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PMDA Update

Presented by Yuki ANDO, PhD.
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Pharmaceuticals and Medical Devices Agency

Meet the Speaker

Yuki Ando, PhD

Title: Principal Senior Scientist for Biostatistics

Organization: Pharmaceuticals and Medical Devices Agency

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.*

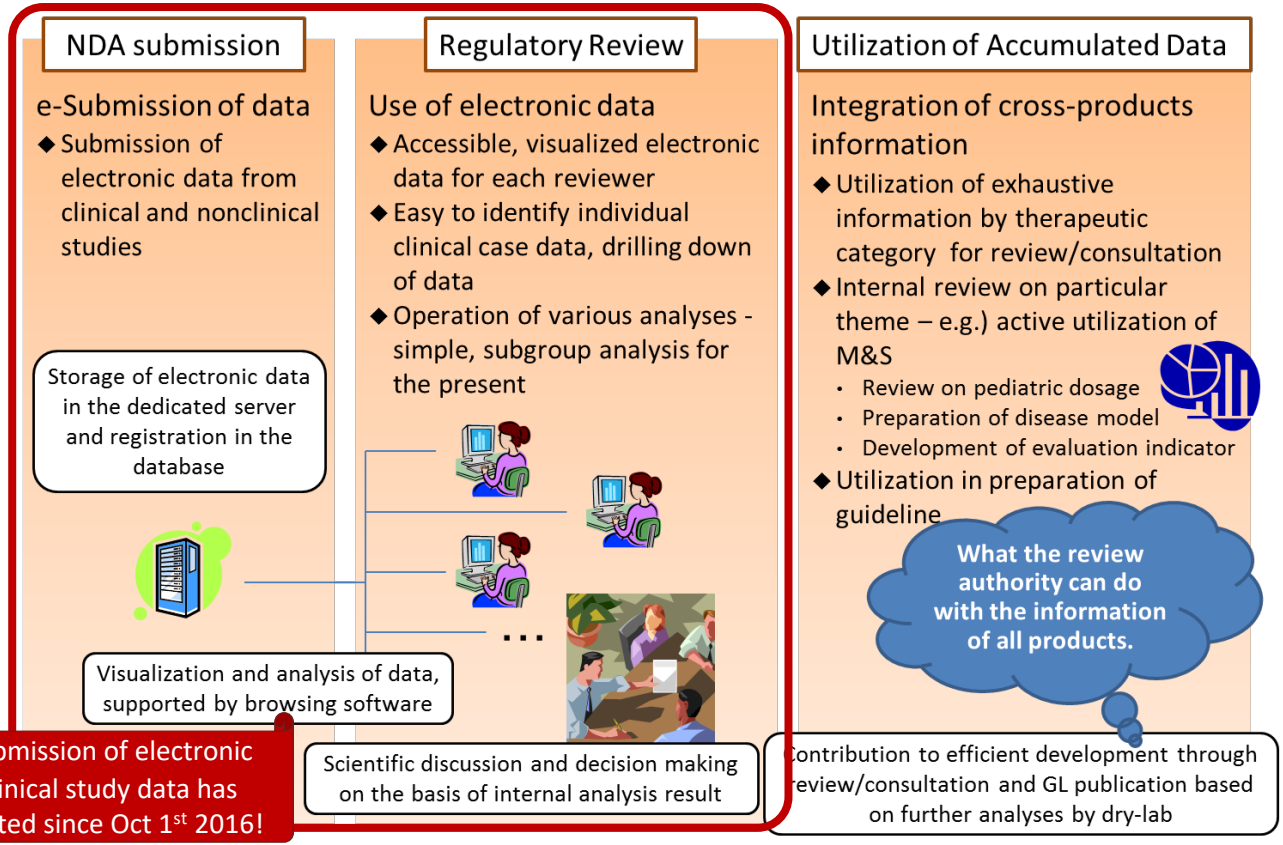
- *The authors have no real or apparent conflicts of interest to report.*

