DIA 2019
GLOBAL ANNUAL MEETING
SAN DIEGO | JUNE 23-27

PMDA Center for Regulatory Science

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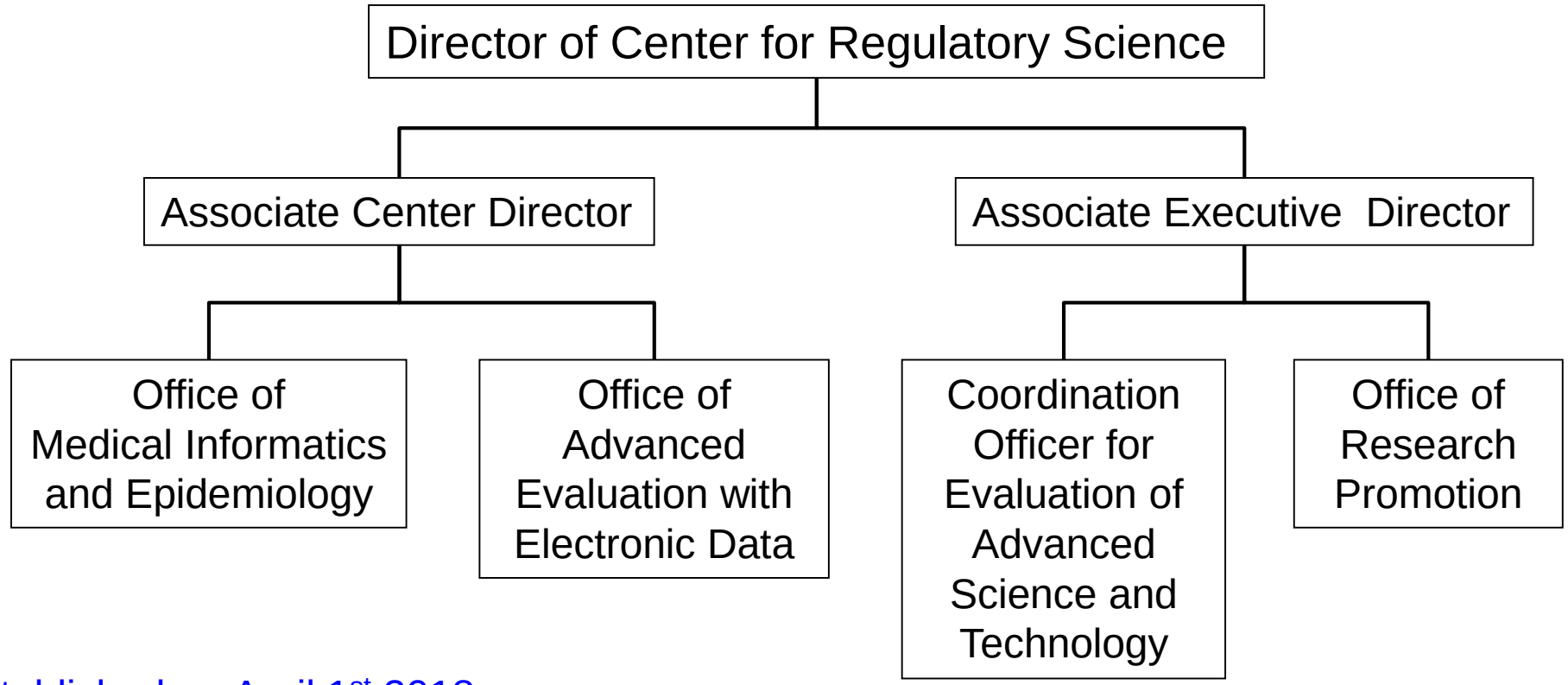
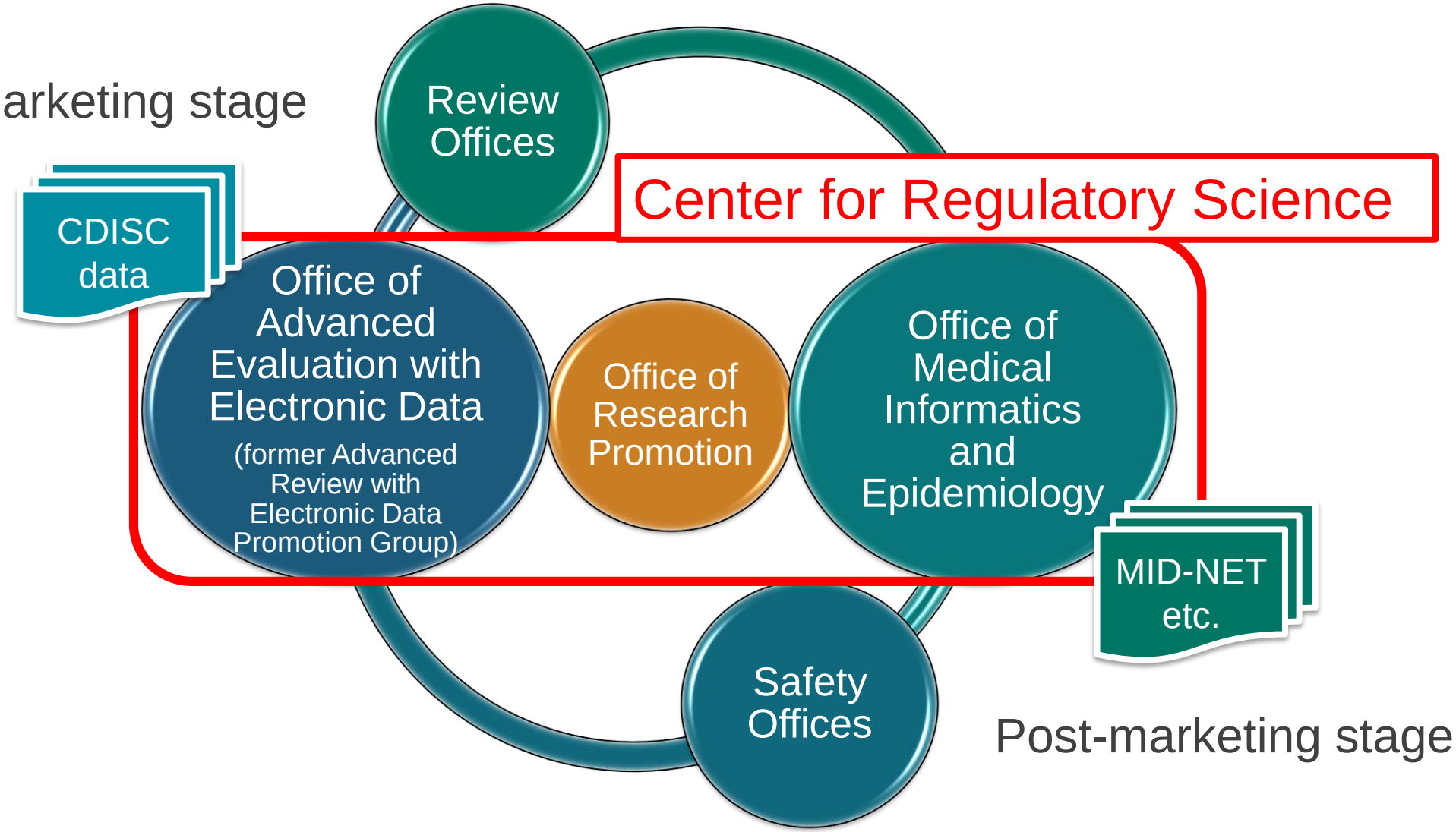
Organization Structure of Center for Regulatory Science



