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PMDA Update

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Meet the Speaker

Yuki Ando, PhD

Title: Principal Senior Scientist for Biostatistics

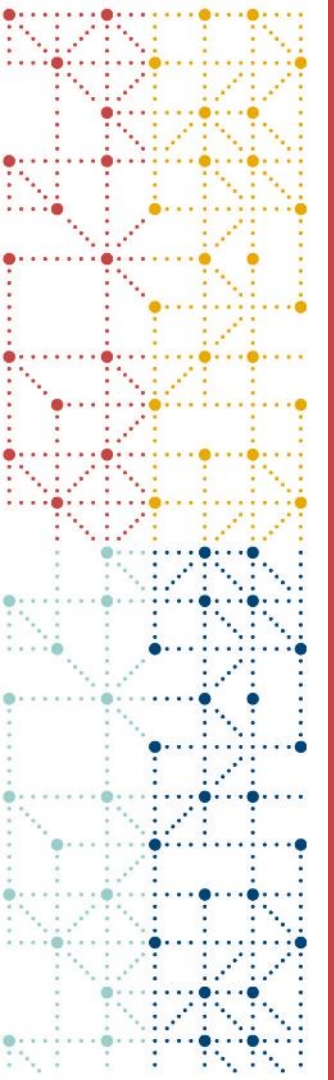
Organization: Pharmaceuticals and Medical Devices Agency

Dr. Yuki Ando is a Principal Senior Scientist for Biostatistics of the Pharmaceuticals and Medical Devices Agency (PMDA), Japan. She has over 20 years‘ experience as Biostatistics Reviewer, and currently she is responsible for the biostatistics review and consultation in the new drug and device review offices in the PMDA. Additionally, she works for Office of Regulatory Science Coordination (formerly Office of Advanced Evaluation with Electronic Data), the office which is responsible for accepting patient level electronic study data that are submitted with new drug applications. She is a member of Real World Data (RWD) Working Group and Global Clinical Study Working Group that are projects across multi-offices in the PMDA.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC or PMDA.*

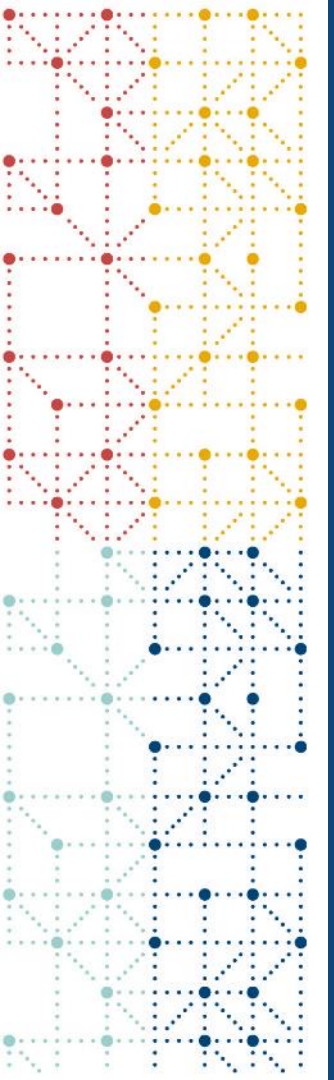
- *The author have no real or apparent conflicts of interest to report.*



Agenda

Recent Update

- Submission and utilization of study data
- Consultation related to study data submission
- Data Standards Catalog and PMDA Validation Rules



Recent update

Submission and utilization of study data

Data submission with new drug applications

- We have not provided the number of NDAs with data submission after FY2021, but after the end of the transitional period (FY2020 and beyond), most new drug applications are submitted to PMDA with electronic study data.

Examples of common issues with data submission and possible reasons -1/2

- Data submission process: abnormal termination of the validation, or violation whose severity is “Reject”
  - Incorrect combination of versions of standards and validation rules
  - Description of unaccepted versions in define.xml
  - Error in XML structure of define.xml
  - XPT files created by SAS CPORT Procedure
  - Lack of descriptions required in define.xml
- Validation results: unexplained “Error”
  - Lack of linked files in define.xml or incorrectly described link
  - Lack of explanation of “Error” that related to cross-check of SDTM and ADaM
  - Lack of details of explanation of “Error”, such as explanation like “Data was stored as collected in CRF”, that is pointed out in FAQ1-23

Examples of common issues with data submission and possible reasons -2/2

- Lack of description in reviewer's guide compared to the items listed in the PMDA Technical Conformance Guide 4.1.2.3
  - Lack of explanation of custom domains
  - Lack of Rule ID in the explanation on conformance to the data standards
  - Lack of information on the program, particularly the analysis environment and software used

Further understanding (…basically almost sufficient in most cases) of the notifications and Technical Conformance Guide and careful review of prepared data prior to data submission are important.

