WITH STANDARDS – UNLOCK THE POWER OF DATA

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PMDA Update

Presented by Daisuke Iwata & Yuki Ando
Pharmaceuticals and Medical Devices Agency

Meet the Speaker

Daisuke Iwata, PhD

Title: Deputy Review Director

Organization: Pharmaceuticals and Medical Devices Agency

He started his career as a Reviewer at PMDA in 2008 and currently he works in Office of Advanced Evaluation with Electronic Data.

Meet the Speaker

Yuki Ando, PhD

Title: Senior Scientist for Biostatistics

Organization: Pharmaceuticals and Medical Devices Agency

She started her career as a Biostatistics Reviewer in 1997 and currently she is responsible for the biostatistics review and consultation in the new drug and device review offices in PMDA. Additionally, she works for Office of Advanced Evaluation with Electronic Data, the office which is responsible for the use of patient level electronic study data that are submitted with new drug applications. She is also a member of Real World Data (RWD) Working Group and Global Clinical Study Working Group that are projects across multi-offices in PMDA.

Disclaimer and Disclosures

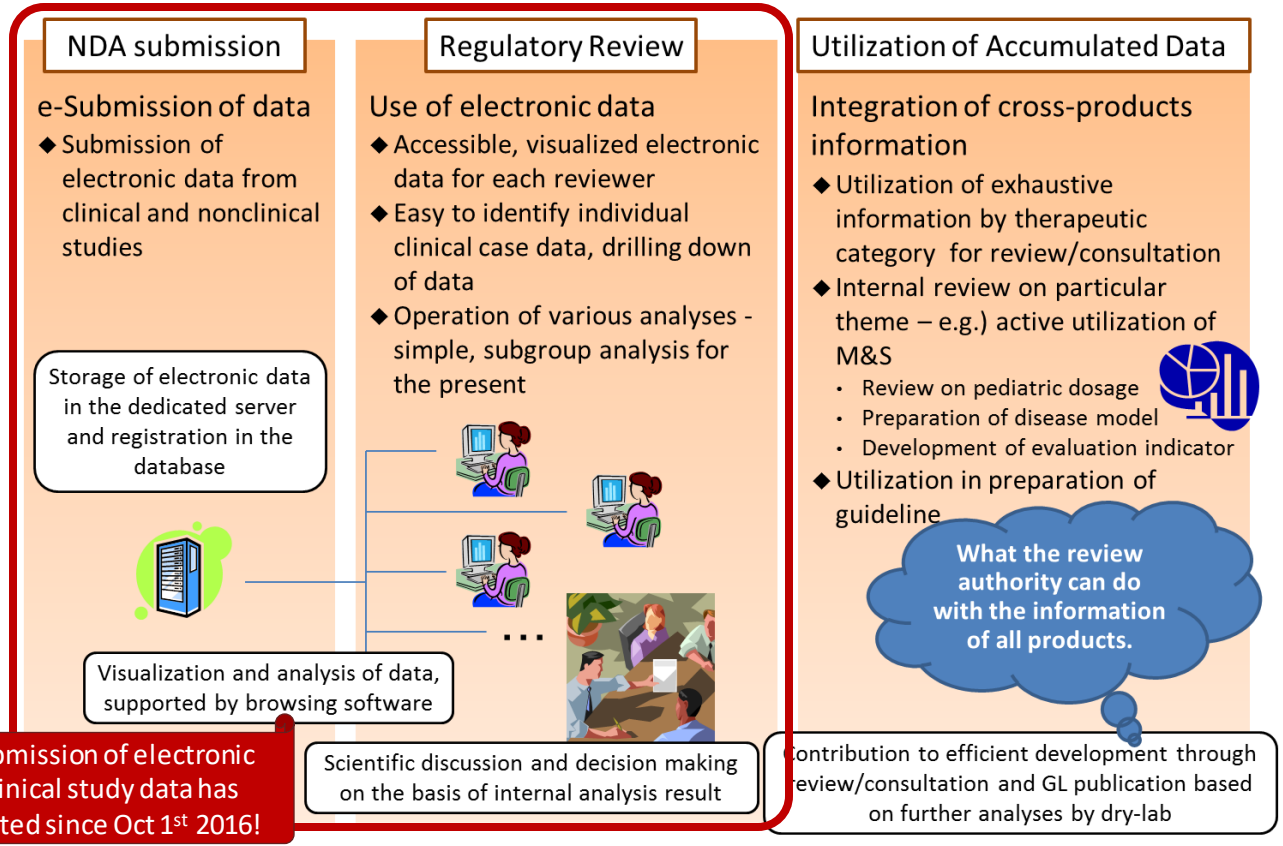
- *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC or PMDA.*

