Cutting-edge technologies and strategies
-Big data utilization

Big Data Utilization
for Post-Marketing Drug Safety Measures in Japan

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Pharmaceuticals and Medical Devices Agency (PMDA)

Today's Agenda

■ MIHARI Project

The project to establish a new framework for pharmacoepidemiological drug safety assessments utilizing electronic medical records.

MIHARI
Medical Information for Risk Assessment Initiative

■ MID-NET® Project

（MID-NET®：Medical Information Database NETwork）

The project to establish a new Medical Information database Network for utilizing in safety assessment by MHLW and PMDA.

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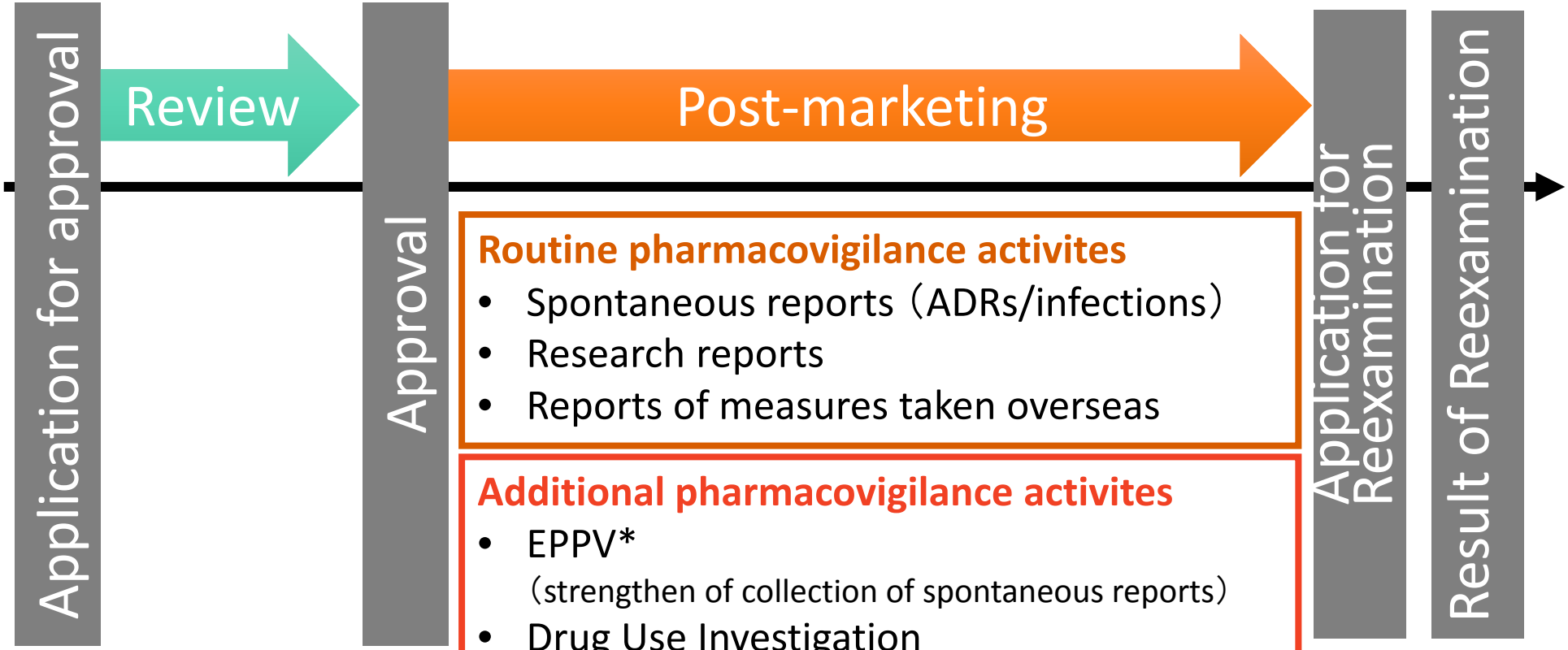
Previous Safety System in Japan