Utilization of study data in review process

Analysis Timing	Contents of Analyses

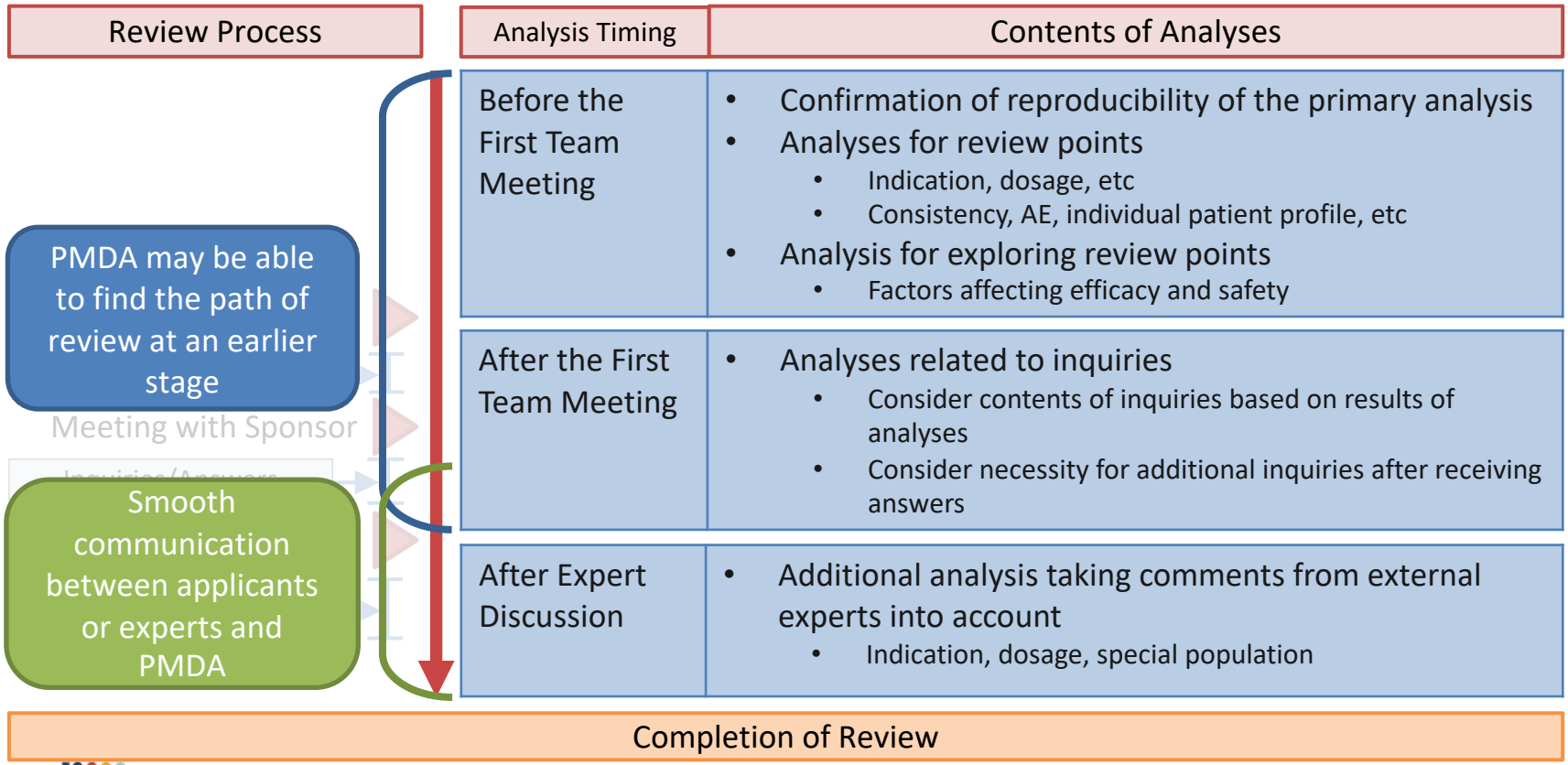
Before the First Team Meeting	• Confirmation of reproducibility of the primary analysis
	• Analyses for review points
	  • Indication, dosage, etc
	  • Consistency, AE, individual patient profile, etc
	• Analysis for exploring review points
	  • Factors affecting efficacy and safety

