Study data submission in Japan - Recent activities in the PMDA

Presented by Hiromi Sugano
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Meet the Speaker

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- *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.*

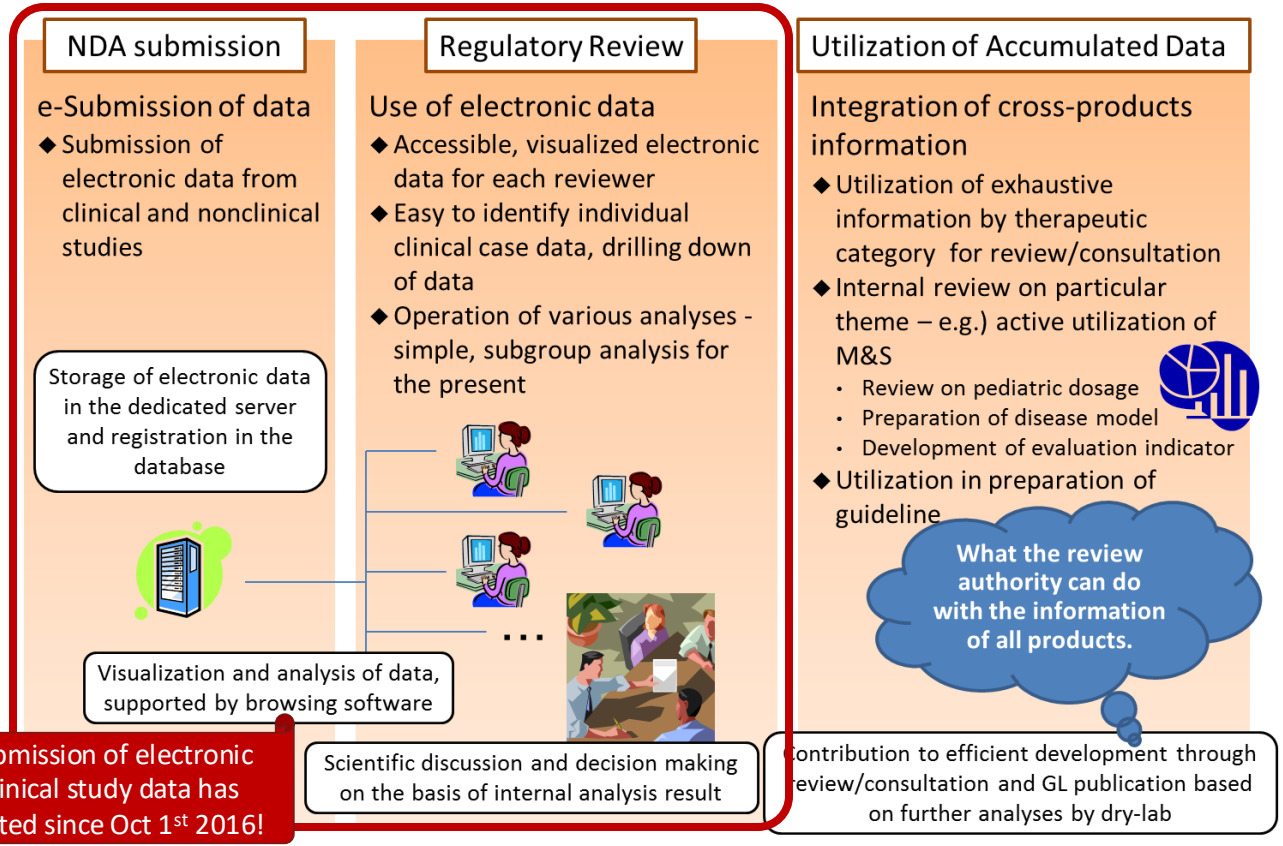
- *The authors have no real or apparent conflicts of interest to report.*

