Sharing Experiences of e-Data Submission to PMDA Using Registry Data

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Disclaimer

- The contents of this presentation represent the opinions of the individual presenters and do not represent the opinions or positions of the organization to which we belong

Agenda

- Background
- Submission Data Package Overview
- Role and Responsibility / Data Traceability
- Timeline
- Consultation with PMDA
- Issues and Lessons Learned
- Future Expectations

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Background [1)]

- **Approximately 3~6% of patients with metastatic colorectal cancer (mCRC) are HER2 positive(HER2+)[2)]**
- **No standard therapy approved globally for HER2+ mCRC before 2022**
  - National Comprehensive Cancer Network (NCCN) guideline has been listing pertuzumab + trastuzumab (PER-HER) based on the promising results for patients with treatment refractory HER2+ mCRC in single arm, multiple basket, phase IIa MyPathway study[3)]
- **Investigator-initiated single arm phase II TRIUMPH study[4)] was conducted in Japan to obtain the approval of this combination therapy**
- **To contextualize results of single arm studies, external controls derived from real-world data (RWD) were used in the regulatory submission**
  - SCRUM-Japan Registry for TRIUMPH study[5)]
  - Flatiron/FMI clinico-genomic database (CGDB) for MyPathway study[6)]

https://phuse.s3.eu-central-1.amazonaws.com/Events/2023/SDEs/SDE+Presentations/Kobe%2C+Japan/1535_Takuya_Yusuke+V2.pdf

1) – 6): References are on slide 22.

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Submission Data Package Overview

- **Chugai's first experience using registry data for the submitting it in CDISC format.**
- **Submission data package**

Study/Data	Phase	Evaluation/Reference	Study Status	CDISC	PMDA data submission
EPOC1602(TRIUMPH) Note: Investigator-initiated Study	II	Evaluation	Completed	**Unhandled**	**Yes**
SCRUM-Japan Registry **Note: External control arm for TRIUMPH study.**	NA	Evaluation	Ongoing	**Unhandled**	**Yes**
PER001JP • MyPathway clinical trial • Flatiron+Foundation Medicine data was used as the external control arm for the MyPathway	NA	Reference	Ongoing	NA	No
SG42530 • Flatiron+Foundation Medicine data	NA	Reference	Ongoing	NA	No

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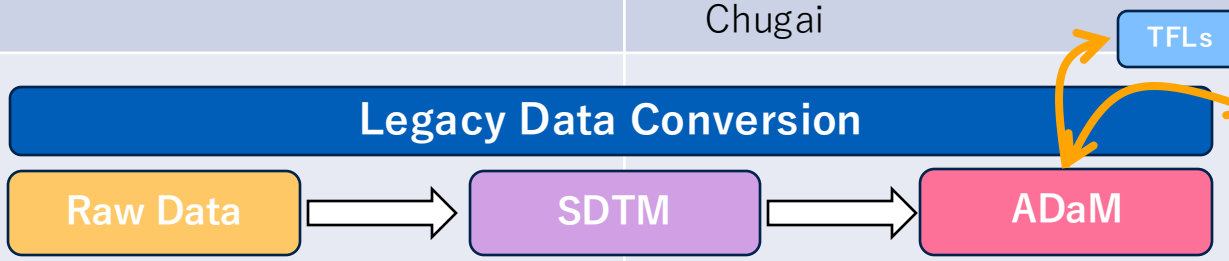
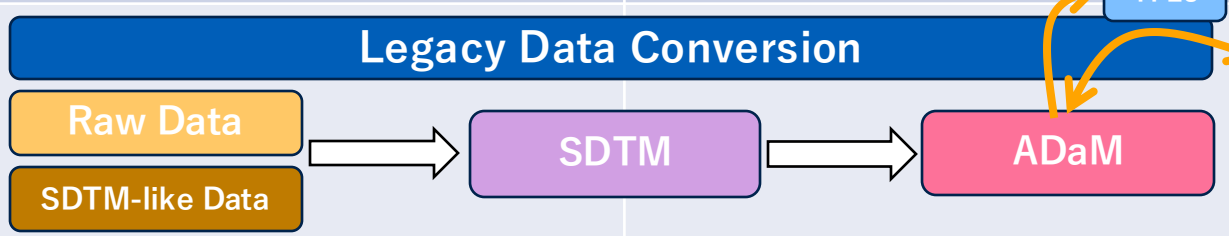
Role and Responsibility / Data Traceability