After the First Team Meeting	• Analyses related to inquiries
	  • Consider contents of inquiries based on results of analyses
	  • Consider necessity for additional inquiries after receiving answers

After Expert Discussion	• Additional analysis taking comments from external experts into account • Indication, dosage, special population

Completion of Review

Utilization of study data in review process



Utilization of study data – based on the activities of Biostatistics reviewers -1/2

- Examples of internal analyses
  - Sensitivity analyses with different statistical assumptions, supplemental analyses with different methodologies, statistical models, analysis sets, etc.
  - Subgroup analyses or analyses adjusted by covariates
  - Further analyses about dose selection
  - Confirmation of definition of primary endpoints
  - Analyses for considerations of trial operation
  - Data visualization for team discussion or further investigations

Utilization of study data – based on the activities of Biostatistics reviewers -2/2

- Examples of findings related to submitted study data for applicants
  - Errors in the program, including that for the primary analysis of the primary endpoint
  - Performing analyses for CSR using analysis methods different from those specified in the statistical analysis plan
  - Errors in specifying flag variables in the reviewer's guide
- Examples of questions or comments from the reviewers regarding the use of submitted study data
  - The PPS flag may not match to the PPS specified in the CSR.
  - Details of the multiple imputation method was not clear and difficult to reproduce.
  - Parameters used in the primary analysis were unclear.
  - Reviewer's guide was useful for the utilization of the data.
  - Analysis Results Metadata is very useful but sometimes not submitted.

We would like to continue to actively use submitted study data for new drug review and share any points we notice with stakeholders.

Recent update

Consultation related to study data submission

Consultation related to study data submission

From April 1, 2021

Clinical trial consultations

A sponsor and the PMDA identify which study data and/or analysis data are subject to be submitted electrically.

Consultation on **preparation** of submission of electronic study data

A sponsor and the PMDA discuss contents such as method of storing data, handling of variables, and strategy of storing data which cause the violations of CDISC conformity, regarding study data and/or analysis data planned to be submitted.

Consultation on **data format** of submission of electronic study data

PMDA confirms the validation results, i.e., the explanation of “Error” of violations and the reasons why they cannot be corrected.

Consultation on **exemption** of submission of electronic study data

A sponsor and the PMDA discuss contents such as,

- whether submission of a part of or whole of the study data could be exempted based on Q2 in “Q&A regarding Notification on Handling of Submission of Electronic Study Data”
- adequacy of the reason why study data would be submitted in another format than the CDISC standards and sufficiency of the contents based on Q10 in the “Q&A regarding Notification on Handling of Submission of Electronic Study Data”

Pre-NDA Meeting

The PMDA does a final confirmation of the contents of materials attached to approval application and scheduled submission date. The Sponsor should explain the contents of electronic study data submission using the Attachment 8/Form A.

Consultation for clinical e-data submission

- 756 consultation meetings have been conducted as of Mar 31, 2023.

Year		Number of consultations	
J-FY 2015 (May 15, 2015) – J-FY 2018		226	
J-FY 2019 (Apr 1, 2019 – Mar 31, 2020)	Consultation on data format	114	161
	Consultation on preparation	44	
	Consultation on exemption	3	
J-FY 2020 (Apr 1, 2020 – Mar 31, 2021)	Consultation on data format	207	282
	Consultation on preparation	57	
	Consultation on exemption	18	
J-FY 2021 (Apr 1, 2021 – Mar 31, 2022)	Consultation on data format	10*	54
	Consultation on preparation	28	
	Consultation on exemption	16	
J-FY 2022 (Apr 1, 2022 – Mar 31, 2023)	Consultation on data format	0	33
	Consultation on preparation	16	
	Consultation on exemption	17	
Total		756	

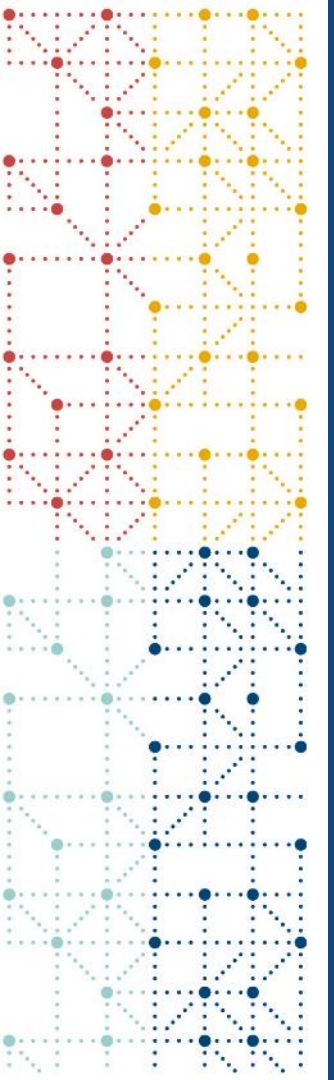
Change of Operation

* Consultations for which requests were received by March 2021 and conducted in this FY, or for which a pre-NDA meeting was not anticipated.