Established on April 1st 2018

Closely working together with Office of New Drugs, Office of Safety and others

Pre-marketing stage



Post-marketing stage

PMDA-Academia collaborations

Collaboration with Academic Organizations

- Comprehensive Partnership Agreements with 9 academic organizations

DATE	Organizations
February 2, 2016	NCC (National Cancer Center)
March 4, 2016	Hiroshima University
March 11, 2016	Keio University
March 30, 2016	University of Tsukuba
July 11, 2016	NCNP (National Center of Neurology and Psychiatry)
October 31, 2016	Tohoku University
March 14, 2017	NCGM (National Center for Global Health and Medicine)
July 24, 2017	NCVC (National Cerebral and Cardiovascular Center)
Jan 22, 2018	NCCHD (National Center for Child Health and Development)

Establishment of an Excellent Cooperation System

- Personnel Exchange
- Human Resources Development
- Joint Research Projects

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Science Board

to close the gap between scientific innovation and product review

Academia

Universities, institutes, medical institutions

Collaboration

PMDA

Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies

Example: Themes of Science Board

Subcommittee of Cellular and Tissue-based Products

(1st term: FY2012 – 2013)

Evaluate tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells (iPSCs)

Subcommittee of Artificial Intelligence

(3rd term: FY2016 – 2017)

Overview new technologies using AI and discuss their totally new characteristics in order to facilitate the future review and consultations on the products.

Subcommittee of Genome Editing

(4th term: FY2018 – 2019)

Assess the risk of genome edited products (The report expected in November 2019)

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“Horizon Scanning”

Without Horizon Scanning…

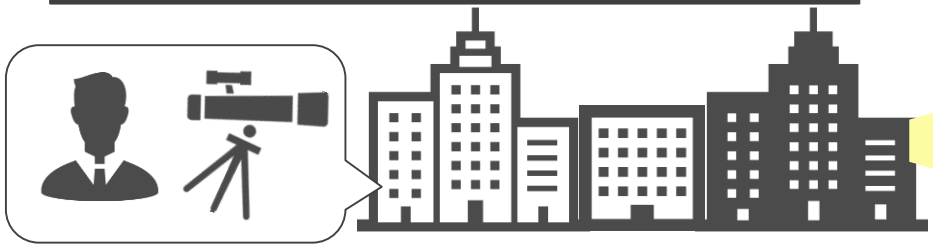
Stakeholders : unsure of regulations…

Report on Technology A

Regulator

Regulators : cannot keep pace with accelerating innovation…

With Horizon Scanning…



Regulator

Emerging Technologies

・Proactively scan the horizon for emerging trends, technologies, etc.

・Make necessary regulatory preparations.

- From October 2017, PMDA led the international project of “Horizon Scanning” under ICMRA (WS1) for promoting regulatory cooperation in the area of state-of-the-art science and technology.
- In light of the ICMRA project outcome, PMDA is going to reinforce the activity to identify, assess, and respond to the emerging technologies.