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

Agenda

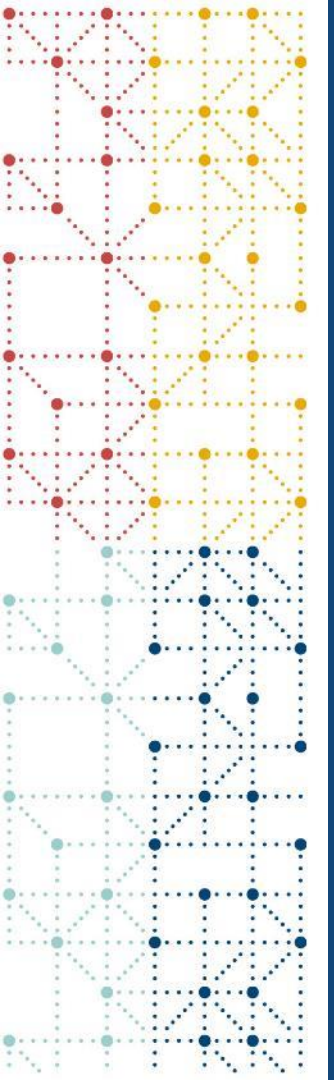
1. Introduction
2. Recent Update
   - Operation change in receiving study data
   - Revision of the notifications and other documents
   - Technical aspects related to the revisions of the notifications
   - Data Standards Catalog and PMDA Validation Rules
3. Other information

Accumulation and utilization of data



Two years have passed since the transitional period ended…

- Since the transitional period of data submission was ended on March 31, 2020, now we have 2-year experiences of the full-scale operation of receiving and using study data at PMDA.
- We changed the operation of the consultation meeting for reviewing results of CDISC validation from April 1, 2021, and we promoted efficiency further this year.
- We consolidated two notifications and corresponding Q&As, and updated our Technical Conformance Guide on April 1, 2022, based on the experiences.
- We published new PMDA Validation Rules and started to accept the new version of the ADaM IG.
- We will continue to proceed the optimization of the operation, in order to improve the efficiency of the data preparation in industry.



Recent update

Operation change in receiving study data

Change of the operation of the consultation meeting for data submission

Explanations in PMDA presentation last year

- Recently, contents of explanations of results of the CDISC validation performed by sponsors in advance has been improved and has included sufficient information.
- Then there have been no major issues in the conclusion of the “Consultation on data format” meeting in most cases.

From April 1, 2021, sponsors should report the results of the CDISC validation of all the clinical studies for submission at “Pre-NDA Meeting”, and do not (need to) apply “Consultation on data format of submission of electronic study data”

- Please refer the FAQ1-23 to include sufficient information in the explanation of the errors.

Explanations in PMDA presentation last year

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 of Basic Principles"
- 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 of Basic Principles"

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

- 723 consultation meetings have been conducted as of Mar 31, 2022.