* Early Post-marketing Phase Risk Minimization and Vigilance

Major Characteristics of Current Pharmacovigilance Activities

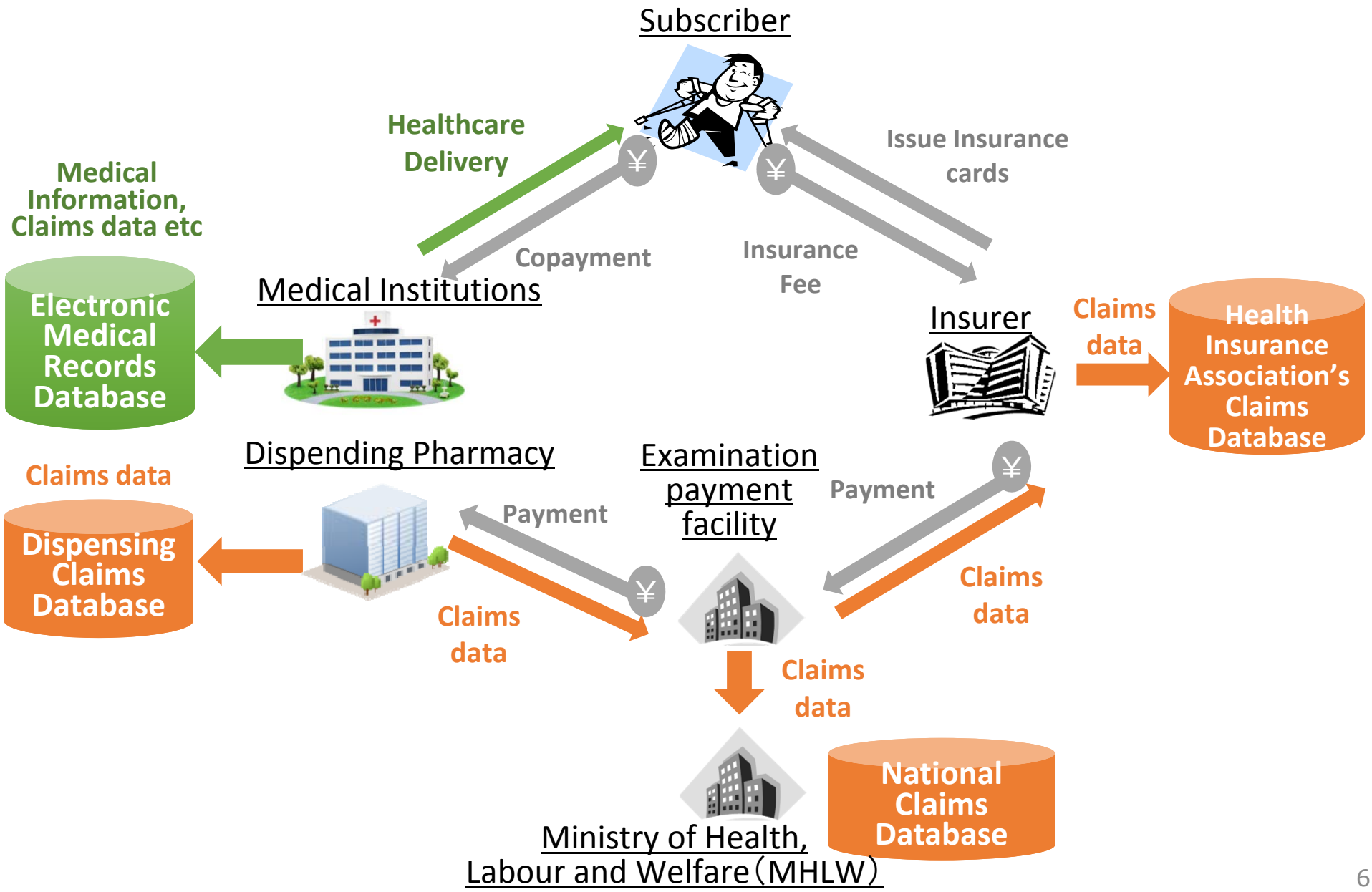
	Spontaneous Reports	Drug Use Investigation /Special Investigation
Strengths	•Useful for detecting uncommon or unexpected Adverse Drug Reactions（ADRs）	•Enable to calculate ADR incidence rates •Useful for examining the safety of an orphan drug（All-patient investigation）
Weaknesses	•Under-reporting of ADRs with long latency or high background rates •Unavailable to calculate ADR incidence rates －Information on population exposed to the drug is lacking	•Lack of adequate denominator for estimating the risk of rare ADRs •Unavailable to compare the risk between drugs －Most of investigations have conducted as single-arm studies