Analysis based on CDISC data

Accumulation and utilization of CDISC data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

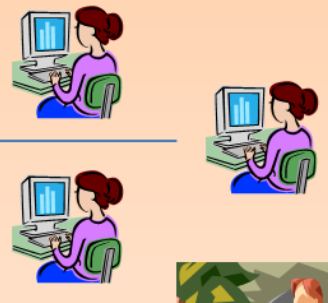
Storage of electronic data in the dedicated server and registration in the database

Submission of electronic clinical study data will be mandatory after April 2020.

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Visualization and analysis of data, supported by browsing software

Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

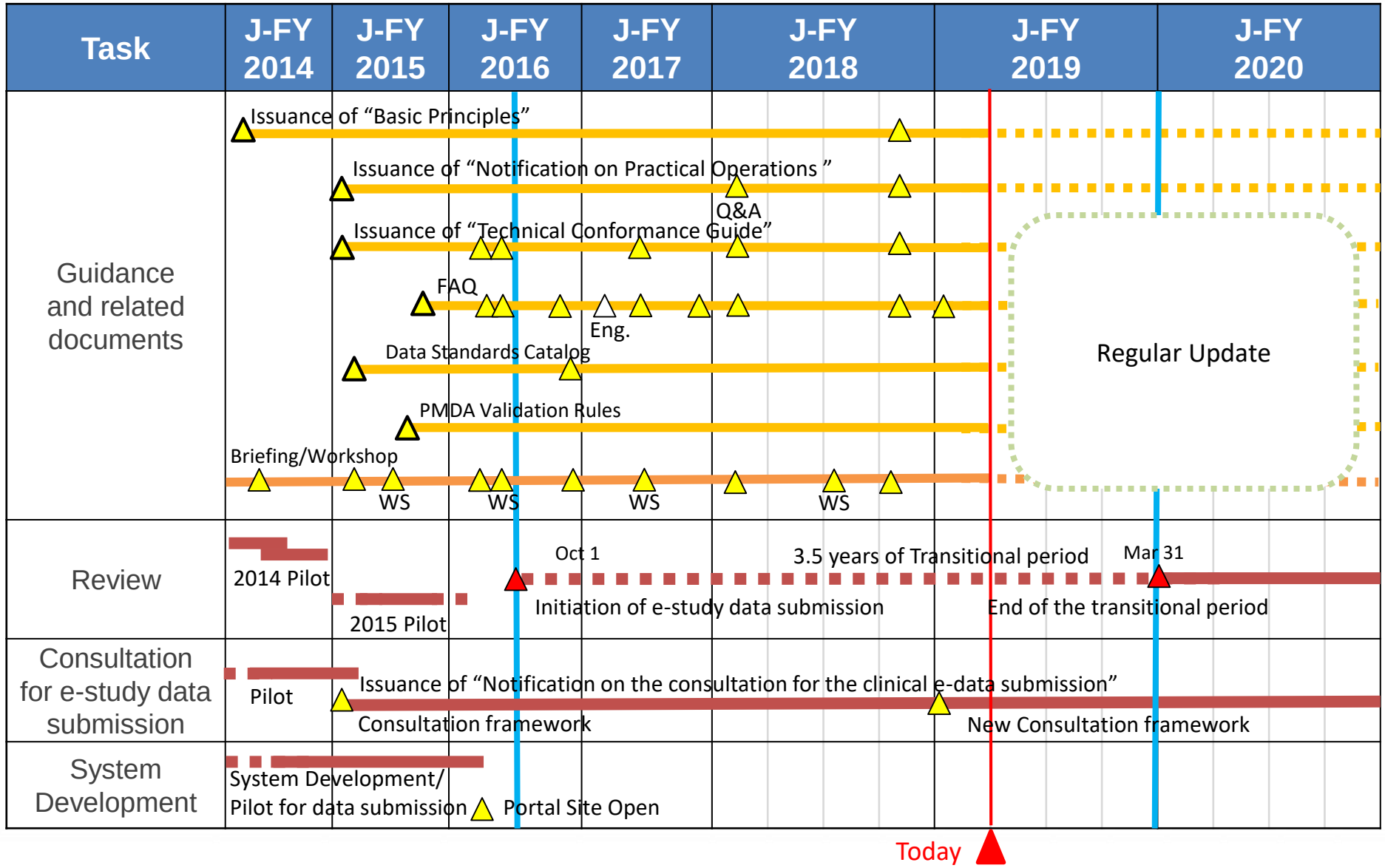
Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Timeline for implementation of e-data submission



Case example of analysis with e-data

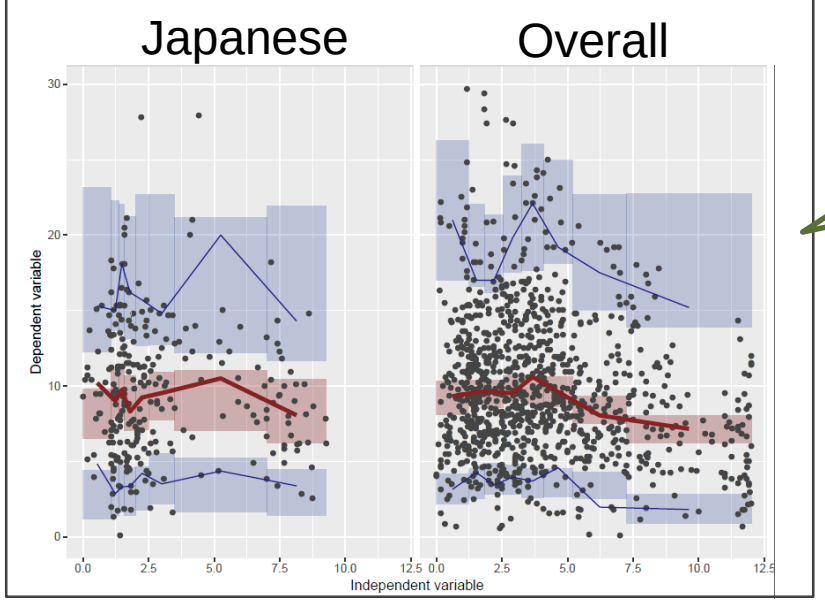
Background

- PopPK analysis using Japanese population and non-Japanese population data
  - Confirm the model validity in Japanese population

