PharmaSUG SDE Japan 2019

Electronic Data Submission and Utilization in Japan

- in Preparation for the End of Transitional Period -

Hiromi Sugano
Principal Reviewer for Biostatistics
Office of New Drug I, II / Office of Advanced Evaluation with Electronic Data
Pharmaceuticals and Medical Devices Agency

Outline

- Preparation for the end of the transitional period
- Current situation of e-data submission
- Examples of
  - utilization of submitted data in review process
  - reviewer-friendly style for submitted data or documents
- Utilization of accumulated data

Accumulation and utilization of data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

Storage of electronic data in the dedicated server and registration in the database

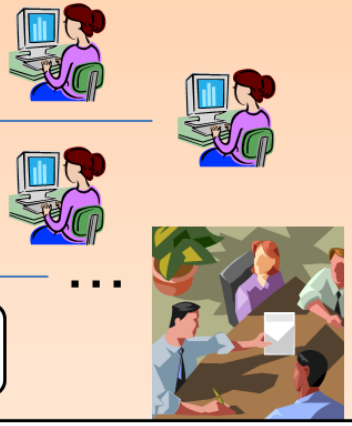
Visualization and analysis of data, supported by browsing software

Submission of electronic clinical study data has started since Oct 1st 2016!

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

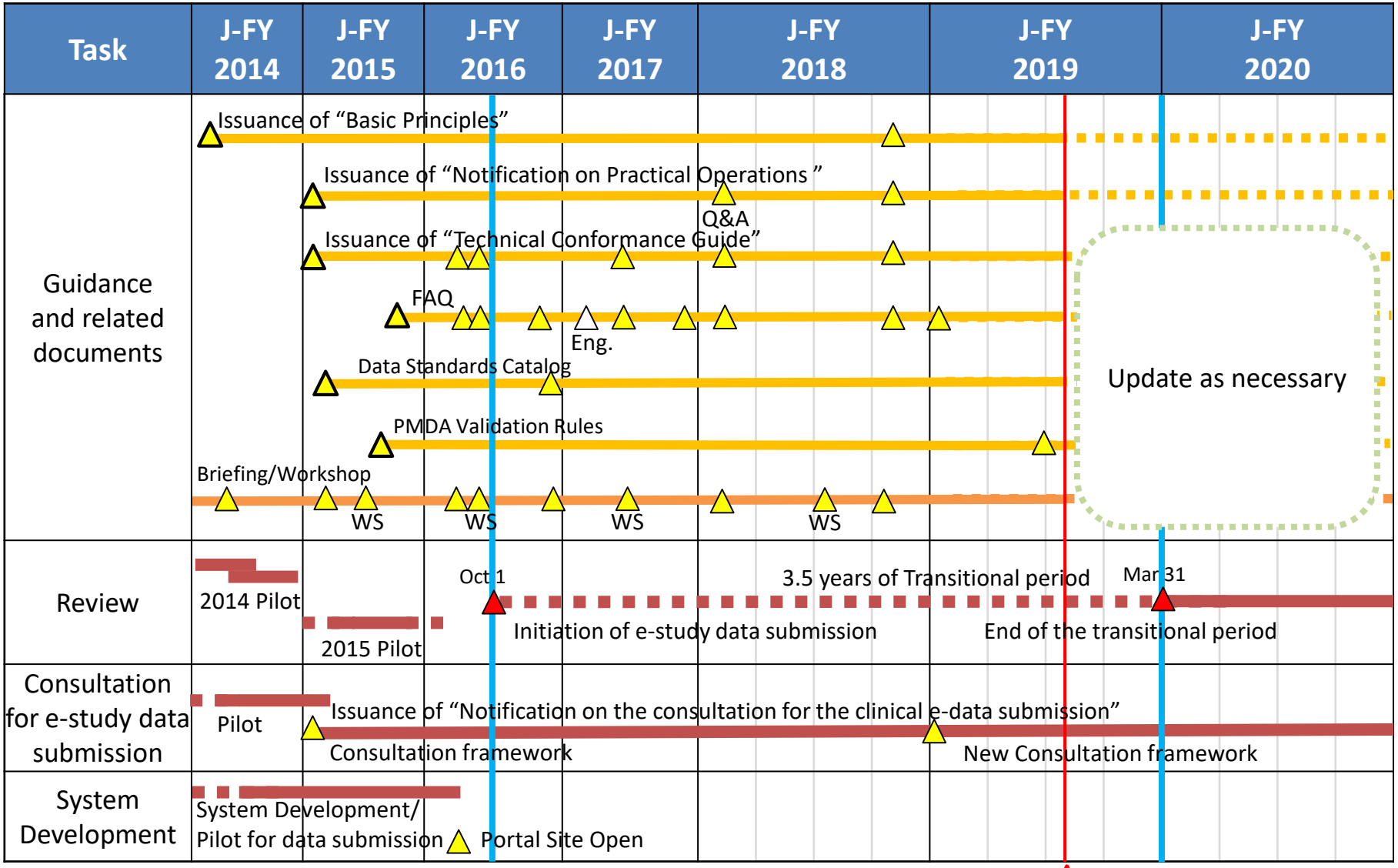
Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