Novel information source and methods are required

－Utilization of large-scale electronic health information databases

－Pharmacoepidemiological drug safety assessments

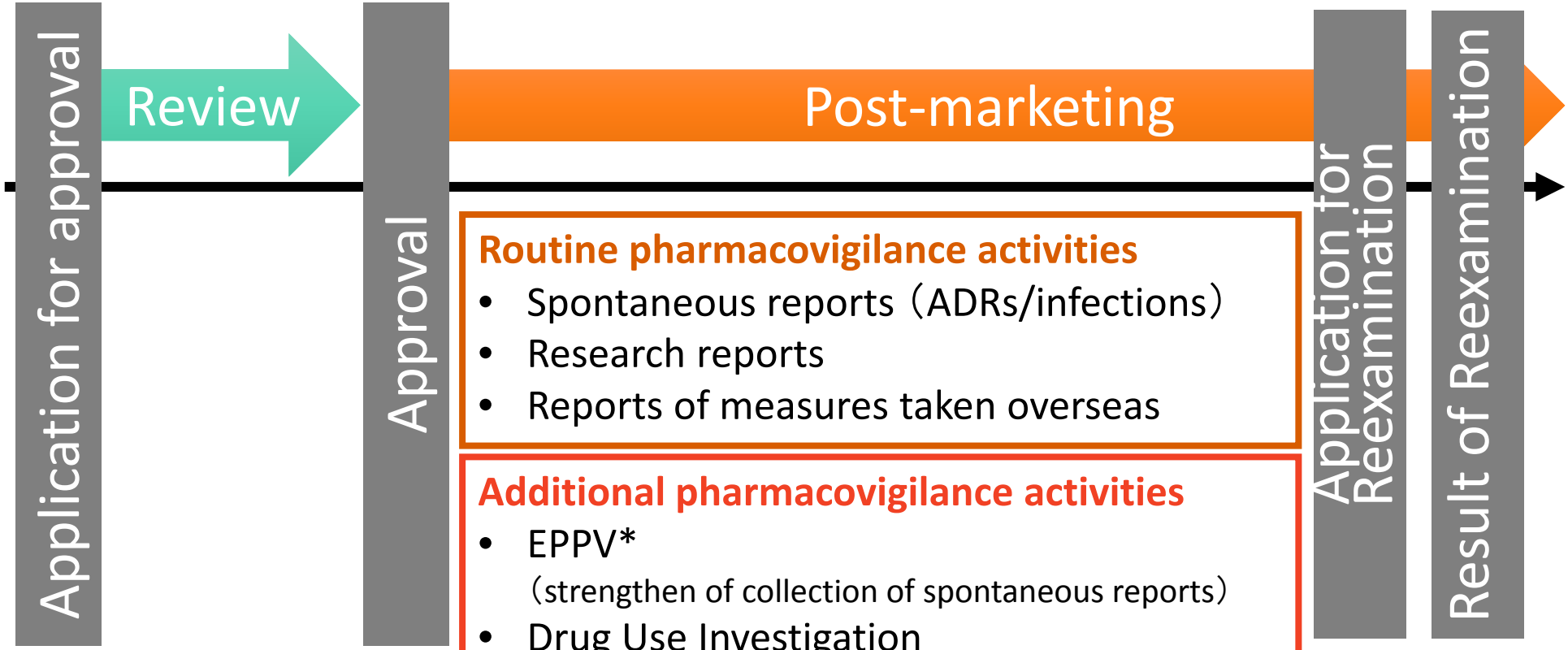
Electronic Healthcare Databases in Japan