Consultation for clinical e-data submission

- Decrease in the number of consultation on preparation
  - It may indicate successful development/improvement of the notifications, Technical Conformance Guide, FAQs, and organizing the yearly workshop with appropriate contents for persons in charge of data preparation.
- Certain number of consultation on exemption each year
  - Most of the consultations are for exemptions from CDISC standardization (or CDISC standardization in strict accordance with PMDA regulations) of orphan drug clinical trial that were initiated prior to April 1, 2020.

We will continue to provide useful information to help preparation of study data submission at appropriate timing.



Recent update

Data Standards Catalog and PMDA Validation Rules

Update of Data Standards Catalog and PMDA Validation Rules (on February 28, 2023)

Data Standards Catalog and Study Data Validation Rules

- Data Standards Catalog (2023-02-28)
- Study Data Validation Rules
  - Version 1.0 (2015-11-18) Acceptable from Oct 1, 2016 to Mar 31, 2021 (application date)
  - Version 2.0 (2019-09-27) Acceptable from Apr 1, 2020 to Mar 31, 2023 (application date)
  - Version 3.0 (2021-12-15) Acceptable from Jan 1, 2022 to Mar 31, 2025 (application date)
  - Version 4.0 (2023-02-28) Acceptable from Apr 1, 2023 (application date)
- CDISC Data Validation Software

  The software that PMDA is using is Pinnacle 21 Enterprise 5.1.2, and the engine corresponding to the validation rules are as follows.
  - PMDA 1511.6 (Validation Rule Version 1.0)
  - PMDA 1810.3 (Validation Rule Version 2.0)
  - PMDA 2010.2 (Validation Rule Version 3.0)
  - PMDA 2211.0 (Validation Rule Version 4.0)

https://www.pmda.go.jp/english/review-services/reviews/0002.html

Data Standards Catalog with SDTM IG v3.3

- The PMDA released its new Data Standards Catalog on February 28, 2023.
- This includes the new standard version, SDTM IG v3.3, with its Date Support Begins, April 1, 2023. SDTM IG v3.3 will be acceptable for new drug applications whose application date is on or after April 1, 2023.
- Also included is the Date Support Ends for Define-XML v1.0, which is March 31, 2025. Define-XML v1.0 will not be acceptable for new drug applications whose application date is on or after April 1, 2025.

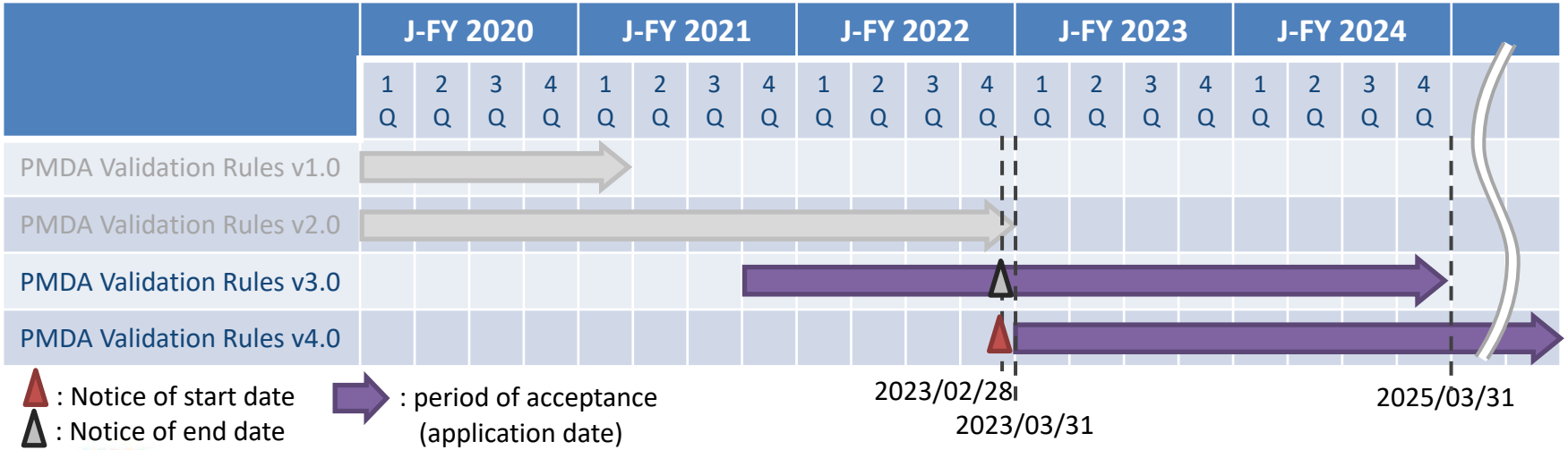
Data Standards Catalog with SDTM IG v3.3