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	
Total		723	

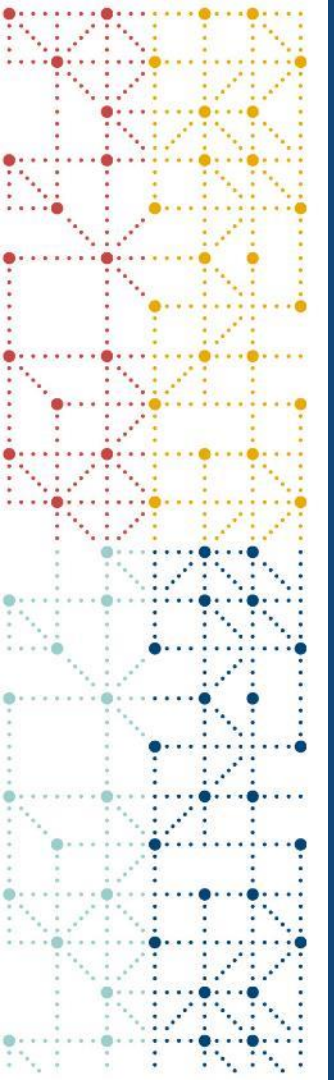
Change of Operation

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

Further optimization to review validation results in the data submission process

- 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.
- Therefore, we have decided to make the following changes, mainly related to the response to the validation results, to the operation of our receiving data.

- At the time of data submission, basically the data will be received unless abnormal termination of the validation, similar issue or violation whose severity is "Reject" occurs.
- If an unexplained "Error" occurs during the validation at PMDA, the applicant is requested to correct the data or add the explanation as an inquiry from review office as early as possible after the application date.
- The applicant who has received an inquiry should correct the data or add an explanation as soon as possible so as not to affect the review process/time.



Recent update

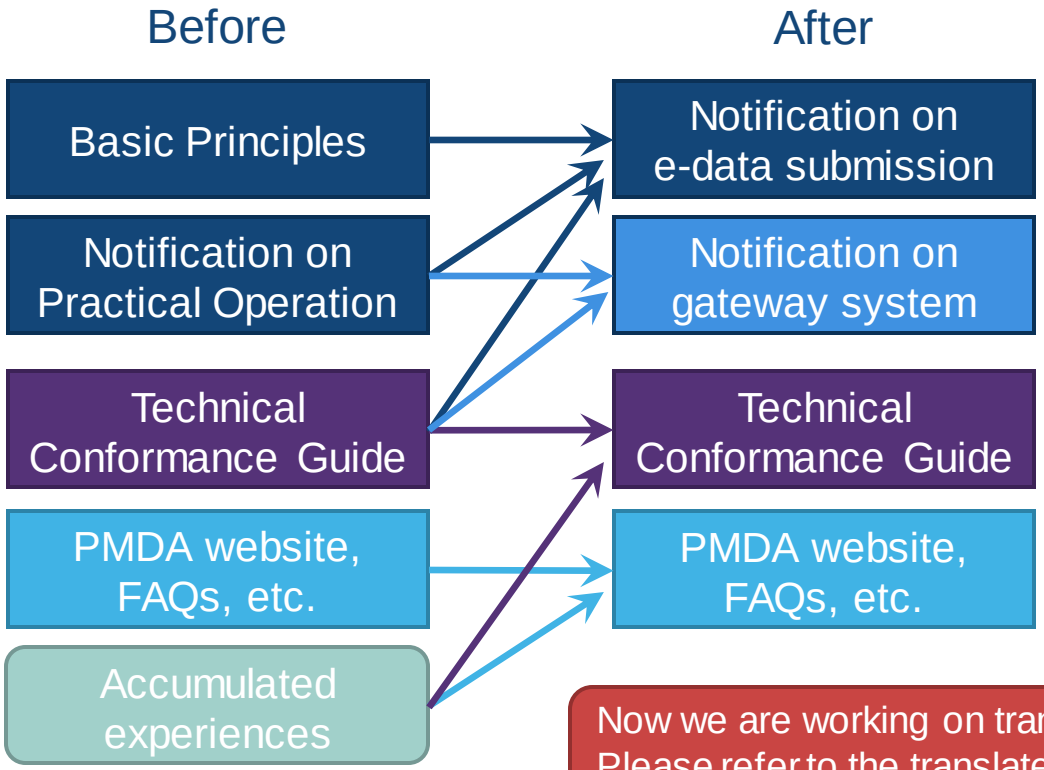
Revision of the notifications and other documents