Major Characteristics of Healthcare Data in Japan

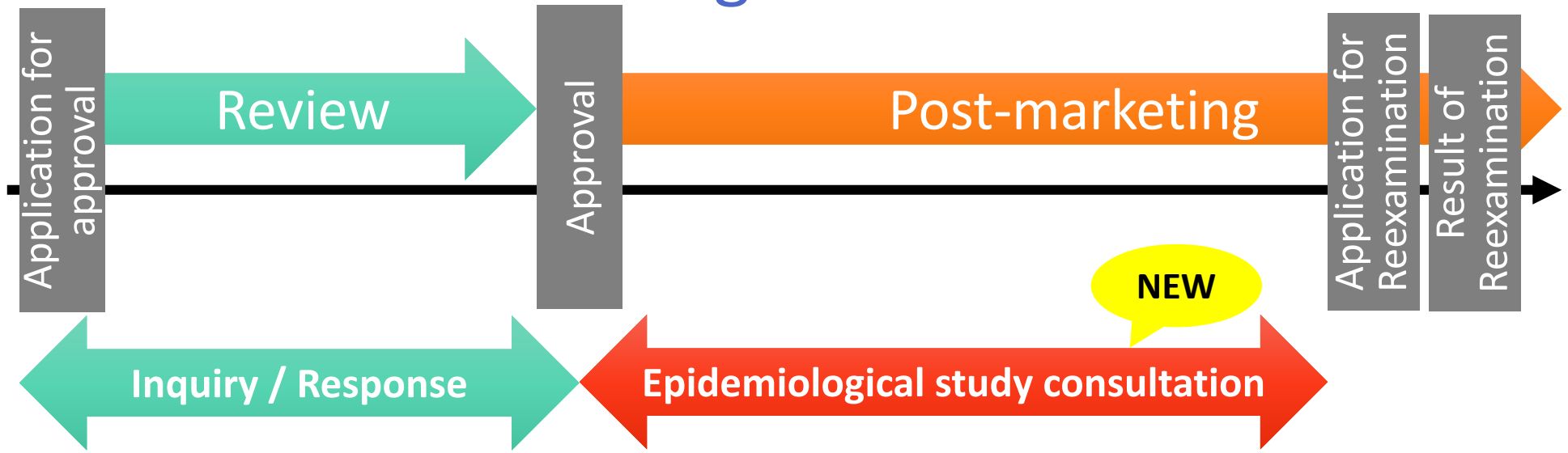
Data Type	Electronic Medical Record data	Claims data	
		Health Insurance	NDB
Main Data Provider	Medical institutions	Insurers	MHLW
Obtainable Health Information	Detailed information on medical practices by each institution	Standardized information relevant to reimbursement	
Diagnosis	YES	YES	
Medical procedure	YES	YES	
Pharmacy Dispensing	YES(on-site pharmacy)	YES	
Laboratory test result	YES	NO	
Covered patients	People provided medical service by each institution	People enrolled in each health insurance system	All patients In Japan

New Safety System in Japan （from Oct.2017）



* Early Post-marketing Phase Risk Minimization and Vigilance

Post-marketing database studies



- Industries should identify Safety Specifications.
- Industries should select the best pharmacovigilance（PV）activities to address safety concerns.
- Industries prepare and submit a draft RMP to PMDA.
- PMDA provides guidance and advice on basic plans of PV activities.

- Industries develop protocols for post-marketing database studies.
- If needed, industries conduct feasibility analyses and validation studies.
- PMDA provides guidance and advice in relation to the conduct of database studies.

Epidemiologists

Roles of Epidemiologists
in cases of big data utilization

Review phase

- Provide guidance and advice
  - to clarify safety specifications
  - to clarify research questions in post-marketing studies to address safety concerns
  - to select the best PV activities to answer research questions
  - to select appropriate database
- Review basic plans of PV activities.

Post-marketing phase

- Review protocols for post-marketing database studies and provide guidance and advice
- Evaluate drug safety based on results from post-marketing database studies
- Conduct database studies to evaluate drug safety and effectiveness of risk minimization activities.

Recent Activities for Promoting Big Data Utilization

Date	
June 9th, 2017	**“Basic Principles on utilizing database in pharmacovigilance for drugs”（Notification）**was issued.
October 26th, 2017	**Revised GPSP ordinance was promulgated.**
November 1st, 2017	**Epidemiological study consultation** system started.
Coming soon	**“Points to consider for protocol of post-marketing database study (for industry)”** is under discussion.
Coming soon	**“Points to consider for ensuring the reliability in conducting post-marketing database study for drugs（for industry）”（Notification）** is under discussion.
April 1st, 2018	**Revised GPSP ordinance** shall come into effect as from April 1st, 2018. • Results from database studies will be available for evidence of efficacy and safety in the application for reexamination.