Review with e-data

- Model Qualification on PopPK by reviewers

Visual Predictive Check for PopPK model based on MRCT data



Goodness of Fit plots and Visual Predictive Check for Japanese subpopulation in addition to overall population

Check whether PopPK analysis result was valid for Japanese or not

Prospect of e-Study data utilization in Japan

Prospect As of Sep 2017
(Subject to Change)

Start e-study data submission for NDA* from Oct 1st, 2016

*NDA=New Drug Application

- e-study data can be received and managed appropriately
- e-study data can be utilized in the review
- Industries' workload is reduced gradually while keeping the review period

- J-FY2017

Setup e-data management and utilization

Promotion of paperless operation

J-FY2018

Ordinary utilization of e-data in the product review

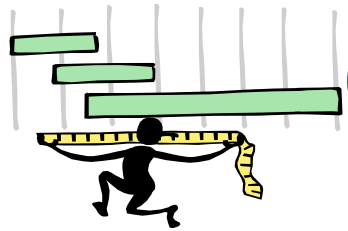
- More predictable efficacy/safety
- Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

Transitional period are taken until March 31st, 2020

- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

J-FY2019 - 2021

Starting earnest cross-product analysis



- Establishment of disease models
- Publication of disease-specific guidelines

First-class review quality

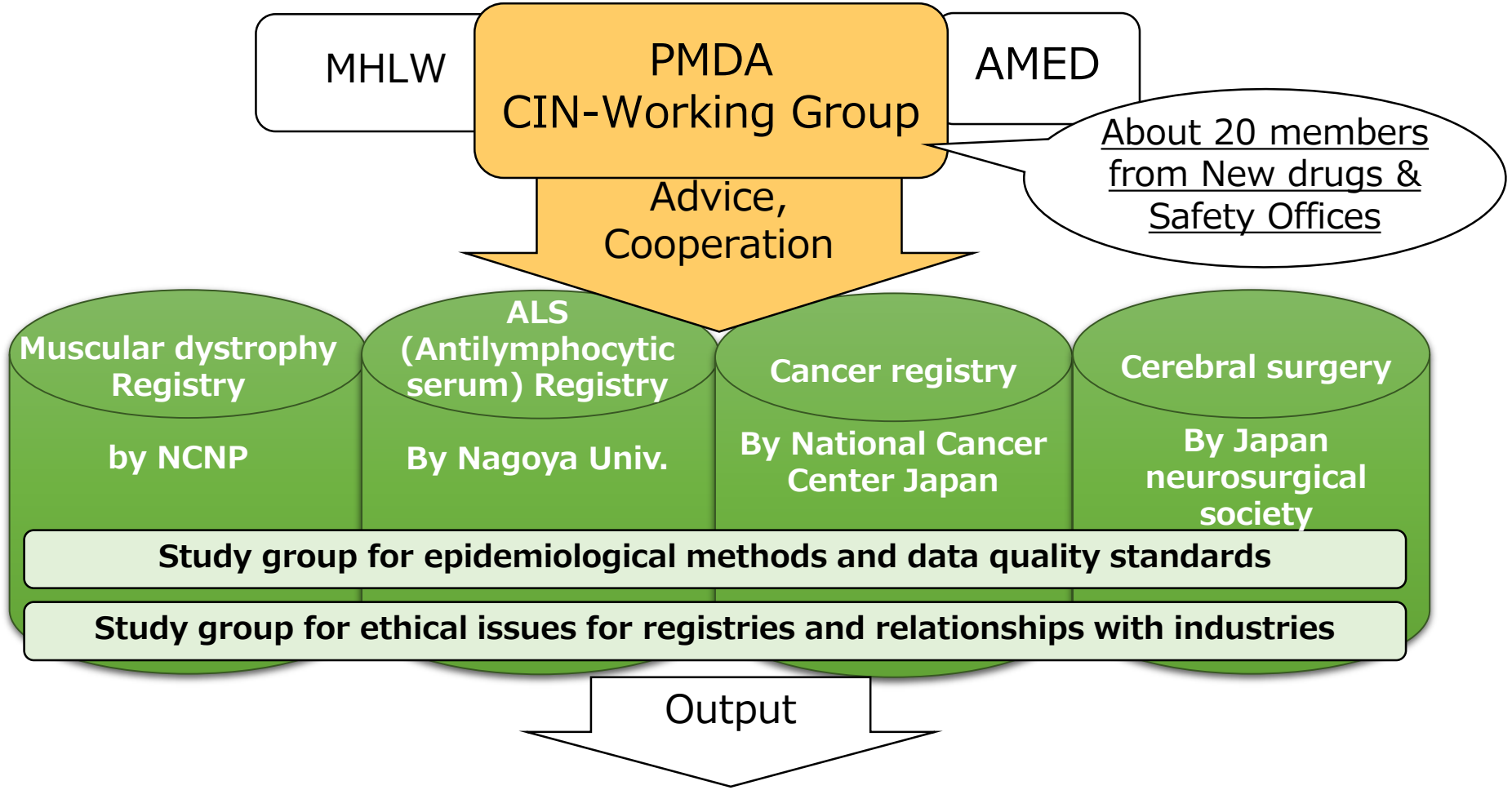
J-FY2022 -

Publication of guidelines to contribute to drug development

e.g. guidelines and disease models based on data on Asian population

Assessment of benefit/risk of drugs based on real world data (RWD)