Revision of the notifications

- From the following perspectives, the changes were made to the notifications and other information related to electronic data submission.
  - A new notification summarizing the contents of applications using the Electronic Submission Gateway was developed.
  - The changes that had been made since the issuance of the notification.
  - In order to make the contents of the notification easier to understand, duplicated information in two notifications were sorted out and combined into a single notification and corresponding Q&A regarding the scope and content of electronic data submission.

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.

Summary of the changes/revisions



Overview of e-data submission, details of study/datasets/other contents to be submitted, eCTD, etc

Submission with using gateway system

Details of data to be submitted and submission methods, details of eCTD related issues, etc

Technical details such as CDISC data validation, available standards, FAQs, etc

Now we are working on translation of the documents into English. Please refer to the translated documents for the details.

Summary of the changes/revisions

- Notification on Handling of Submission of Electronic Study Data for New Drug Applications (and Question and Answer Guide)
  - The basic contents remain the same as those of the two notifications.
  - In the Question and Answer Guide, the Q&As are sorted in order based on content.
- New Drug Applications Using the Gateway System
  - Topics related to the use of gateway are selected and organized from notifications and guide.
  - There will be no major changes in actual operation.
- Technical Conformance Guide on Electronic Study Data Submissions
  - Items that should be included in reviewer's guide are added. (As mentioned later)
  - Slight revisions around the CDISC validation
  - Some revisions on topics of clinical pharmacology data with including some topics from the previous version of FAQs

Tentative English translation may be included.
Please refer the translation that will be provided on the PMDA website in the near future.

Recent update

Technical aspects related to the revisions of the notifications

Proactive use of Reviewer's Guide (as materials providing information for Form A)

- "Form A", which contains detailed information of the study data to be submitted, is the document required by PMDA and is used for the following purposes.
  - A part of materials for consultation meeting on electronic data submission
  - Materials for confirmation of prior explanation of CDISC validation results and the contents of the submission datasets
- It has been pointed out that some of the contents of Form A have been duplicated in other documents such as Reviewer's Guide.
- Recently, only for the section of prior explanation of the results of CDISC validation in the Form A, we have recommended that the Reviewer's Guide be attached to the Form A and be referred to in the Form A.

Proactive use of Reviewer's Guide (as materials providing information for Form A)

- In order to help applicants prepare their documentation more efficiently, we have decided to make the following changes to the format and utilization of Form A.
  - For CDISC standardized data, if all the information that PMDA would like to review on Form A is included in the Reviewer's Guide, the applicant should clearly indicate that in the Form A, and PMDA will review the Reviewer's Guide submitted with the study data.
  - The Form A should be submitted to the review office between the pre-NDA meeting and the data submission.
  - Note that information on the application and the studies included, as well as information of the data of clinical pharmacology study/analysis, should continue to be provided on Form A. Also, it is still possible to refer to Reviewer's Guide, only for the CDISC validation results as before.

For the provision of information on CDISC standardized data, we basically would like to switch to the reference to the Reviewer's Guide, so we have added items that should be included in the Reviewer's Guide to the Technical Conformance Guide 4.1.2.3.

Now we are working on translation of the documents into English. Please refer to the translated documents for the details.