Study/Data	SDTM	ADaM	TFLs and CSR
TRIUMPH	• Chugai • CRO commissioned by Chugai	• Chugai • CRO commissioned by Chugai	• National Cancer Center Hospital East (NCCHE)
		• Confirm reproducibility between Analysis Dataset and ADaM	 • TFLs were created from the analysis dataset (non-CDISC) created by NCCHE. • The reproducibility of TFLs was confirmed by creating major TFLs from ADaM and comparing them with those generated from Analysis Dataset.
SCRUM-Japan Registry	• Chugai • CRO commissioned by Chugai	• Chugai • CRO commissioned by Chugai	• NCCHE
	 • Created from two types of data: SDTM-like data created by NCCHE and commissioned to a CRO, and raw data	• Confirm reproducibility between Analysis Dataset and ADaM.	 • TFLs were created from the analysis dataset (non-CDISC) created by NCCHE. • The reproducibility of TFLs was confirmed by creating major TFLs from ADaM and comparing them with those generated from Analysis Dataset.

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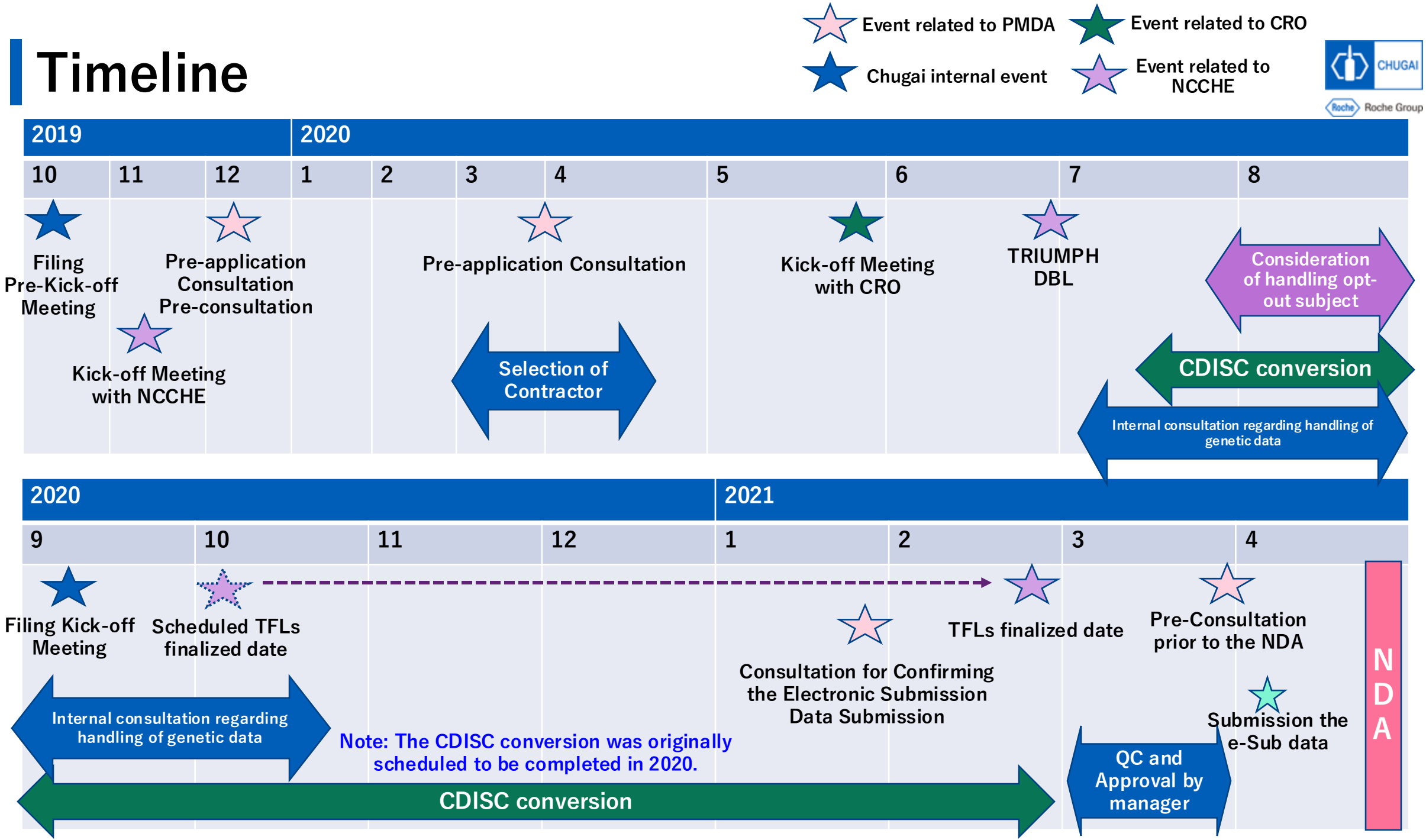
Timeline