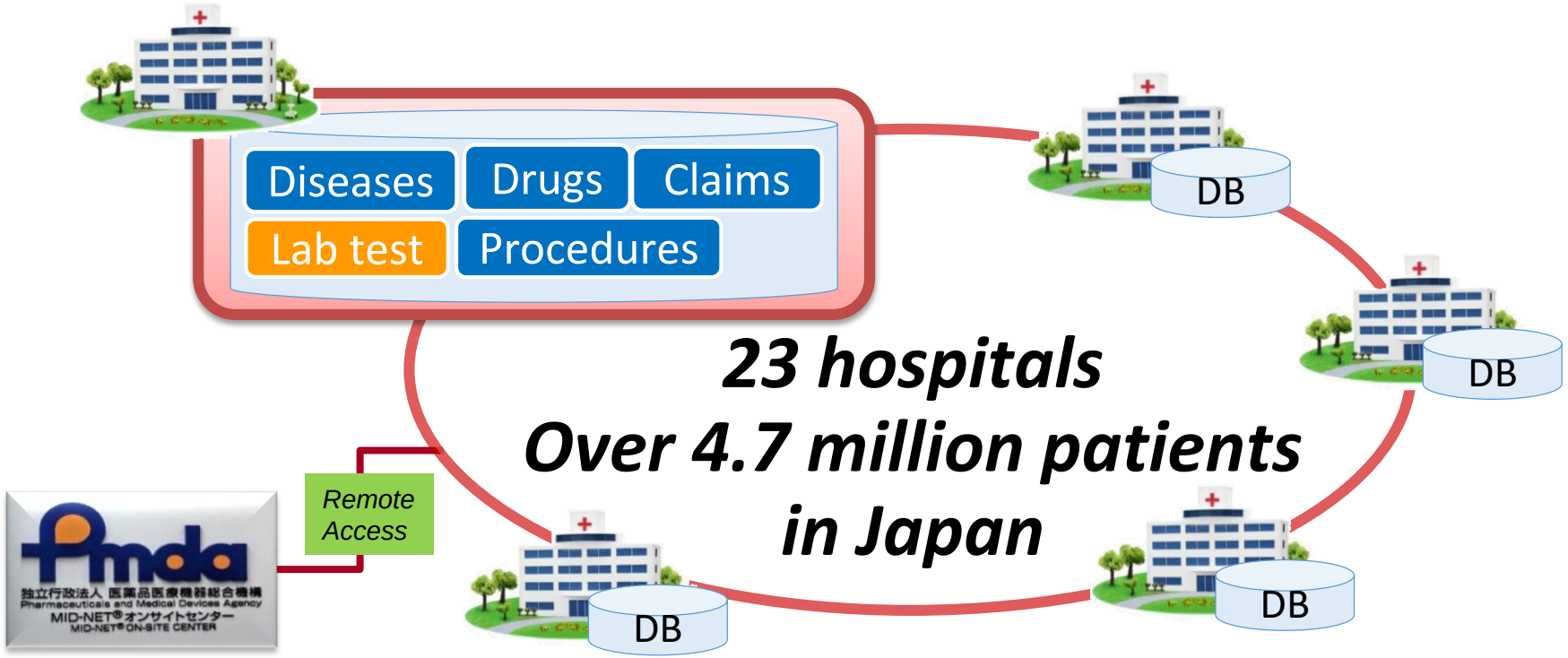
Clinical Innovation Network (CIN)



Utilizing patient registry data for promoting cost effective clinical studies, quantitative B/R assessment and accelerating drug development

RWD utilization (MID-NET®)

- The Medical Information Database Network in Japan for a real-time assessment of drug safety
  - currently >4.7M patients
- PMDA has led the project for establishing an integrated real time EMRs database with high quality



MID-NET® pilot studies

ORIGINAL REPORT

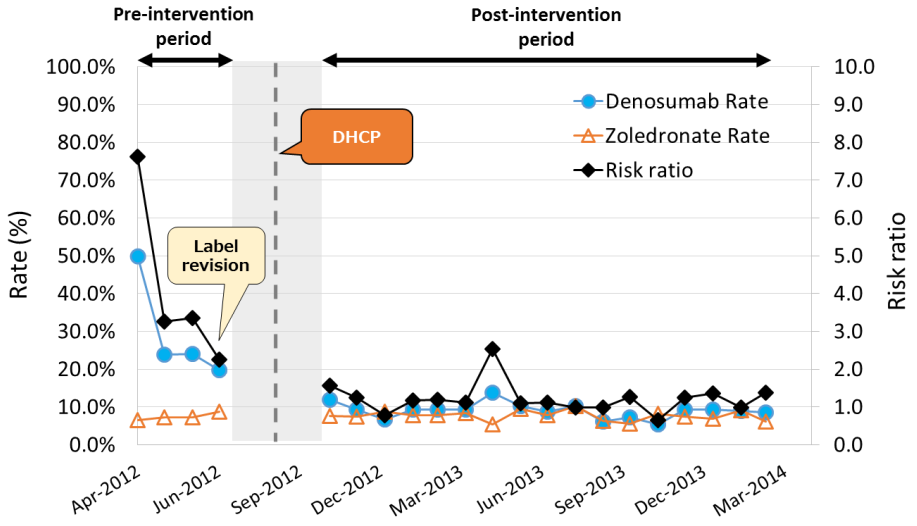
Pharmacoepidemiol Drug Saf. 2019;28:601–608.