Agenda

- Past activities
- Current situation of e-study data
- Recent updates

Past activities

Accumulation and utilization of data



History of the project - activities and notifications

J-FY	Activities	Issuance of notifications
2013	• Establishment of a working group with industry • Initiation of the pilot studies (- J-FY2015)	
2014	• Pilot of the e-study data consultation system	• Notification on Basic Principles and Q&A
2015	• Initiation of the e-study data consultation system • Starting the workshop for people in charge of practical implementation	• Notification on Practical Operations and Q&A, • Technical Conformance Guide • Data Standards Catalog, PMDA Validation rules • FAQs
2016	• Portal site open Initiation of submission of e-study data (with 3.5-year transitional period)	
2019	• Establishment and reorganization of consultation categories	Updated as necessary
2020	End of the transitional period	
2021	• Operation change of the consultations	Optimization of operations based on accumulated experience
2022	• Changes to the handling of validation results and the timing of submitting explanatory materials	Reorganization of the notifications • Notification on Handling of Submission of e-Study Data for New Drug Applications • Notification on New Drug Applications Using the Gateway System
2024		Revision of the Notification of Handling of Submission of e-Study data

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),

Consultation for e-data after the transitional period

Year	Data format	Preparation	Exemption	Total
J-FY 2020 (Apr 1, 2020 – Mar 31, 2021)	207 Change of Operation	57	18	282
J-FY 2021 (Apr 1, 2021 – Mar 31, 2022)	10*	28	16	54
J-FY 2022 (Apr 1, 2022 – Mar 31, 2023)	0	16	17	33
J-FY 2023 (Apr 1, 2023 – Mar 31, 2024)	0	12	8	20

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

The number of consultation on preparation, that we discuss strategies and methods of storing data and technical details, etc., is decreasing.
We think that basically we are sharing sufficient information for e-study data submission with sponsors and will continue to do that.

Utilization of study data in review process

Analysis Timing	Contents of Analyses

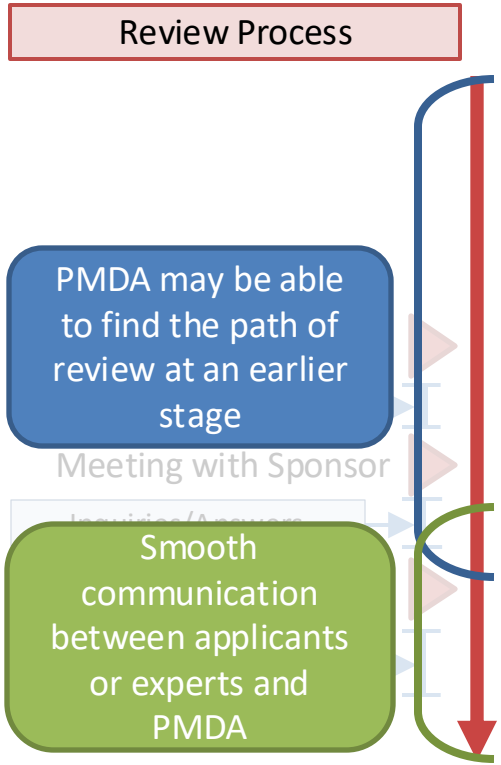
Before the First Team Meeting	• Confirmation of reproducibility of the primary analysis
	• Analyses for review points
	  • Indication, dosage, etc
	  • Consistency, AE, individual patient profile, etc
	• Analyses for exploring review points
	  • Factors affecting efficacy and safety

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

- 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

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

- Examples of remarks on submitted data
  - Errors in programs including that of primary analysis of the primary endpoint
  - 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

Recent updates

Revision of notification, guide, etc.

Four years have passed since the transitional period ended…

- Since the transitional period of data submission was ended on March 31, 2020, now we have 4-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 and also in April this year.
- We will continue to proceed the optimization of the operation, in order to improve the efficiency of the data preparation in industry.