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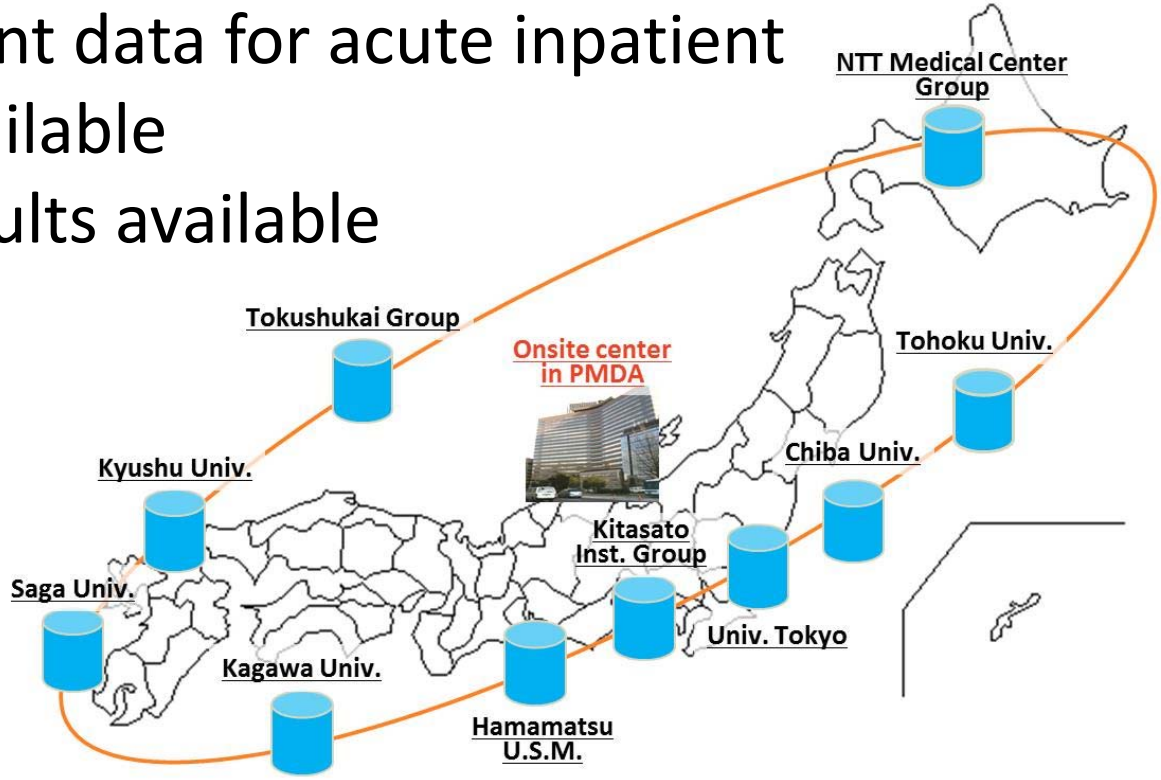
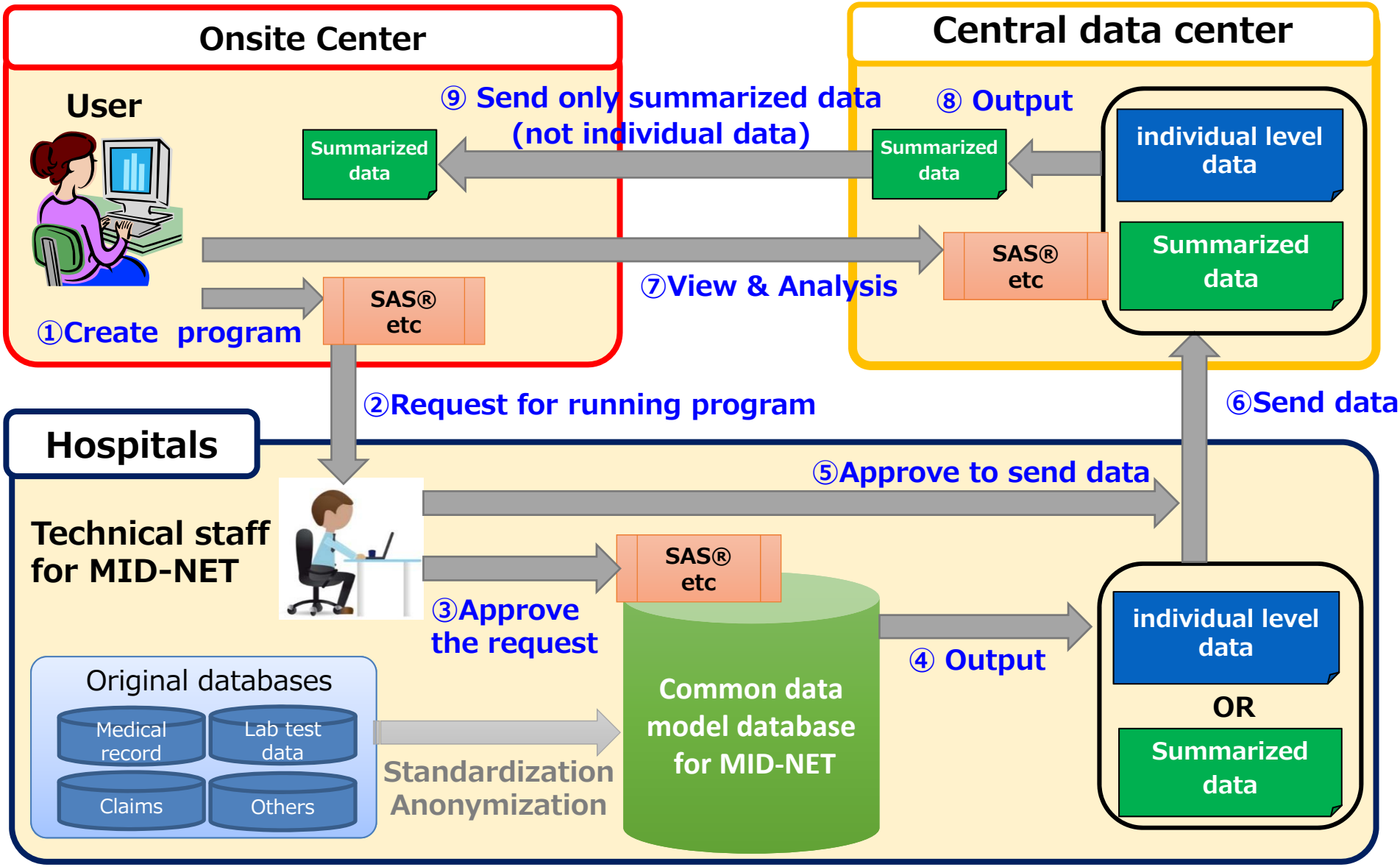
Key features of MID-NET®

