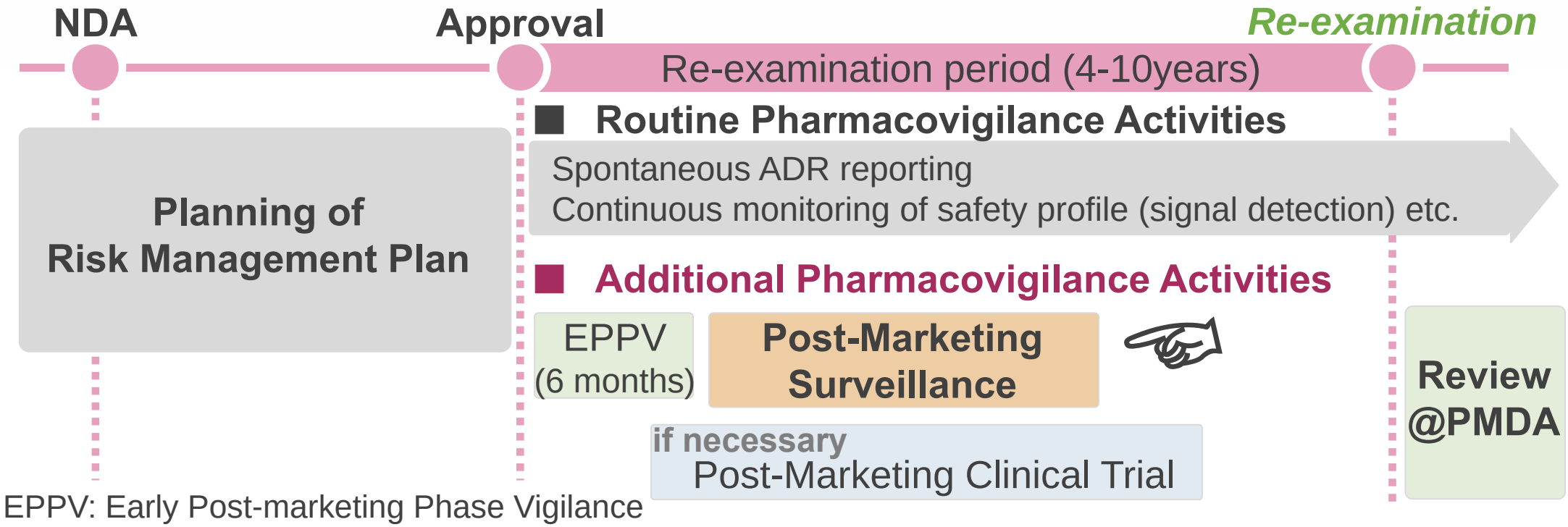
Re-examination System in Japan



EPPV: Early Post-marketing Phase Vigilance

- **Purpose of re-examination :** To **reconfirm safety and clinical effectiveness** of the new drugs at post-market stage after approval.

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Renovation of Good Postmarketing Study Practices

- Nov. 2017: Amendment of the Good Postmarketing Study Practices (GPSP) **“Post-marketing Database Surveillance”** was newly defined.

Old GPSP

Primary data collection was only mentioned as a post-marketing study of new drugs

Selectable design for post-marketing study

- Primary data collected from hospitals
- Post-marketing Clinical Trial

Renovated GPSP

Secondary use of database is allowed as a post-marketing study in addition to the primary data collection.

Selectable design for post-marketing study

- Primary data collected from hospitals
- Real World Data provided by database holder (including patients registry)
- Post-marketing Clinical Trial

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Guidelines & notifications for utilizing RWD by MAH

- “Points to consider for ensuring the reliability in conducting post-marketing database surveillance” (Notification No. 221, MHLW, Feb. 2018)
- “Points to consider for planning Pharmacovigilance activities” (PMDA, Feb. 2018)
- “Contents and format of a study protocol for Post-marketing Database Surveillance” (PMDA, Jan. 2018)
- A revision of “Case Examples of Risk Management Plan” (PMDA, Dec. 2017), including a case of database study
- “Basic principles in utilizing medical information database on Pharmaco-vigilance” (Notification No. 609, MHLW, June 2017)

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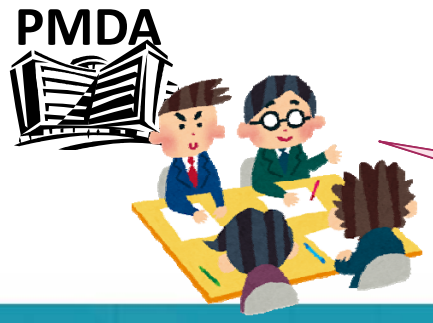
Planning Steps for RMP/Pharmacovigilance Activities

pre-/during NDA review

Inquiries & Responses



After Approval

Step 1. Clarification of serious concerns about post-marketing safety and/or effectiveness.

Step 2. Selection of scientific approaches as Pharmaco-vigilance activities.

Step 3. Understanding obligation to comply with regulatory requirements.

Step 4. Making a detailed plan for Pharmacovigilance activities, including a planning of study protocol

Oct. 2017, PMDA started a new consultation service for planning Pharmacoepidemiological study as a Pharmacovigilance activity

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Challenges and Actions for Accelerating Adequate Utilization of RWD

Challenges	Actions
Conducting scientifically appropriate PMS	☑ Publish regulatory guidelines to promote post marketing studies utilizing RWD ☑ PMDA Consultations for planning Pharmaco-Epi Study
Ensure the quality of study plan & results	☑ Amendment of GPSP and regulatory inspections ☑ Publish regulatory guideline on the reliability of post-marketing studies utilizing RWD
International cooperation	? More collaborations for sharing experiences and knowledge about utilization of RWD for regulatory purpose ? International harmonization on standards for data quality and analytical methods in utilizing RWD

Scientific approaches and careful considerations in utilizing and evaluating RWD are the key to avoid causing chaos and unrest on RWD utilization

Moving Toward the Improvement of Medical Care

PMDA

Regulatory decisions based on better scientific evidences

- PMDA had started routine use of medical information data for assessing safety concerns on daily clinical practice in Japan.

Industries

Risk Management Plan implementation utilizing Big RWD

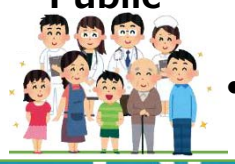
- Rapid, effective and efficient risk management
- Better quality of safety information

Medical Institution

Provide leading-edge medical therapy with ensuring safety

- Scientific and speedy safety measure

Public



Better quality of medical care

- Maximize benefit/risk ratio

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