Items should be included in SDRG

- Clinical study name, protocol number
- Explanation of the clinical study design
- Standards, controlled terminologies, and dictionaries used when creating datasets and their versions (SDTM, SDTM IG, SDTM Controlled Terminology, Define-XML, MedDRA, and WHODrug Global)
- Explanation of the annotated CRF
- List of datasets to be submitted
  - SDTM datasets of the trial design
  - SDTM datasets of the subject data (including information about custom domains, SUPP, and use of Japanese in the datasets and SUPP)
  - Other datasets to be submitted
- Explanation of the subject data (including explanation of custom domains)
- Explanation on conformance to the data standards
  - Validation tool used for the validation and its version
  - Version of the validation rules used for the validation
  - Explanation on conformance to the data standards (explanation of the validation results including the identification number and importance of a rule with a detected violation)

Tentative English translation may be included.
Please refer the translation that will be provided on the PMDA website in the near future.

Items should be included in ADRG

- Clinical study name, protocol number
- Explanation of the clinical study design related to the analysis datasets
- Standards, controlled terminologies, and dictionaries used when creating datasets and their versions (ADaM, ADaM IG, ADaM Controlled Terminology, Define-XML, MedDRA, and WHODrug Global)
- Considerations related to multiple analysis datasets
- Considerations on creating the analysis datasets
- List of datasets to be submitted
  - ADaM datasets (including information that uses Japanese)
  - Other datasets to be submitted
- Explanation of the datasets
- Explanation on conformance to the data standards
  - Validation tool used for the validation and its version
  - Version of the validation rules used for the validation
  - Explanation on conformance to the data standards (explanation of the validation results including the identification number and importance of a rule with a detected violation)
- Information on the program
  - Analysis environment and software used
  - Explanation of programs that were used to create the ADaM datasets to be submitted and programs for analyses (if they cannot be submitted, specifications that demonstrate the analysis algorithm) to be submitted

Tentative English translation may be included.
Please refer the translation that will be provided on the PMDA website in the near future.

Revision of FAQs

- There are some changes consistent with the revisions of other documents.
- Some contents are moved to the Technical Conformance Guide.
- Answers to the frequently asked questions in the consultation on preparation of submission of electronic study data are added or compiled with some of the related contents.
  Examples:
  - Data of integrated analysis for orphan drug which is allowed to submit in a format other than the CDISC standards (FAQ1-34)
  - Relationship between a study folder [study id / iss / ise] and a folder that stores the clinical study report in eCTD M5 (FAQ3-7-1)
  - Possible submission folders for files that cannot be stored in folders storing SDTM datasets or ADaM datasets (FAQ4-22-1)
  - Submission of a set of datasets for multiple data cutoff points (FAQ4-36)

Revision of FAQs

- As a new FAQ (FAQ1-35), we added the information on submission of electronic data of registry.
  The major points are as follows.
  - Importance of submitting registry data in CDISC standardized format when such data are used as the major evidence for the efficacy, safety, and dosage and administration
  - Recommendation of prior consultation with PMDA with using corresponding consultation meetings, because we think that the content and format of e-data submission regarding registry should be decided depending on the content and intended use of the registry
  - Submission of datasets for analysis of comparison with external controls using the registry in ADaM format.

Recent update

Data Standards Catalog and PMDA Validation Rules

Update of Data Standards Catalog and PMDA Validation Rules

Data Standards Catalog and CDISC Data Validation

- Data Standards Catalog (2021-12-15)
- CDISC 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 (application date)
- CDISC Data Validation Software

  The software that PMDA is using is Pinnacle 21 Enterprise 4.0.2, 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)