Event related to PMDA
Event related to CRO
Chugai internal event
Event related to NCCHE
CHUGAI
Roche Roche Group
2019
2020
10
11
12
1
2
3
4
5
6
7
8
Filing Pre-Kick-off Meeting
Pre-application Consultation Pre-consultation
Kick-off Meeting with NCCHE
Pre-application Consultation
Selection of Contractor
Kick-off Meeting with CRO
TRIUMPH DBL
Consideration of handling opt-out subject
CDISC conversion
Internal consultation regarding handling of genetic data
2020
2021
9
10
11
12
1
2
3
4
Filing Kick-off Meeting
Scheduled TFLs finalized date
Consultation for Confirming the Electronic Submission Data Submission
TFLs finalized date
Pre-Consultation prior to the NDA
Submission the e-Sub data
NDA
Internal consultation regarding handling of genetic data
Note: The CDISC conversion was originally scheduled to be completed in 2020.
CDISC conversion
QC and Approval by manager

Timeline

Event related to PMDA
Event related to CRO
Chugai internal event
Event related to NCCHE

CHUGAI
Roche Group

2019			2020							
10	11	12	1	2	3	4	5	6	7	8

It took approximately 8 months from obtaining the registry data to completing the CDISC package.
（Typical duration: about 6 months）
Overall, it took about 1 year and 6 months from the Kick-off Meeting with NCCHE to the NDA.

Internal consultation regarding handling of genetic data

Note: The CDISC conversion was originally scheduled to be completed in 2020.

CDISC conversion

QC and Approval by manager

Submission the e-Sub data

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Consultation with PMDA（1/2）

- **Consultation on Utilization of Registry for Pharmaceuticals/Regenerative Medical Products（医薬品／再生医療等製品レジストリ活用相談）（Carried out in 2019）**
  - Consultation on the procedures and conditions required to ensure reliability when using the registry for approval applications
- **Pre-application Consultation（医薬品申請前相談）**
  - Consultation of Submission Data Package
  - We initially planned to treat the SCRUM-Japan Registry as reference data and did not intend to submit CDISC data. However, PMDA responded that the data would serve as the major evidence for efficacy and therefore the submission of CDISC data as evaluation data is necessary.

    Note: At that time, FAQ Q1-35 did not exist.