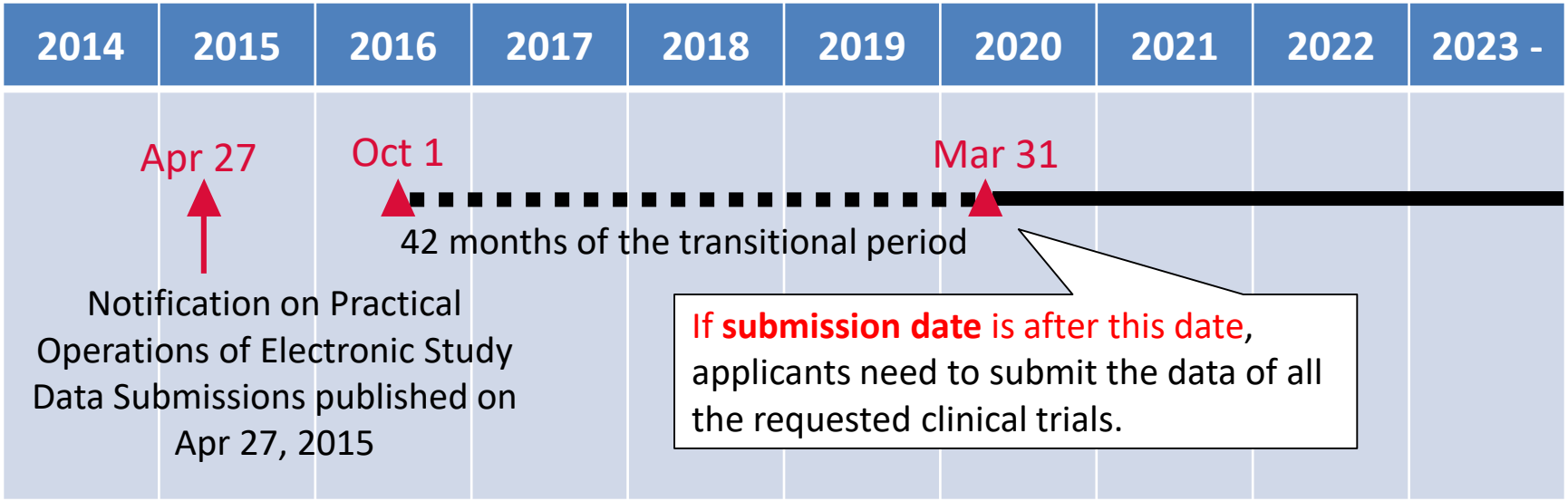
Timeline for implementation of e-data submission



- Preparation for the end of the transitional period

Transitional period will be ended…

- The transitional period will be ended on March 31, 2020.
  - During the transitional period, applicants can 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.



Recent Updates

Latest update on Jan 24, 2019

- Basic Principles on Electronic Submission of Study Data for New Drug Applications and Q&A
  - The first official announcement that MHLW/PMDA will require CDISC-standardized study data for NDA.
- Notification on Practical Operations of Electronic Study Data Submissions and Q&A
  - Practical issues on e-Study data submission
- Technical Conformance Guide on Electronic Study Data Submissions
  - Technical details on e-Study data submission

- 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 Apr 10, 2019

- PMDA Data Standards Catalog
  - List of acceptable versions of Data Exchange Standards and Terminology Standards

Latest update on Mar 3, 2017

under consideration for next update

- Information about CDISC Validation
  - Validation software version, List of PMDA validation rules

Latest update on Sep 27, 2019

Preparation for the end of transitional period

- Revisions of the notifications, Technical Conformance Guide, and FAQs to add clarifications of our requests for various situations
  - Submission of post-marketing study data
  - Data submission in special cases, such as situations where the data were not electronically maintained
  - Data submission with NDAs of orphan drugs
  - Data submission with NDAs of anti-HIV drugs
  - Clarification of timing of data submission for special situation, where actual review is mainly conducted before official submission of new drug application
- New categorization of consultation meetings

We are proceeding the project with continual discussion with industry for the smooth transition to the next phase.