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

Data Standards Catalog with ADaM IG v1.1

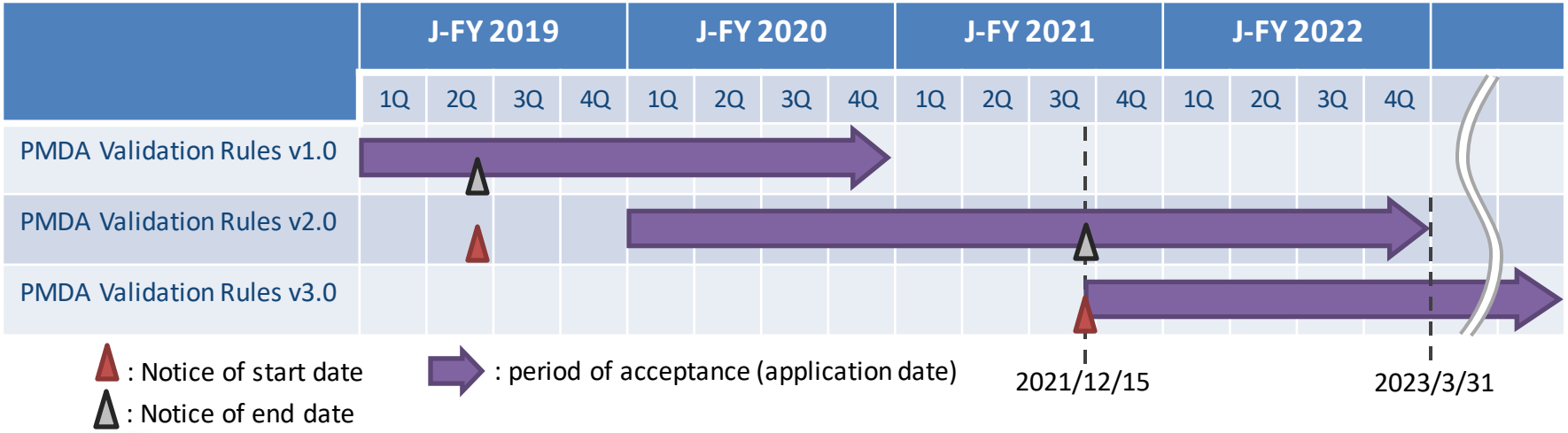
- On December 15, 2021, ADaM IG v1.1 was added to the PMDA Data Standards Catalog.

PMDA Data Standards Catalog (2021-12-15) - 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	1.4	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		
Documents	PDF	1.4-1.7	-	PDF	2016-10-01		In principle, eCTD PDF specification should be referenced for details.

PMDA Validation Rules v3.0

- The new PMDA Validation Rules (v3.0) was published on December 15, 2021.
- V3.0 became available from January 1, 2022, based on the application date.
- The end date for the current PMDA Validation Rules v2.0 is March 31, 2023, based on the application date.



PMDA Validation Rules v3.0

- Engine version when the Pinnacle 21 Enterprise/Community is used
  - PMDA 2010.2
- Major changes from PMDA Validation Rules v2.0
  - Support for ADaM IG v1.1
  - Bug fixes
- Other changes
  - Deletion of some rules
    - Some rules that were removed in ADaM Conformance Rule v3.0
    - SNOMED related rules
  - Others
    - Review and maintenance of target domains and classes of some rules
    - Improvement of Message and Description

Please note that there have been some changes to the rules regarding existing standard versions.
We have limited examples of application this time. We will share information if there are any issues in the future.

Other information

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 its 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 v1.7 & SDTM IG v3.3	• Draft validation rules are under review in PMDA
	SDTM v2.0 & SDTM IG v3.4	• Will be reviewed after the implementation of SDTM IG v3.3
	ADaM IG v1.2	
	Define-XML v2.1	• Updated contents and impact on the Electronic Submission Gateway will be reviewed
Old	Define-XML v1.0	• Specific timing to stop accepting this version is under consideration

Summary

- Advanced Review with Electronic Data Project is being executed on schedule and successfully, so far.
  - All data has been successfully received since Oct 1, 2016 and we smoothly shifted to post-transitional phase.
- Based on the 2-year full-scale operation of receiving study data, we have reviewed the experiences and have optimized the operation and revised the notifications, in order to improve the efficiency of the data preparation in industry.
- PMDA will continue to provide 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)