    A: Even if registry data are utilized in document of clinical data, it is still important, as with the case of clinical studies, to submit data that provide the major evidence for the efficacy, safety, and dosage and administration for a new drug application in a format conforming to the CDISC standards basically.
    On the other hand, the scope, contents and format of registry data to be submitted may require individual judgment, depending on the contents and purpose of registry data. Therefore, please consult with the PMDA in advance at an applicable consultation.
  - We also consulted on the scope of ADaM data submissions for the TRIUMPH and SCRUM-Japan Registries.
    - Submitting the datasets necessary to replicate the primary efficacy and safety results.

PMDA FAQ：https://www.pmda.go.jp/files/000267941.pdf

Consultation with PMDA（2/2）

- **Post-consultation of Pre-application Consultation (医薬品申請前相談の事後相談)**
  - Consulted how to handle opt-out subjects in registry data
    - PMDA commented that data excluding opt-out subjects should be submitted, but the principal investigator insisted on including opt-out subjects in the CSR. As a result, it was agreed that the data of opt-out cases would be treated as reference data.
      - CSR : Sections 1 to 16.3 consist of data excluding opt-out subjects, and section 16.4 describes the data for opt-out subjects.
      - e-Submission data : There is no problem with submitting the data including opt-out subjects. However, it was commented that if there is a request for deletion from the opt-out subjects, it should be promptly shared with the responsible personnel in the New Drug Review Department and the Next Generation Evaluation Methods Promotion Department.
- **Consultation for Confirming the Electronic Submission Data Submission (申請電子データ提出確認相談)**
  - Advance explanation of "Error" in CDISC data
- **Pre-Consultation prior to the NDA (審査予定事前面談)**
  - Review Timeline for NDA
  - Scope of reliability investigation, documents to be submitted (EDC management sheet for registry data, whether or not there is an overview explanation, etc.)

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Issues

- **Lack of coordination before legacy conversion**
  - Provided materials：There were cases where it was discovered after work had begun that additional data (popuration data, deviation data, query conversion tables, etc.) or specifications were needed. In some cases, this was discovered by comparing analysis data for creating TFLs with ADaM.
  - Registry data extraction conditions：The extracted registry data was received without any detailed align to the conditions before the initial data provision from NCCHE. After work had started, it was discovered that the data was different from what was assumed, so rework was occurred.
- **Complexity of EDC systems makes data interpretation difficult**
  - There are rules and DM operational that cannot be understand from the CRF Entry Manual and it became necessary to confirm with NCCHE each time.
- **The impact of EDC system migration**
  - During the collection of registry data, the EDC system was changed. There were discrepancies in item names and terminology between the old and new systems. As a result, it took a significant amount of time to interpret the data.
  - When EDC migrating, a query was raised, but the data was locked without being corrected in the EDC. The query confirmation results were handled using a conversion table. It was discovered towards the end of the work that this data needed to be imported.
- **Quality of provided intermediate data (SDTM Like data)**
  - Part of the registry source data was SDTM-like data created by a CRO commissioned by NCCHE. During the legacy conversion, errors in the specifications and data were discovered, leading to several corrections.

Lessons Learned

1) Close information sharing and collaboration among the Site, applicant, and the CRO commissioned for the legacy data conversion.

2) Elimination of implicit understandings through explicit documentation

3) Consider a timeline with plenty of time

- The source data and specifications (including the version information) required for creating TFLs are listed and align the understanding of both. Pay special attention if hard coding or conversion tables are required.
- Consider a timeline that takes into account the increased communication with site for data interpretation.
- When using intermediate data (e.g. SDTM-like data), consider the possibility of revisions and account for that period in the timeline. There is also the advantage that SDTM-like data is easier to handle.

Supplement

- **Currently, as for the complexity of the EDC structure, the following approaches have been taken at NCCHE, making it easier to use.**
  - EDC system has been unified, making data interpretation simpler.
  - EDC system has a function to output either raw data or SDTM-like data.

