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PMDA Update

Presented by Yuki ANDO, PhD.
Principal Senior Scientist for Biostatistics
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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 is responsible for the biostatistics review and consultation in the new drug and device review offices in PMDA and is a leader of Biostatistics Reviewers who are the primary users of the patient level electronic study data that are submitted with new drug applications. Additionally, she works for Office of Regulatory Science Coordination, the office which is currently responsible for receiving e-study data. She is also a member of the Real World Data (RWD) Working Group and the Global Clinical Study Working Group that are projects across multi-offices in 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
- Activities for optimization of the process and the documents

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.

Recent examples of common issues with data submission and possible reasons

- Data submission process: abnormal termination of the validation, or violation whose severity is “Reject” (… very rare)
  - Incorrect combination of versions of standards and validation rules
  - Description of unaccepted versions in define.xml
- Validation results: unexplained “Error”
  - Lack of linked files in define.xml or incorrectly described link
  - 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
- 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 of the analysis environment and software used

We think that the contents of PMDA notifications and Technical Conformance Guide are well understood in most cases.
Please continue to carefully review and prepare the submission data.

Utilization of study data in review process

Analysis Timing	Contents of Analyses

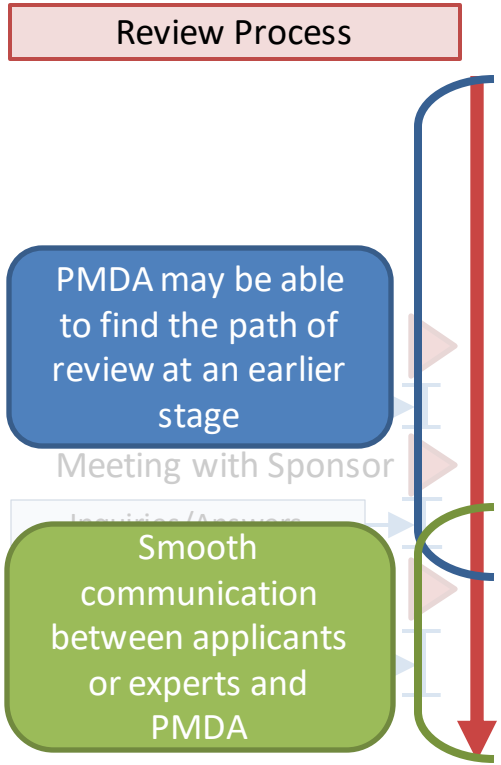
Before the First Team Meeting	• Confirmation of reproducibility of the primary analysis
	• Analyses for review points
	  • Indication, dosage, etc
	  • Consistency, AE, individual patient profile, etc
	• Analysis for exploring review points
	  • Factors affecting efficacy and safety

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



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Completion of Review

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

  Please note that when submitting electronic study data to the PMDA via the gateway system, only one version of the validation rules must be selected for a single application, even if it involves multiple studies.

  - 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 the 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.

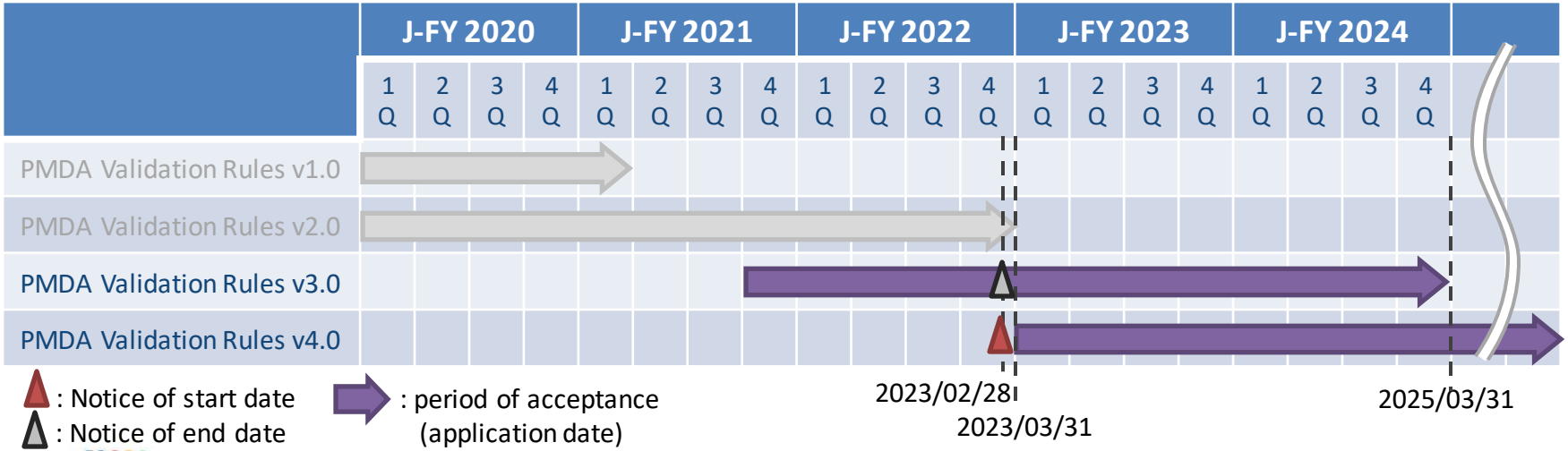
Data Standards Catalog with SDTM IG v3.3