The utilization and challenges of Japan's MID-NET® medical information database network in postmarketing drug safety assessments: A summary of pilot pharmacoepidemiological studies

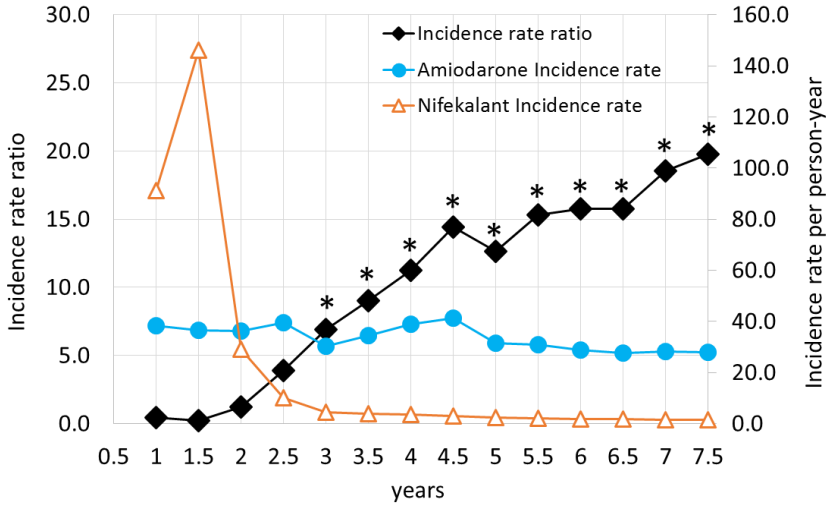
Kaori Yamada[1] | Maori Itoh[1] | Yoshiaki Fujimura[2] | Michio Kimura[3] | Koichiro Murata[4] | Naoki Nakashima[5] | Masaharu Nakayama[6] | Kazuhiko Ohe[7] | Takao Orii[8] | Eizaburo Sueoka[9] | Takahiro Suzuki[10] | Hideto Yokoi[11] | Chieko Ishiguro[1] | Yoshiaki Uyama[1] | on behalf of MID-NET® project group

DOI: 10.1002/pds.4777

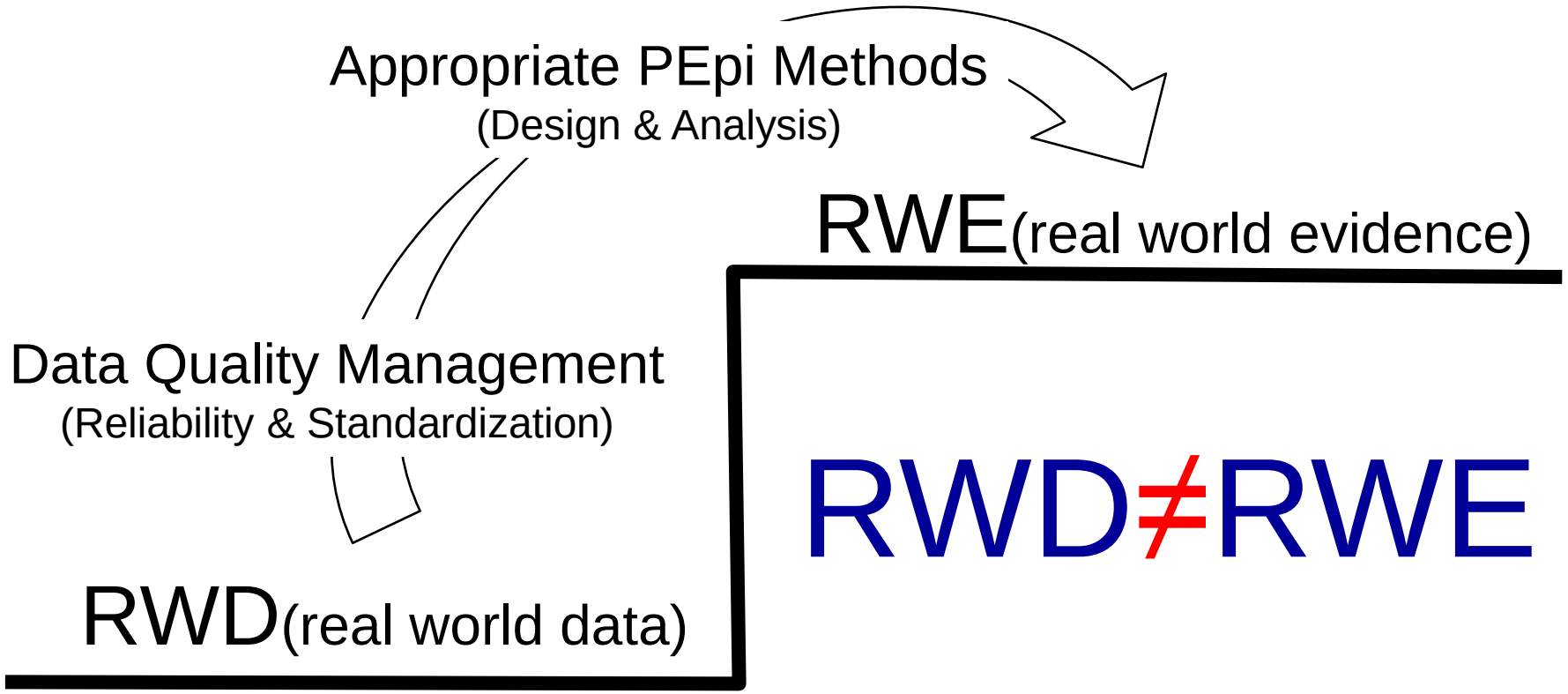
Hypocalcemia risk associated with denosumab