PMDA Data Standards Catalog (2023-02-28) - Data Exchange Standards

Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
Clinical study datasets - Transport	SAS Transport (XPORT)	5	-	XPT	2016-10-01		
Clinical study datasets	SDTM	1.7	3.3	XPT	2023-04-01		
Clinical study datasets	SDTM	1.4	3.2	XPT	2016-10-01		
Clinical study datasets	SDTM	1.3	3.1.3	XPT	2016-10-01		
Clinical study datasets	SDTM	1.2	3.1.2 Amendment1	XPT	2016-10-01		
Clinical study datasets	SDTM	1.2	3.1.2	XPT	2016-10-01		
Clinical study datasets	ADaM	2.1	1.1	XPT	2022-01-01		
Clinical study datasets	ADaM	2.1	1.0	XPT	2016-10-01		
Clinical study data definition files	Define	2.0	-	XML	2016-10-01		
Clinical study data definition files	Define	1.0	-	XML	2016-10-01	2025-03-31	
Documents	PDF	1.4-1.7	-	PDF	2016-10-01		In principle, eCTD PDF specification should be referenced for details.

PMDA Validation Rules v4.0

- PMDA Validation Rules v4.0 was published and this version supports SDTM IG v3.3 and does not support Define-XML v1.0. It can be used for new drug applications with its application date on or after April 1, 2023.
- Additionally, it was announced that the PMDA Validation Rule 3.0 can be used until March 31, 2025.



PMDA Validation Rules v4.0

- Pinnacle 21 Enterprise engine and software
  - Engine version when the Pinnacle 21 Enterprise/Community is used: PMDA 2211.0
  - PMDA updated the P21E version from 4.0.2 to 5.1.2 at this timing.
- Major changes from PMDA Validation Rules v3.0
  - SDTM
    - Support for SDTM IG v3.3
    - Add some rules to ensure data quality and to prevent misunderstanding when using data
    - Improve “Message”, “Description”, and organize “Domains”
  - Define
    - Define v1.0 is not supported with “Reject” rule for define version 1.0 (DD0020A)
    - Severity change of the rule for checking acrf.pdf (DD0102) from “Warning” to “Error”
    - Improvement of Description
  - (No changes of ADaM rules)

Please note that there have been some changes to the rules regarding existing standard versions.
So far we have few experience of application with PMDA validation rules v4.0, but we will share information if there are any issues in the future.

New and old versions of CDISC standards

- PMDA plans to include the new versions of CDISC standards in the PMDA Data Standards Catalog after the investigation of their impact and development of the validation rules. Also, PMDA plans to exclude the old versions based on the investigation on actual usage in the industry.

	Standards	Status
New	SDTM v2.0 & SDTM IG v3.4	• Updated contents will be reviewed
	ADaM IG v1.2 & v1.3	
	Define-XML v2.1	• Updated contents and the impact on the Electronic Submission Gateway have been reviewed. • Consideration is underway for the implementation.
Old	Define-XML v1.0	• Acceptance will be ended on March 31, 2025, with the end of acceptance of Validation Rule Version 3.0.

The schedules for each standard will be announced as soon as they are finalized.

Summary

- Advanced Review with Electronic Data Project is being executed successfully, so far.
  - All data has been successfully received since Oct 1, 2016 and we smoothly shifted to post-transitional phase.
- We are constantly reviewing our experiences to optimize our operation and to revise the notifications/guide/FAQs if needed, in order to improve the efficiency of the data preparation in the industry.
- PMDA will continue to provide clear and useful information on data submission for industry.
- We appreciate your continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug, with preparation and submission of standardized study data.

Thank You!

New Drug Review with Electronic Data, PMDA

https://www.pmda.go.jp/english/review-services/reviews/0002.html (English)

https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0003.html (Japanese)