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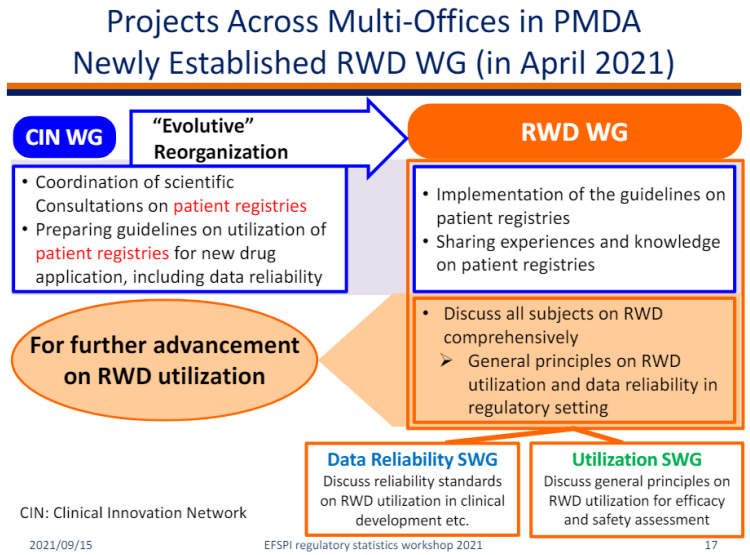
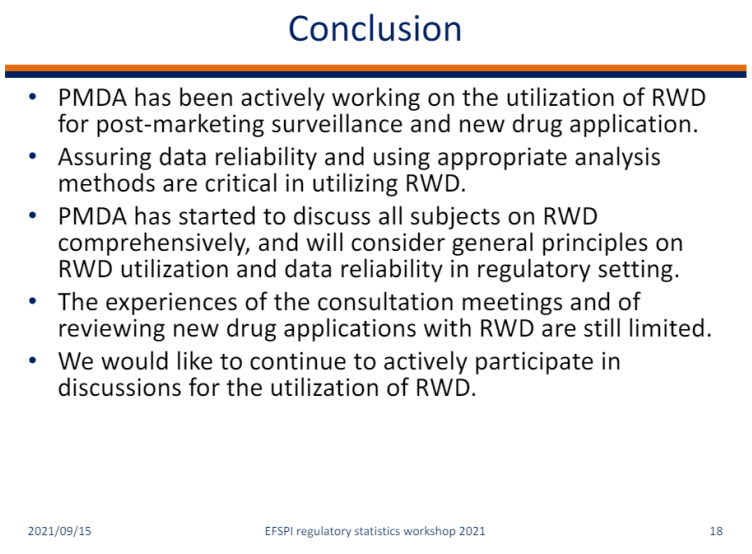
Future Expectations

- PMDA promote the use of RWD in applications.
- The CDISC conversion of RWD requires two to three times the load of normal legacy data conversion. However, considering the cost and time required to conduct one clinical trial, the use of RWD in applications is very beneficial.
- Relaxing the requirements for submitting CDISC-compliant RWD may lead to a shortened application timeline and an increase in the number of applications using RWD for rare diseases, etc.
- **The authorities, applicants, and RWD owners need to work together to identify issues and the minimum requirements for RWD applications, and to promote the use and application of RWD in the future.**





https://www.efspi.org/Documents/Events/Events%202021/6th%20Regulatory%20Workshop/37%20Ando.pdf

Reference

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3. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al: Pertuzumab and trastuzumab for HER2-amplified metastatic colorectal cancer: an updated report from MyPathway, a multicentre, open-label, phase 2a multiple basket study. Lancet Oncol 20:518-530, 2019.

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6. Narita Y, Yoshimoto T, Namai T, et al: Pertuzumab plus trastuzumab for treatment-refractory HER2-amplified metastatic colorectal cancer: comparison of the MyPathway trial with a real-world external control arm. JCO Clin Cancer Inform 6:e2200022, 2022.

INNOVATION BEYOND IMAGINATION