Liver dysfunction during antiarrhythmic drug administration



Challenges in transforming RWD into RWE



- The useful RWE can be obtained only under the following conditions.
  - ➢ Collection of RWD with high quality and standardization
  - ➢ Analyze data with appropriate study design and analytical methods

Roles of Center for Regulatory Science in PMDA
-Future Vision-

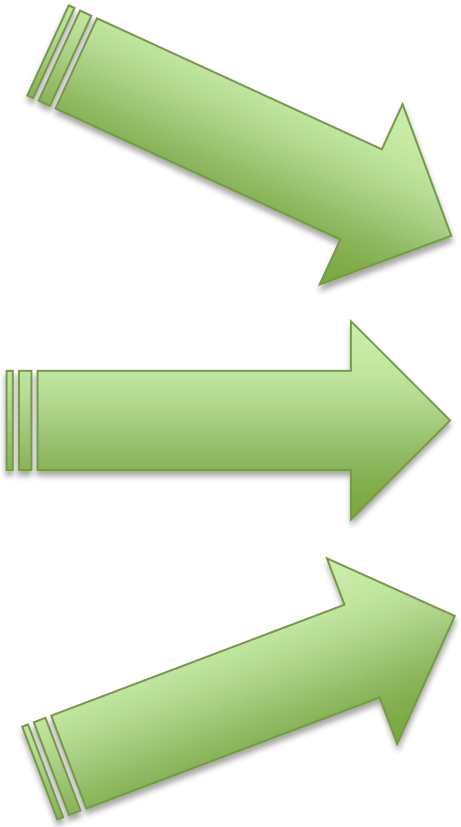
Past-Present

Pilot/Cluster approach

Academic collaborations

CDISC data analysis

RWD utilization



4th MID-TERM plan (FY2019-FY2023)

Unified approach as the center

- More collaborations with academia and other regulatory agencies
- Cross product analysis based on accumulated data for sophisticated review and consultation
- More utilization of RWD for better benefit/risk assessment
- More regulatory guidelines corresponding to the latest science