New categorization of consultation meetings

Consultation on preparation of submission of electronic study data — 方法相談

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 — 確認相談

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 — 免除相談

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"

Please refer to the FAQ1-5 for the details

Consultation for clinical e-data submission

- 292 consultation meetings have been conducted as of September 30, 2019.

Year		N of consultations	
J-FY 2015 (May 15, 2015 – Mar 31, 2016)		11	
J-FY 2016 (Apr 1, 2016 – Mar 31, 2017)		55	
J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)		70	
J-FY 2018 (Apr 1, 2018 – Mar 31, 2019)		90	
J-FY 2019 (Apr 1, 2019 – Sep 30,2019)	Consultation on preparation of submission of electronic study data（方法相談）	51	66
	Consultation on data format of submission of electronic study data（確認相談）	15	
	Consultation on exemption of submission of electronic study data（免除相談）	0	
Total			292

Consultation for clinical e-data submission

- Multiple meetings have been held for some products.
- Various characteristics
  - With/without official minutes
  - Japanese/foreign company
  - Almost all therapeutic areas

Frequently raised issues at consultation on preparation (方法相談) of submission of e-data

- Product/study dependent issues
- Legacy data conversion, ADaM dataset creation
- Explanation of traceability
- Organization of SDTM domains and variables, use of SUPPQUAL and custom domains, and data in Japanese language
- Information to be included in the Trial Design Model
- Issues related to WHO DDs coding, SI units
- Necessity of revise or update the Controlled Terminology
- How to submit study data of multiple time points
- Submission of Analysis Results Metadata, SAS programs
- Submission format for Clin-Pharm data
- Handlings to deal with “Reject” or “Error” in validation

- Current situation of e-data submission

Data submitted with new drug applications

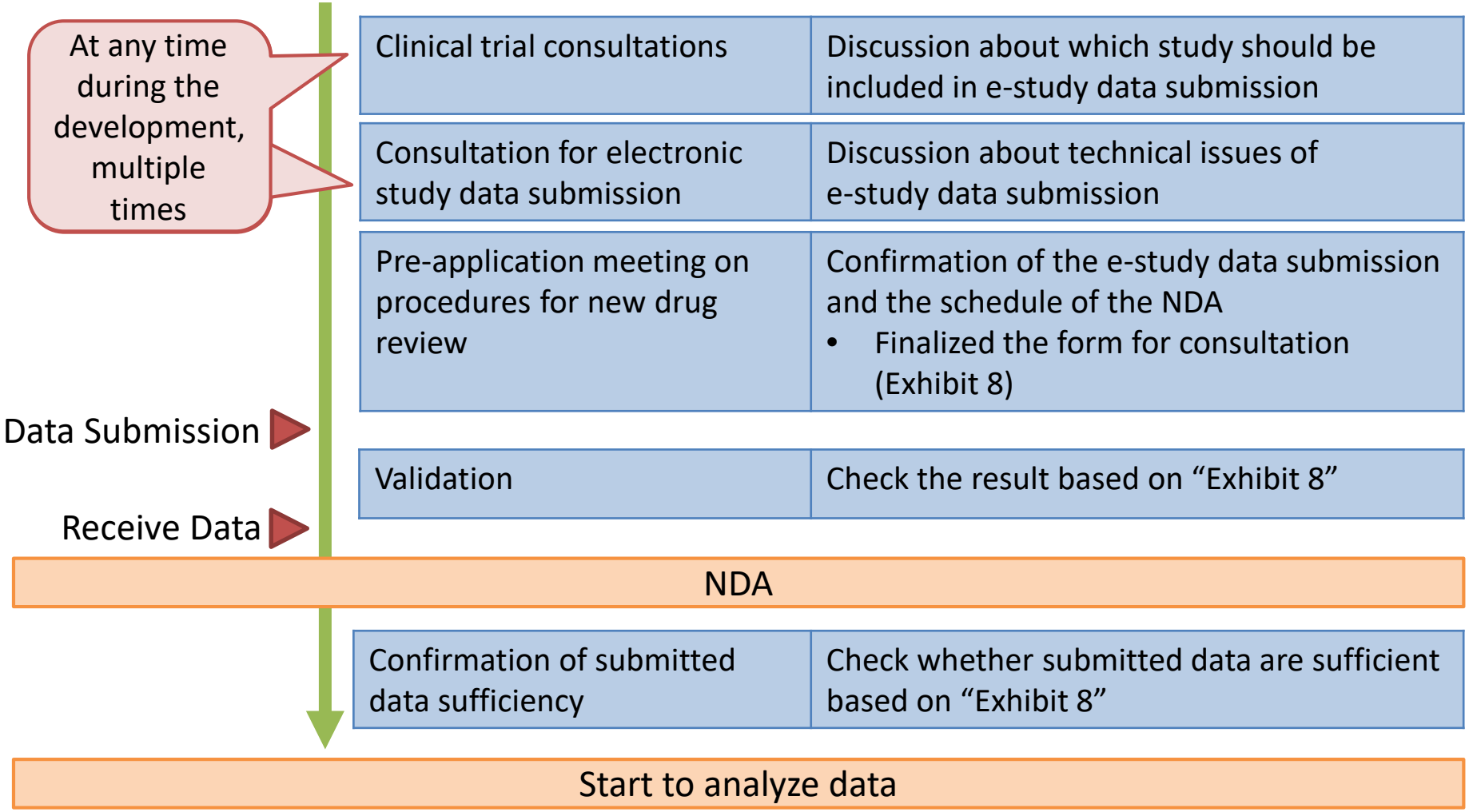
- 90 NDAs were submitted with electronic study data as of Sep 30, 2019.