Agenda

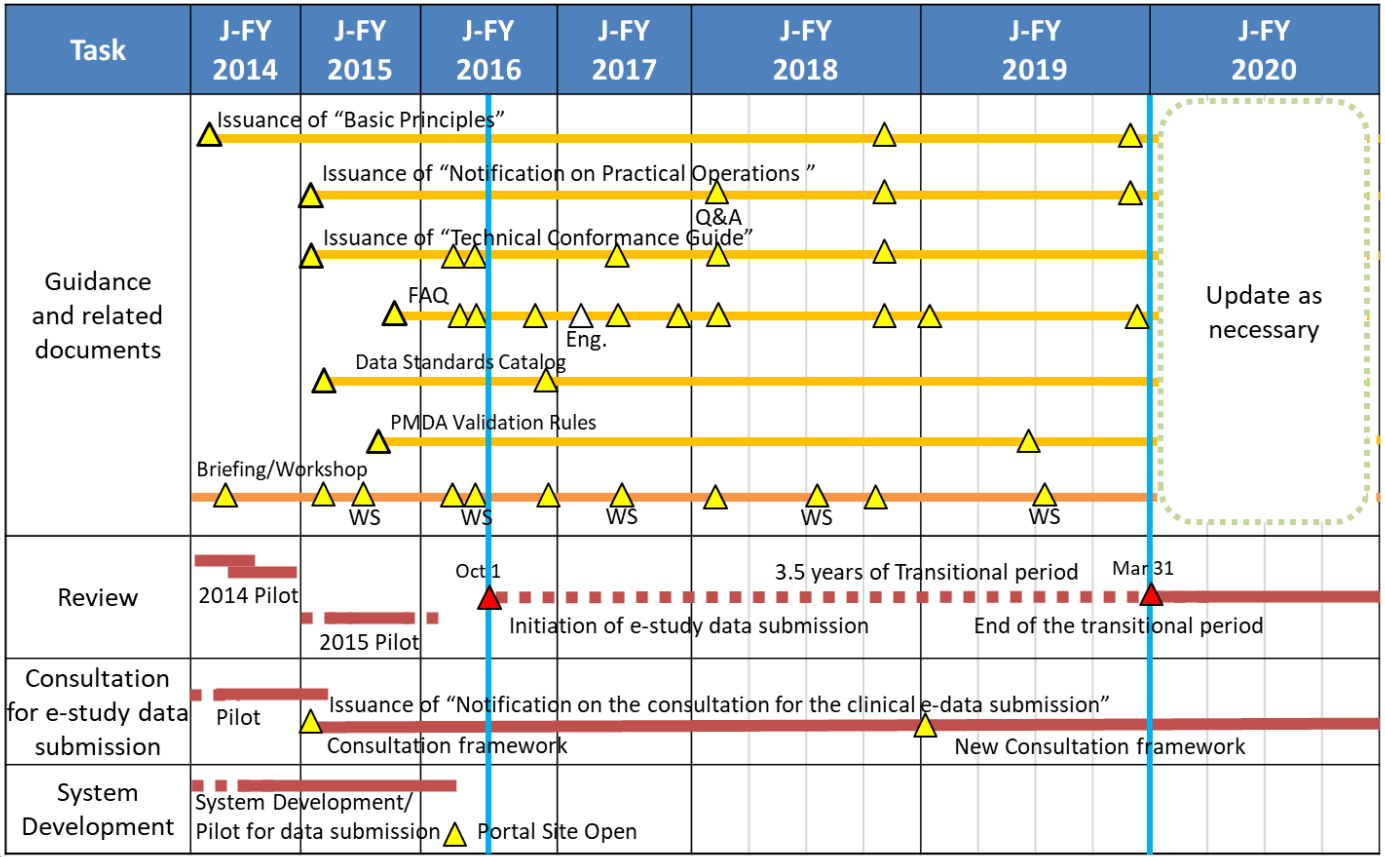
- Activities for the end of the transitional period
- Activities since the end of the transitional period – Optimization of the process and the documents
- Current situation of e-study data
- Data Standards Catalog and PMDA Validation Rules