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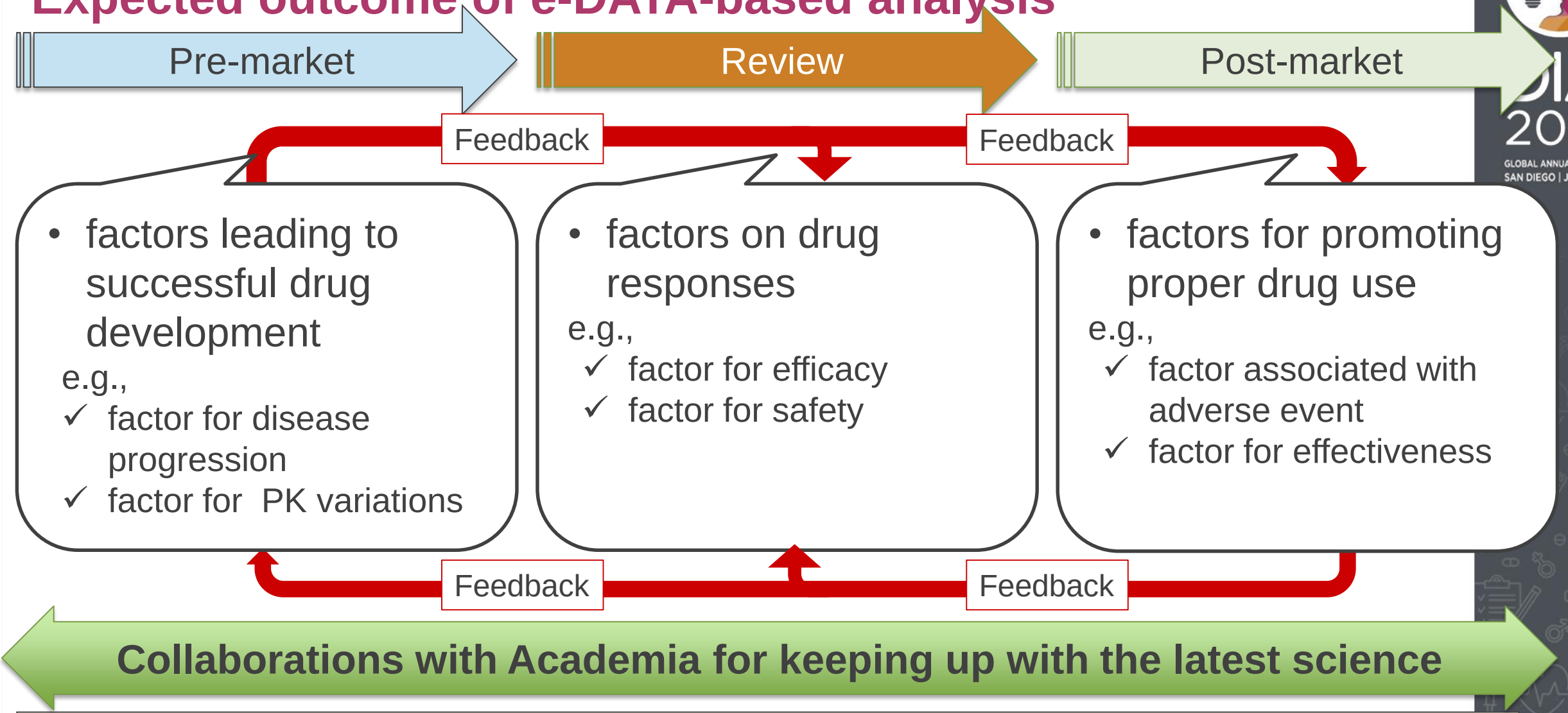
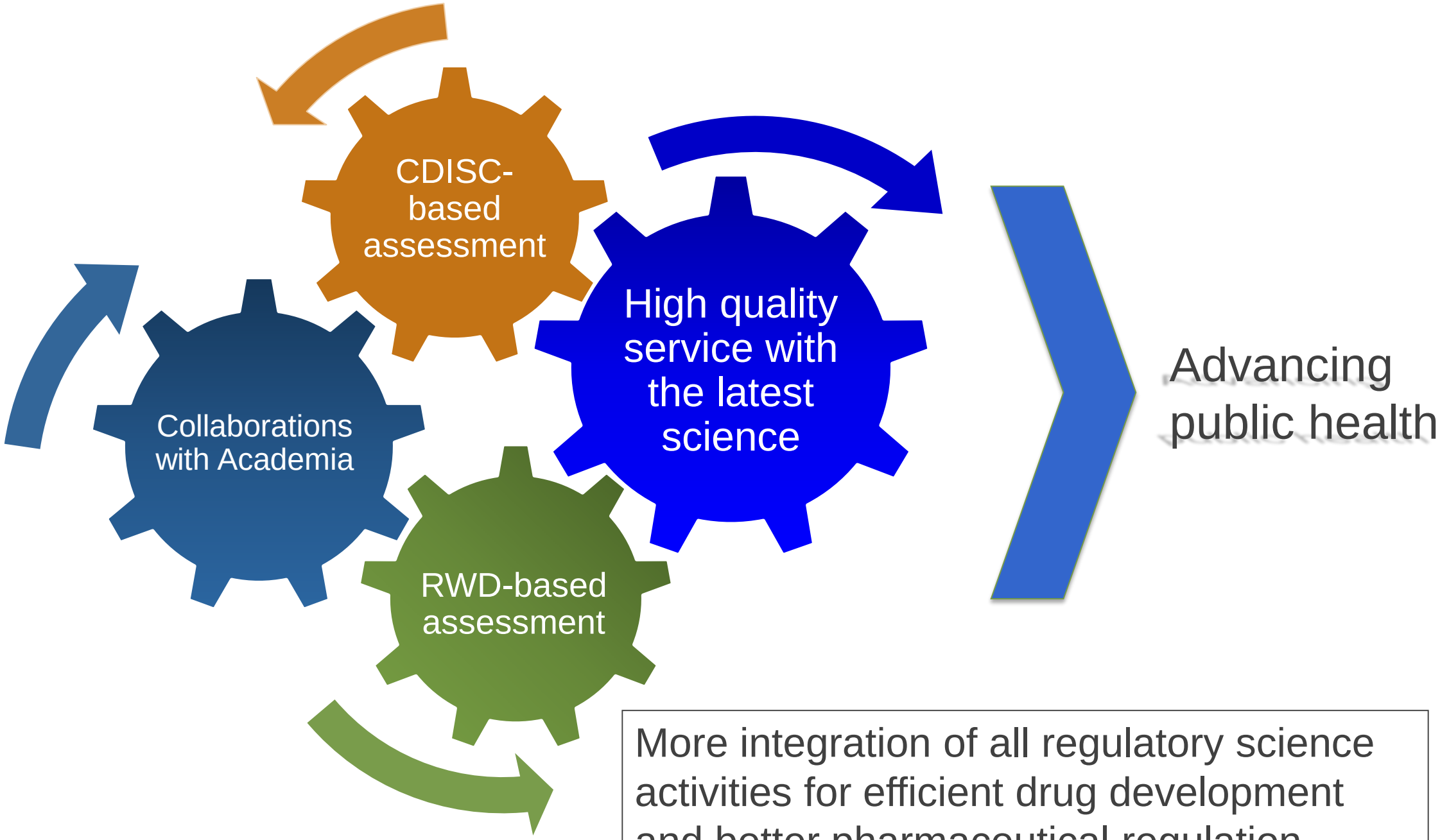
Example:
Expected outcome of e-DATA-based analysis



e-DATA-based regulation for maximizing an efficiency of drug development and ensuring the positive benefit/risk balance of a drug throughout product life cycle



More integration of all regulatory science activities for efficient drug development and better pharmaceutical regulation

Thank You

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