Notifications, Guide, FAQs

- Notification on Handling of Submission of Electronic Study Data for New Drug Applications (and Question and Answer Guide)
  - Overview of e-data submission, details of study/datasets/other contents to be submitted, eCTD, etc
  - Latest update on April 8, 2024 New
- Notification on New Drug Applications Using the Gateway System
  - Issues of submission with using gateway system
  - Published on April 1, 2022
- Technical Conformance Guide on Electronic Study Data Submissions
  - Details of data to be submitted and submission methods, details of eCTD related issues, etc
  - Latest update on April 8, 2024 New
- FAQ website
  - Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and the guide
  - Latest update on April 8, 2024 New

Overview of the major revisions

- For particular clinical pharmacology studies initiated prior to April 1, 2020, non-CDISC compliant data can be accepted.
- Form A had been no longer required to be submitted on and after October 1, 2023, and this is reflected in the Technical Conformance Guide.
  - Please note that any information previously provided on Form A should be described in the Reviewer's guide.
- Technical details corresponding to the revision of the notification and guide are added to the FAQs.
  - Also some internal operation changes are reflected to the FAQs.

Revision of the notification and its Q&A guide

Notification on Electronic Study Data

Adding new sentence

4 Standards of electronic study data to be submitted and details on the data

(1) Data standards for submission

Clinical study data subject for submission should be in a format conforming to the CDISC standards.

However, it is not applied to studies of orphan drugs, etc. that had started before April 1, 2020.

Regarding studies categorized in 2 (1) b (b) and (c) with the exception of Phase I studies of oncology drugs, the submission of electronic study data in a format other than the CDISC standards is sufficient for studies that had started before April 1, 2020.

Moreover, in data in 2 (1) b (c), the datasets on clinical pharmacological analyses may be acceptable for submission according to standards other than the CDISC standards based on the applicants' current condition of preparing analysis data.

Revision of the notification and its Q&A guide

Q&A regarding Notification on Electronic Study Data

Revision corresponding to the notification

Table: Types and submission formats of documents subject to electronic submission

Section in notification on electronic study data	Content		Individual clinical study data	Analysis dataset	
				Concerning efficacy and safety analysis	Concerning PK or PK/PD analysis
2 (1) b (a)	Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be a major evidence for evaluation of efficacy, safety, and dose and administration		SDTM	ADaM	
2 (1) b (b)	Data on result from phase I studies and clinical pharmacology studies listed right	Phase I studies of oncology drugs	SDTM	ADaM	
		Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies)	SDTM*1	ADaM*2	In principle, ADaM*2, but other formats may be acceptable in certain cases
		QT/QTc studies based on ICH E14 guideline			ADaM*2
2 (1) b (c)	Other Phase I studies and clinical pharmacology studies, which were deemed necessary by PMDA	Clinical studies where standard pharmacokinetic analysis was performed	SDTM*1	ADaM*2	ADaM is preferable, but other formats are acceptable
		Population analysis	Formats other than CDISC standard would be sufficient		
		Physiologically-based pharmacokinetic model analysis			
2 (1) b (c)	References other than a and b, which were deemed necessary by PMDA		SDTM*3	ADaM*3	
2 (1) b (c)	Integrated summary of safety and efficacy (ISS/ISE)		SDTM*4	ADaM	

*1: Format other than SDTM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020
*2: Formats other than ADaM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020
*3: If necessary, consult in advance
*4: In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset had been used for analysis, submission of SDTM dataset is acceptable

Revision of Technical Conformance Guide

3. Submission of electronic study data

Deletion of unnecessary request

3.1 Basic flow of the submission of electronic study data

The applicant must confirm with the PMDA on the scope of the submission of electronic study data and the planned date of a new drug application by utilizing clinical trial consultations, a consultation on preparation of submission of electronic study data, and a pre-NDA consultation, etc., if necessary.