- Distributed database in common data model format
- 23 medical institutions of 10 organizations
- 4 million patients in 2009-2017
- Real time update （1-4 times/month）
- MID-NET® holds medical information, claim data and prospective payment data for acute inpatient
- Standard codes available
- Laboratory test results available
- High data quality



Overview of MID-NET® System



Data characteristics of MID-NET®

Contents		Medical information	Claim data	Prospective payment data for acute inpatient
Disease	Name/Date	**Yes**	**Yes**	**Yes**
Medicine (ordered)	Name/Date/ Volume	**Yes**	**Yes**	**Yes**
Medicine (complied)	Name/Date/ Volume	**Yes (Injection only)**	No	No
Laboratory /Bacteriological test	Name/Date	**Yes**	**Yes**	**Yes**
	Result	**Yes**	No	No
Image/Physiological test	Name/Date	**Yes**	**Yes**	**Yes**
	Result	No	No	No
Surgery	Name/Date	No	**Yes**	**Yes**
Medical material	Name/Date	No	**Yes**	**Yes**
Fee	Name/Date	No	**Yes**	**Yes**

Mapping to Standard Code

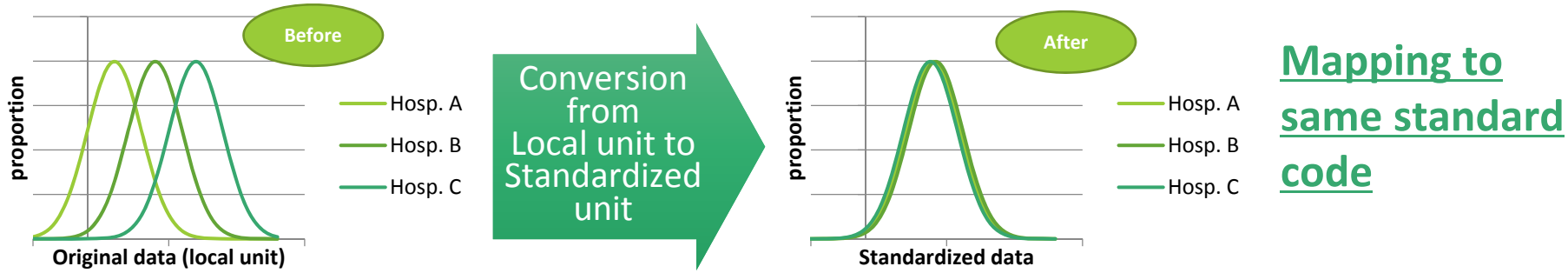
- Local code of each content is mapped to standard code to analyze data from all medical institutions data together.

Contents	Medical information	Claim data	Prospective payment data for acute inpatient