Activities for the end of the transitional period

Accumulation and utilization of data



Preparation for the end of the transitional period

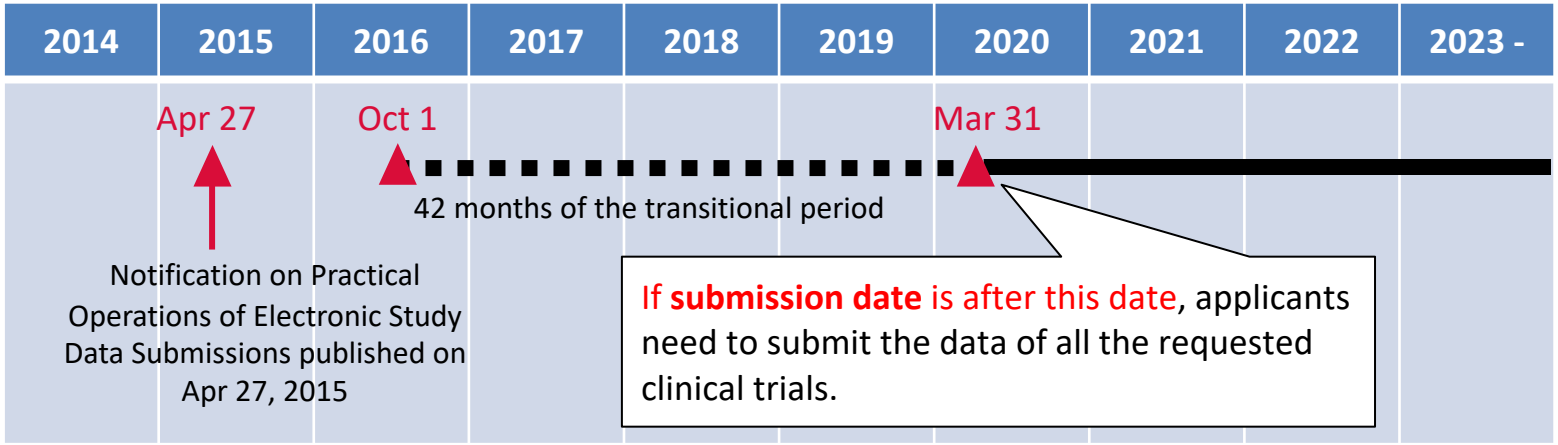


Preparation for the end of the transitional period

- Revisions of the notifications, Q&A, and FAQs website in March 2020, to consider special circumstances based on the experiences during the transitional period and the discussion with the industry
  - Data submission of drugs to prevent health and hygiene hazards
  - Data submission of orphan drugs, etc.
  - Cases when data submission after the approval application may be acceptable

Transitional period was ended

- The transitional period was ended on March 31, 2020.
  - During the transitional period, applicants could submit the data of at least one clinical trial included in their clinical data packages.
  - After the period, applicants need to submit the data of all the requested clinical trials.



Activities since the end of the transitional period – 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 PMDA.
- We summarized the information based on the experiences and provided that to the sponsors at the workshop/conference held in Japan.
- We changed the operation of the consultation meeting for e-data submission, particularly for the “consultation on data format” on April 1, 2021, and revise the notifications on April 1, 2022.
- We will continue to proceed the optimization of the operation, in order to improve the efficiency of the data preparation in industry.

Consultation related to study data submission

FAQ1-5, as of Mar 31, 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 appr
submission date. The Sponsor should explain the contents of electronic study dat
Attachment 8/Form A.

Consultation on submission of electronic study data

Change of the operation of the consultation meeting for data submission based on the experiences

- There were few cases that PMDA requests correction of the data based on the results of the CDISC data validation by sponsor.
- The contents of explanations of results of the CDISC validation performed by sponsors in advance had been improved and had included sufficient information, and there had been no major issues in the conclusion of the “Consultation on data format” meeting in most cases.

From April 1, 2021, sponsors can 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”

Consultation related to study data submission

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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 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

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

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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.

Further optimization to review validation results in the data submission process (From April 1, 2022)

- 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 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.

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.

Current situation of the consultation meetings

- 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.