~~Applicants must outline the contents of electronic study data that will be submitted to the NDA using the "Explanation of Electronic Study Data (Form A)" on the PMDA's website. This document should preferably be submitted at the time of the pre-NDA consultation that will be conducted before the submission of electronic study data.~~

In accordance with the notification on gateway application, the applicant shall make an advance notice of the application from the gateway system and obtain the information (e.g., in the case of the eCTD, the eCTD receipt number) required to manage the electronic files to be submitted. The applicant shall then enter and register the information related to the application and send the electronic files necessary for the application [such as application form data (hereinafter referred to as "FD application data"), eCTD, and electronic study data] using the gateway system.

Major revisions of FAQs

- Newly added
  - FAQ4-32-1: Details of submission of non-CDISC data for particular clinical pharmacology studies initiated prior to April 1, 2020
  - FAQ5-34: Possibility of not submitting the datasets before the model update if the dataset of a population analysis after the model update has been submitted
- Revision
  - FAQ1-16, 1-18: Reflection of operation change of reviewing validation results
  - FAQ1-23: Removal of request for specific details of the validation results

Recent update of Data Standards Catalog, etc.

- New Data Standards Catalog on March 29, 2024
  - This includes the new standard version, ADaM IG v1.2, 1.3, and Define-XML v2.1 with their Date Support Begins, April 1, 2024. They are acceptable for new drug applications whose application date is on or after April 1, 2024.
- New PMDA Validation Rules on March 29, 2024
  - Corresponding to the new Data Standards Catalog
  - It includes the rules for ADaM IG v1.2, 1.3, and Define-XML v2.1.
- Change of the regulation of the validation by applicants on April 1, 2024
  - Removal of the restriction that a single version of the PMDA validation rules should be used for validation for multiple clinical trials in one submission by applicant before submission
- Minor update of PMDA validation engine on December 15, 2023
  - From PMDA 2211.0 to PMDA 2211.1, to resolve report output issue

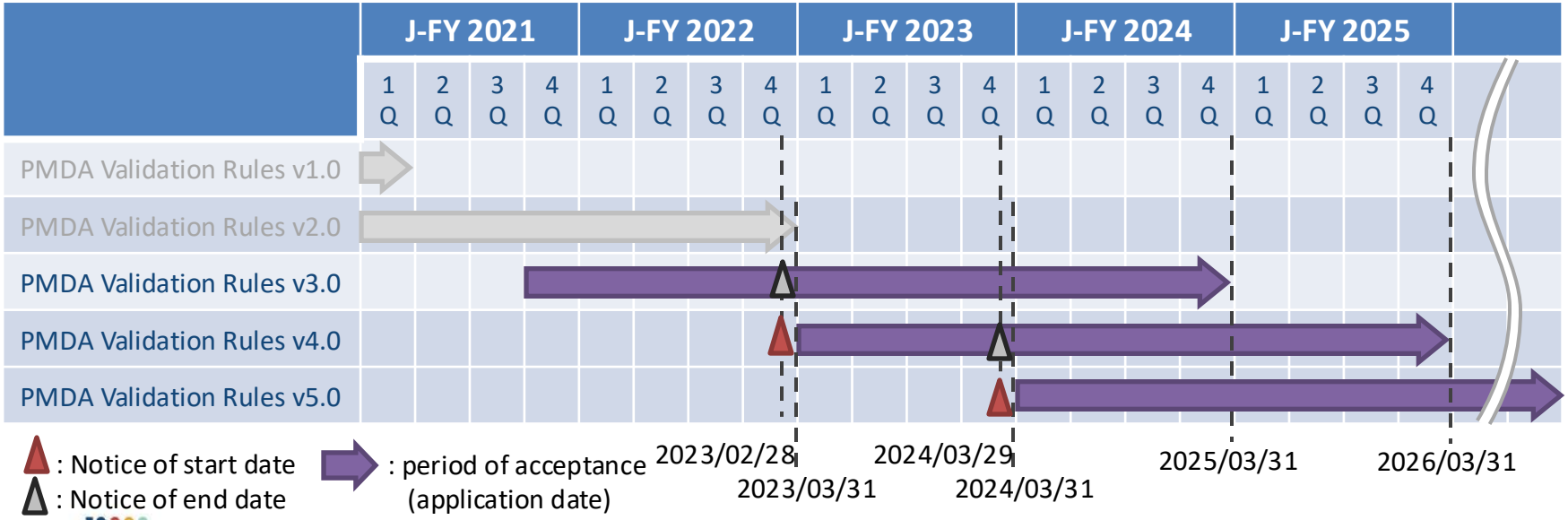
New Data Standards Catalog (2024-03-29)