Year	N 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 – Sep 30, 2019)	16
Total	90

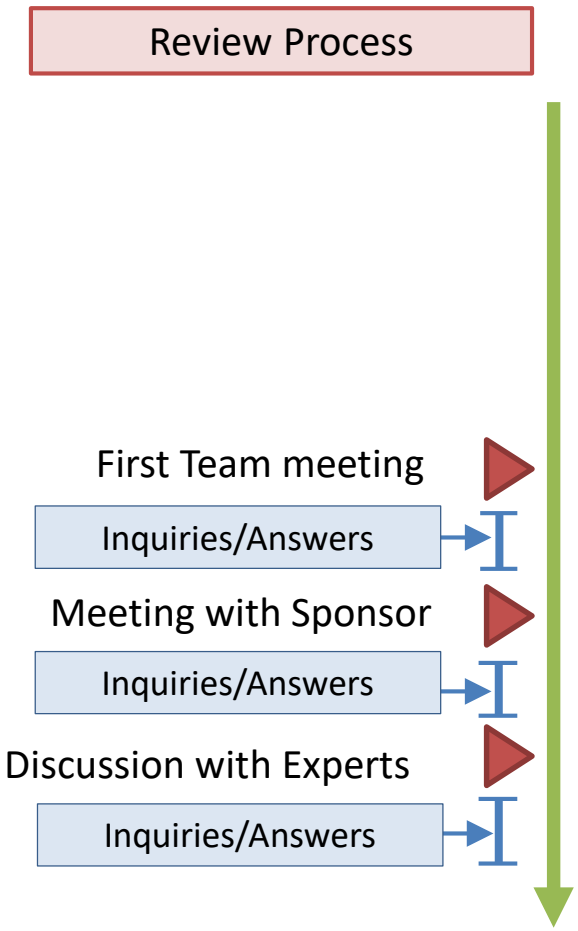
- Various characteristics on the NDAs
  - Domestic/global company
  - Clinical pharmacology study for 53 NDAs (59%) as of Sep 30, 2019
  - There have been accumulated data of multiple products for same disease area and data of one active ingredient for multiple diseases.

- Examples of
  - utilization of submitted data in review process
  - reviewer-friendly style for submitted data or documents

Process of starting to analyze data



Review process and data analysis



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

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

Examples of utilization of submitted data in review process (1)

Before the first team meeting

- Reviewer(stat) initially conduct the primary analysis to confirm the reproducibility of the main result.
  - To check the robustness of the primary result, reviewer performed supplementary analysis (based on several analysis populations, different models, several imputation methods) as much as time allows.