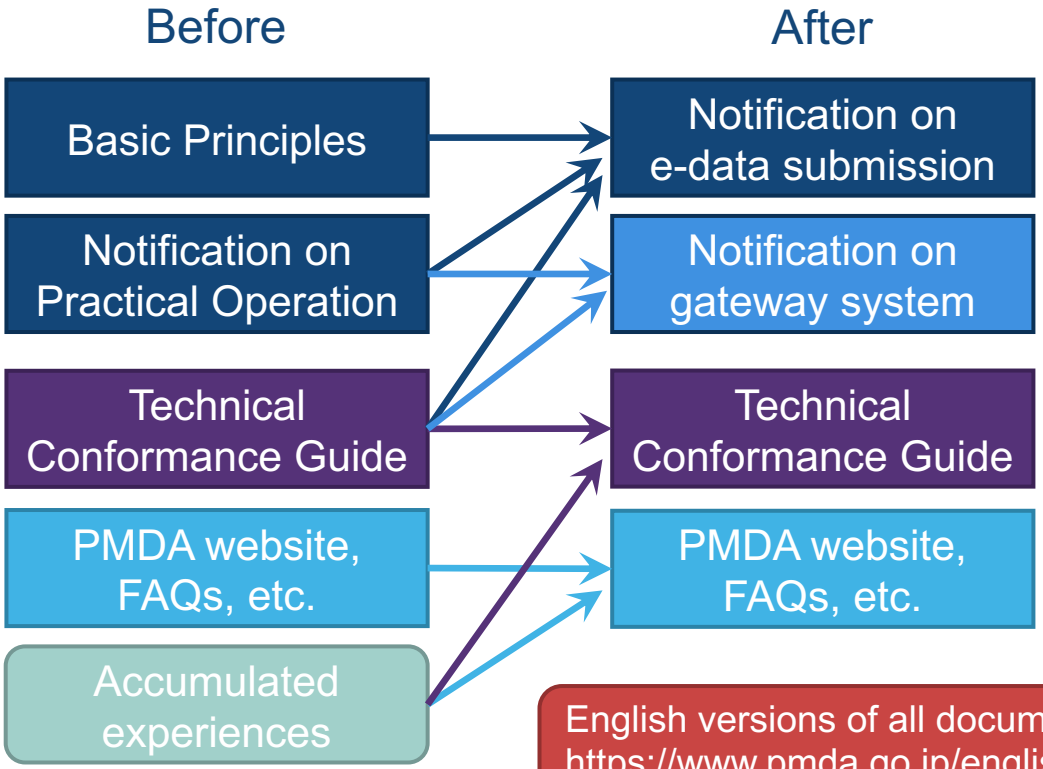
We will continue to provide useful information to help preparation of study data submission at appropriate timing.

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 on April 1, 2022



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

Submission with using gateway system

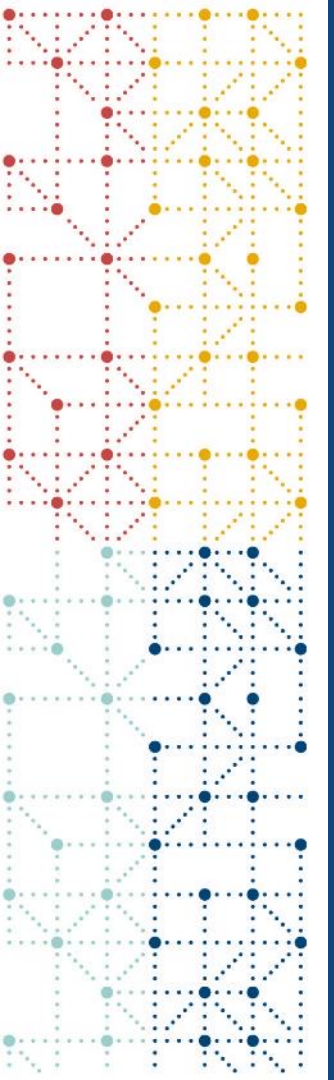
Details of data to be submitted and submission methods, details of eCTD related issues, etc

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

English versions of all documents are available at:
https://www.pmda.go.jp/english/review-services/reviews/0002.html

Summary of the changes/revisions on April 1, 2022

- 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.
  - Slight revisions around the CDISC validation
  - Some revisions on topics of clinical pharmacology data with including some topics from the previous version of FAQs



Current situation of e-study data

Data submitted with new drug applications

- 238 NDAs were submitted with electronic study data as of Mar 31, 2021.

Year	Number of NDAs
J-FY 2016 (Oct 1, 2016 – Mar 31, 2017)	10
J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)	31
J-FY 2018 (Apr 1, 2018 – Mar 31, 2019)	33
J-FY 2019 (Apr 1, 2019 – Mar 31, 2020)	42
J-FY 2020 (Apr 1, 2020 – Mar 31, 2021)	122
Total	238

After the transitional period

Since the transitional period ended on March 31, 2020, this number got close to the average number of NDAs per year.
We have not provided the number of NDAs with data submission after this timepoint, but most new drug applications are submitted to PMDA with electronic study data after the end of the transitional period (FY2020 and beyond),