PMDA Data Standards Catalog (2024-03-29) - 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	1.3	XPT	2024-04-01		
Clinical study datasets	ADaM	2.1	1.2	XPT	2024-04-01		
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	2.1	-	XML	2024-04-01		
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 v5.0

- PMDA Validation Rules v5.0 including ADaM IG v1.2, 1.3, and Define-XML v2.1 was published.
- Additionally, it was announced that the PMDA Validation Rule 4.0 can be used until March 31, 2026.



Update of Data Standards Catalog and PMDA Validation Rules (on March 29, 2024)

Data Standards Catalog and Study Data Validation Rules

- Data Standards Catalog (2024-03-29) [24.6KB]

- 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. Also, when additionally submitting electronic study data after the application, the version of the validation rules at the time of the application must be selected.

  For the validation and the explanation of the results performed by applicant prior to submission, all versions of the validation rules, including those that have already been closed for acceptance, can be used for each study. In addition, different versions of the validation rules can be used for SDTM and ADaM datasets of the same study.

  - Version 1.0 (2015-11-18) [82.0KB] Acceptable from Oct 1, 2016 to Mar 31, 2021 (application date)
  - Version 2.0 (2019-09-27) [97.9KB] Acceptable from Apr 1, 2020 to Mar 31, 2023 (application date)
  - Version 3.0 (2021-12-15) [103KB] Acceptable from Jan 1, 2022 to Mar 31, 2025 (application date)
  - Version 4.0 (2023-02-28) [112KB] Acceptable from Apr 1, 2023 to Mar 31, 2026 (application date)
  - Version 5.0 (2024-03-29) [124KB] Acceptable from Apr 1, 2024 (application date)

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

Background of the operation changes

- Validation rules are becoming more stable.
- The rules for the same version of the standards are basically the same between the versions of validation rules.
- We have accumulated experience and further understanding of the validation rules and the differences between versions (in case there are).
- We think that the prior validation by applicants with any of the versions of PMDA validation rules will provide a certain amount of information about the quality of the data.

Update of Data Standards Catalog and PMDA Validation Rules (on March 29, 2024)

- 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 2211.1 (Validation Rule Version 4.0)
  - PMDA 2311.0 (Validation Rule Version 5.0)

  On December 15, 2023, PMDA changed the engine from PMDA 2211.0 to PMDA 2211.1 for validation rule version 4.0. This change is intended to resolve an issue of report output and does not change validation results. Therefore, if the validation has been already performed using the previous PMDA 2211.0, there is no need to perform the validation again using the current PMDA 2211.1.

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

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.

	Standards	Status
New	SDTM v2.0 & SDTM IG v3.4	• Updated contents have been reviewed
Old	-	

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

Summary

- Advanced Review with Electronic Data Project has been executed successfully.
  - So far, no major problems have arisen in the receipt and use of electronic study data.
- The PMDA is constantly considering how to optimize the procedure in the PMDA and the data preparation in the industry, based on the experience of data submission, receipt, and dialogue with the stakeholders.
  - Revisions of the notification and other documents have been appropriately implemented.
- We appreciate your continual cooperation and collaboration regarding the preparation for the submission of standardized study data.
- The PMDA will continue to provide clear and useful information on data submission for the stakeholders so that the submitted data can be better used in the new drug review by the reviewers.

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)

I would like to thank Dr. Yuki Ando in PMDA for her assistance in preparing today's slides.