Examples of utilization of submitted data in review process (2)

Before and after the first team meeting

- Based on discussions with review team members, several analyses listed below were done and they provided meaningful result to judge the degree of necessity for inquiries, and the content of inquiries.
  - Subgroup analysis (ex. by study site, by age/renal function, by device, by concomitant medication)
  - Output of detailed demographics report (ex. the highest dose for each subject)

Examples of utilization of submitted data in review process (3)

Before and after the meeting with applicant

- To investigate the issues caused by the change of study plan during the trial, reviewer performed subgroup analyses listed below and checked the distributions of enrolled subjects and the efficacy/safety results.
  - Subgroup analysis divided by the time point of
    - change of inclusion/exclusion criteria
    - change of dosage
    - interim analysis

Examples of utilization of submitted data in review process (4)

after the meeting with applicant

- Pooled analysis for subjects from different studies of almost the same design (in the same clinical data package) was conducted to know the efficacy and safety information among small subgroups.

Examples of utilization of submitted data in review process (5)

after the meeting with applicant

- To assess the need for emphasizing the cautions in PI, reviewer checked the consistency of the magnitude of interaction term (●*treatment arm) between the two studies of almost the same design (in the same clinical data package).

Examples of utilization of submitted data in review process (6)

Before the discussion with external experts

- Conducting several analyses listed below, the review team was able to quickly and efficiently deal with the items pointed out from the external experts.
  - Output the distribution of baseline characteristics (ex. concomitant drugs A∩B)
  - Subgroup analysis
  - Responder analysis
  - Supplemental analysis under several assumptions (ex. non-parametric)
  - Output the clinical course of a subject

Examples of reviewer-friendly style for submitted data or documents(1)

NDA

- Reviewers can perform analyses based on submitted data and attached documents without inquiry about dataset.
- SAS program for main efficacy analysis and ARM are very useful to understand which variable used, how the analysis population defined, how the imputations done.

Examples of reviewer-friendly style for submitted data or documents (2)

NDA

- In the dose titration design trial, it is favorable that some variables which summarize the dose distribution (ex. final dose, mean dose) are prepared in ADaM dataset for the supplementary efficacy or safety analysis.

Examples of reviewer-friendly style for submitted data or documents (3)

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

NDA

確認相談

- The errors identified during the validation process must be explained both in the Data Guide (SDRG/ADRG) and in the Attachment 8.
- To avoid a discrepancy between the two documents, the applicant can use the Data Guide as an appendix of the description of the errors in Attachment 8 (see FAQ 1-26).

Examples of reviewer-friendly style for submitted data or documents (4)

Consultation on **preparation** of submission of electronic study data — 方法相談

Consultation on **data format** of submission of electronic study data — 確認相談

- Adding a supplementary explain about unregulated variable is helpful to understand the point when you consult about ADaM dataset.

Summary of e-data review (1)

- Reviewers can develop an understanding about the e-data, trial design, and the product than ever.
- The timeline of review process isn't change.
- Sometimes inquiries from PMDA can be more reasonable (reduce the request for comprehensive analysis more than necessary) or no need for inquiry.
- It becomes possible to quickly and efficiently deal with a point from the external expert.
- It is important to continue the internal trainings.

Summary of e-data review (2)

- Schedule management and business efficiency improvement are more important than ever.
- It is necessary for reviewers to cooperate among their specialties(ex. stat and clinical) more than ever from an early stage.
- Having e-data discussions between Applicant and PMDA from early stage of clinical development is meaningful.

➢Utilization of accumulated data

Utilization of accumulated data

- Accumulation and integration of exhaustive information about the drugs by therapeutic category or drug mechanism of action
  - Cross-product information of particular diseases (efficacy, safety, and placebo effects)
  - Cross-indication evaluation of drug safety
- Internal review on particular theme, e.g. M&S
  - Investigation of exposure-biomarker-clinical outcome
  - Similarity of exposure-clinical outcome relationship between populations
- Guidance development
  - Guidance for therapeutic areas and specific topics
  - Points to be considered of particular methodologies

Now our biostatisticians/pharmacometricians actively working on the use of accumulated data as one of the research projects in PMDA

Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - All data has been successfully received since Oct 1, 2016.
- PMDA will continue to provide information on the e-data submission for industry with considering the end of transitional period.
  - The transitional period will be ended on Mar 31, 2020.
- We appreciate your continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug.

Thank you for your attention.

Back-up

- Communication with other regulatory authorities
  - FDA
  - EMA
- Utilization of e-data in GCP document-based conformity inspection by PMDA