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.

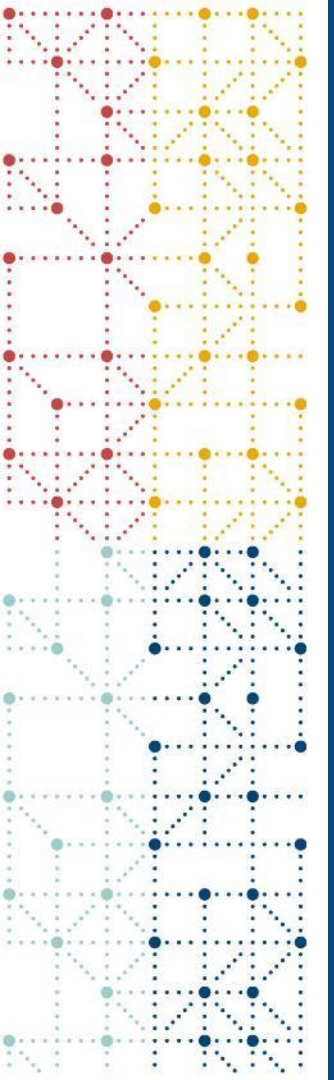


New and old versions of CDISC standards

- 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 have been reviewed
	ADaM IG v1.2 & v1.3	• Preparation for the implementation
	Define-XML v2.1	• Updated contents and the impact on the Electronic Submission Gateway have been reviewed. • Preparation 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.



Recent update

Activities for optimization of the process and the documents

Three years have passed since the transitional period ended…

- Since the transitional period of data submission was ended on March 31, 2020, now we have 3-year experiences of the full-scale operation of receiving and using study data at the PMDA.
- Based on our experience with receiving the study data, we thought that, for most of the applications, submitted study data was in compliance with the requirements such as CDISC standardized data described in the notifications and guide.
- In order to improve the efficiency of the data preparation in industry and data acceptance in the PMDA, we have proceeded the optimization of the operation.

We will continue to reduce redundant materials and procedures, while ensuring data quality and information about the data to the extent that data utilization in the new drug review offices is not compromised.

Recent operation changes

- Changed the operation of the consultation meeting for e-data submission, particularly for the “consultation on data format” on April 1, 2021
- Revision of the notifications on April 1, 2022
  - Combined notification and corresponding Q&A on e-data submission, newly developed notification on application with using the gateway system, and revised Technical Conformance Guide were published on April 1, 2022.
- Improvement of the process of reviewing validation results in the PMDA on April 1, 2022
  - At the time of data submission, basically the data will be received unless abnormal termination of the validation or violation whose severity is “Reject” occurs.
- Stop requesting submission of Form A and Form B, which are the forms only for the PMDA, provided that the Reviewer’s Guides contain the information required by the PMDA Technical Conformance Guide on October 1, 2023

Stop requesting submission of Form A and Form B

Explanation of Electronic Study Data (Form A and Form B)

- Explanation of Electronic Study Data (Form A)
- Explanation of Electronic Study Data (Form B)

From October 1, 2023 (application date), PMDA does not require to submit "Explanation of Electronic Study Data (Form A)" and "Explanation of Electronic Study Data (Form B)", that describe the contents of electronic study data planned to be submitted to the PMDA, before electronic study data submission for the new drug application.

Please note that Form A and Form B still must be submitted to the PMDA for consultations related to submission of electronic study data for new drug applications.

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

Please check that the Reviewer's Guides contain the information required by the PMDA Technical Conformance Guide 4.1.2.3, before the submission.

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 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)