Disease	**Standard codes (ICD-10 and JP-specific codes)**	**Standard codes (ICD-10 and JP-specific codes)**	**Standard codes (ICD-10 and JP-specific codes)**
Medicine (ordered)	**Standard codes (JP-specific codes)**	**Standard codes (JP-specific codes)**	**Standard codes (JP-specific codes)**
Medicine (complied)	**Standard code (JP-specific codes)**	No data	No data
Laboratory /Bacteriological test	**Standard codes (JP-specific codes)**	**Standard code (JP-specific code)**	**Standard code (JP-specific code)**
Image/Physiological test	Local code	Local code	Local code
Surgery	No data	**Standard codes (JP-specific codes)**	**Standard codes (JP-specific codes)**
Medical material	No data	**Standard code (JP-specific code)**	**Standard code (JP-specific code)**
Fee	No data	**Standard code (JP-specific code)**	**Standard code (JP-specific code)**

Mapping of Laboratory Test Name to Standard Code

- PMDA and MID-NET® collaborative medical institutions have examined the distribution of laboratory test results by the medical institution.

Corresponded distribution after unit conversion



Mapping to same standard code

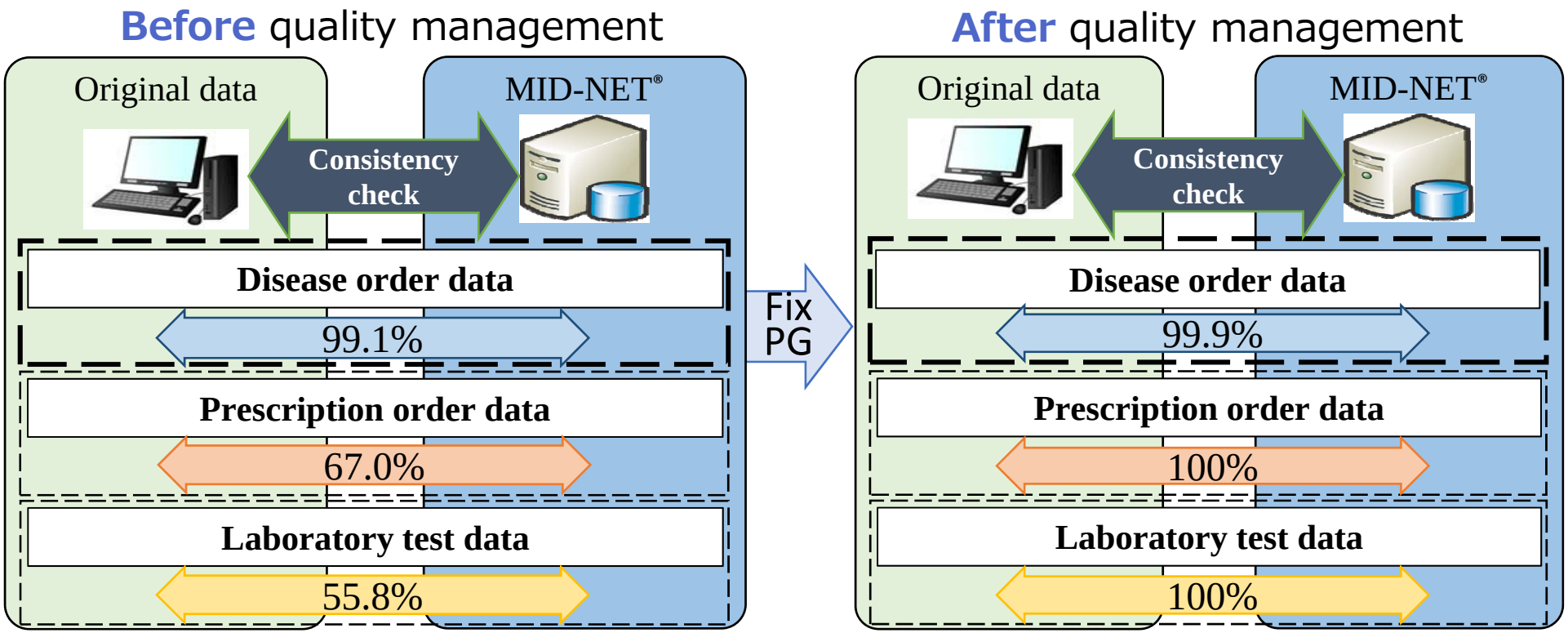
- We are aiming to map approximately 200 laboratory test names to standard codes.