Utilization of study data in review process

Analysis Timing	Contents of Analyses

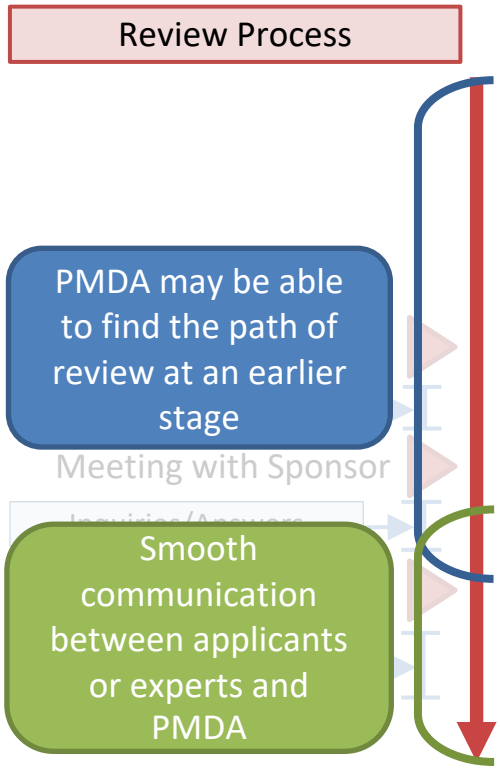
Before the First Team Meeting	• Confirmation of reproducibility of the primary analysis
	• Analyses for review points
	  • Indication, dosage, etc
	  • Consistency, AE, individual patient profile, etc
	• Analysis for exploring review points
	  • Factors affecting efficacy and safety

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



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

Utilization of study data – based on the activities of Biostatistics reviewers

- 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
- Examples of remarks on submitted data
  - Errors in programs including that of primary analysis of the primary endpoint
  - Performing analyses for CSR using methods different from those specified in the SAP
  - Errors in specifying flag variables in the reviewer's guide
- Examples of questions or comments on submitted data
  - Inconsistency between CSR and data
  - Difficulty of reproducing MI because of the lack of details
  - Uncertain parameter for primary analysis
  - Usefulness of reviewer's guide and analysis results metadata

Data Standards Catalog and PMDA Validation Rules

Update of Data Standards Catalog and PMDA Validation Rules

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

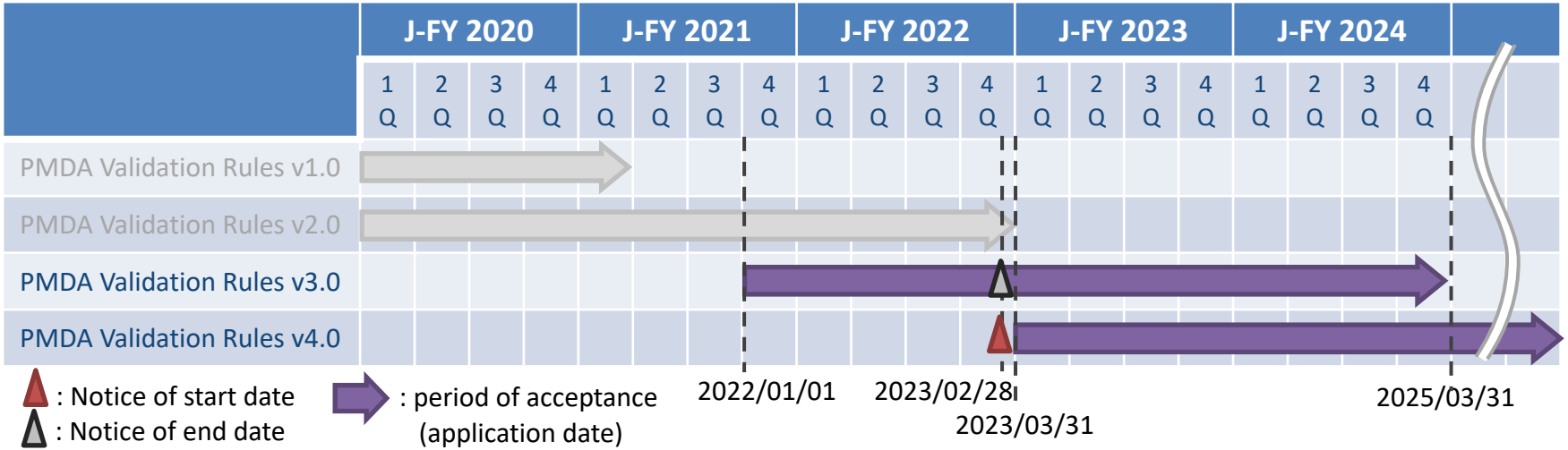
Current Data Standards Catalog

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

- PMDA Validation Rules v4.0, which is the latest version was published on Feb 28, 2023, and this version supports SDTM IG v3.3 and does not support Define-XML v1.0
- Additionally, it was announced that the PMDA Validation Rule 3.0 can be used until March 31, 2025.



New and old versions of the CDISC standards

- PMDA plans to include the new versions of the CDISC standards in the PMDA Data Standards Catalog after the investigation of their impact and the 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 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)