Example : Available laboratory test result for analysis

ALT, AST, BUN, K, Creatinine, LDH, Gamma-GT, Cl, ALP, MCHC, MCH, Uric Acid, cGFR, TG, Cholesterol, Amylase, Blood Glucose, LDL-C, Inorganic Phosphate, HDL-C, PT-INR, HbA1c, PT, APTT, CEA, Fe, FT4, IgG, TSH, Sedimentation rate, RPR, IgM, HbA1c（NGSP）, TPHA, AFP, Ferritin, Hb, Reticulocyte, Blood Gases（TCO_2）, Blood Gases（pH）,etc

Data Quality of MID-NET®

- PMDA has worked with collaborative medical institutions and IT companies for assuring data quality of MID-NET®.
- We have checked consistency between the original data and the standardized data stored into MID-NET®.



- Periodic data check will be needed to maintain the high data quality of MID-NET®.

SAS® program library for analysis utilizing MID-NET®

Develop SAS® program for typical pharmacoepidemiological studies.

Descriptive analysis for feasibility study	• Identify cohort and exposure of interest. • Calculate background rate of an event in cohort. • Frequency of laboratory test in cohort.
Drug utilization study	• Volume of prescriptions, days of prescriptions and interval of prescriptions (to use other programs)
Cohort study	• Single Cohort（Investigation of event occurrence and patient background ） • Double Cohort（Adjust covariates and investigate the relationship between risks and exposures）
Nested case control study	• Focusing on a specific outcome, investigate the risk by the presence or absence of risk factors
Interrupted time series	• Investigate transitions before and after regulatory actions to evaluate effects of regulatory actions

Validation of Outcomes

- A new project was launched in 2017 to promote the conduct of reliable pharmacoepidemiological studies utilizing electronic medical records.
- PMDA and the collaborative medical institutions are going to conduct validation studies of approximately 20 health outcomes.
  - To verify that the electronic codes in database validly and reliably identify individuals with particular medical conditions.

Promotion of Regulatory Science based on Utilization of Big Data

- **In 2018,**
- Full-scale utilization of MID-NET® will start.
  - Pharmaceutical industries and academia in addition to the collaborative medical institutions and MHLW/PMDA.
- Results from database study will be available for evidence of efficacy and safety in the application for reexamination.
- Regulatory Science Center will be established in PMDA*.
  - In close collaboration with relevant academics, societies and industry around the globe, activities such as identification of safety risks using electronic medical records, simulation and model building based on clinical trial data（CDISC data） across products will be conducted.

PMDA will, based on regulatory science, promote public health globally by communicating the outcomes of its first-in-the-world product reviews, safety measures, and relief services.

* http://www.pmda.go.jp/english/int-activities/outline/0017.html

Thank you for your kind attention!

- MIHARI Project (in English)
  http://www.pmda.go.jp/english/safety/surveillance-analysis/0001.html
- MID-NET® Project (in Japanese)
  http://www.pmda.go.jp/safety/mid-net/0001.html