PhUSE Single Day Event
Tokyo, Japan
10 December, 2019

Update of electronic data submission in Japan

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Outline

- Recent regulatory update on e-data submission to PMDA
- Current situation of e-data submission
- Utilization of accumulated data
- Relationship with PhUSE

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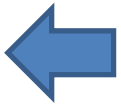


Accumulation and utilization of e-study data

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

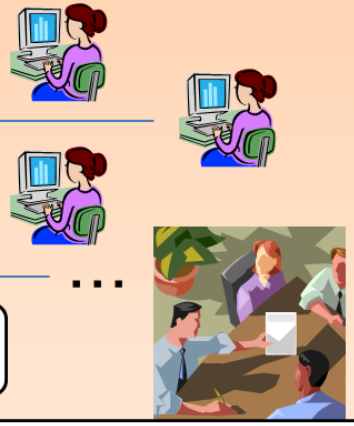
Visualization and analysis of data, supported by browsing software

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

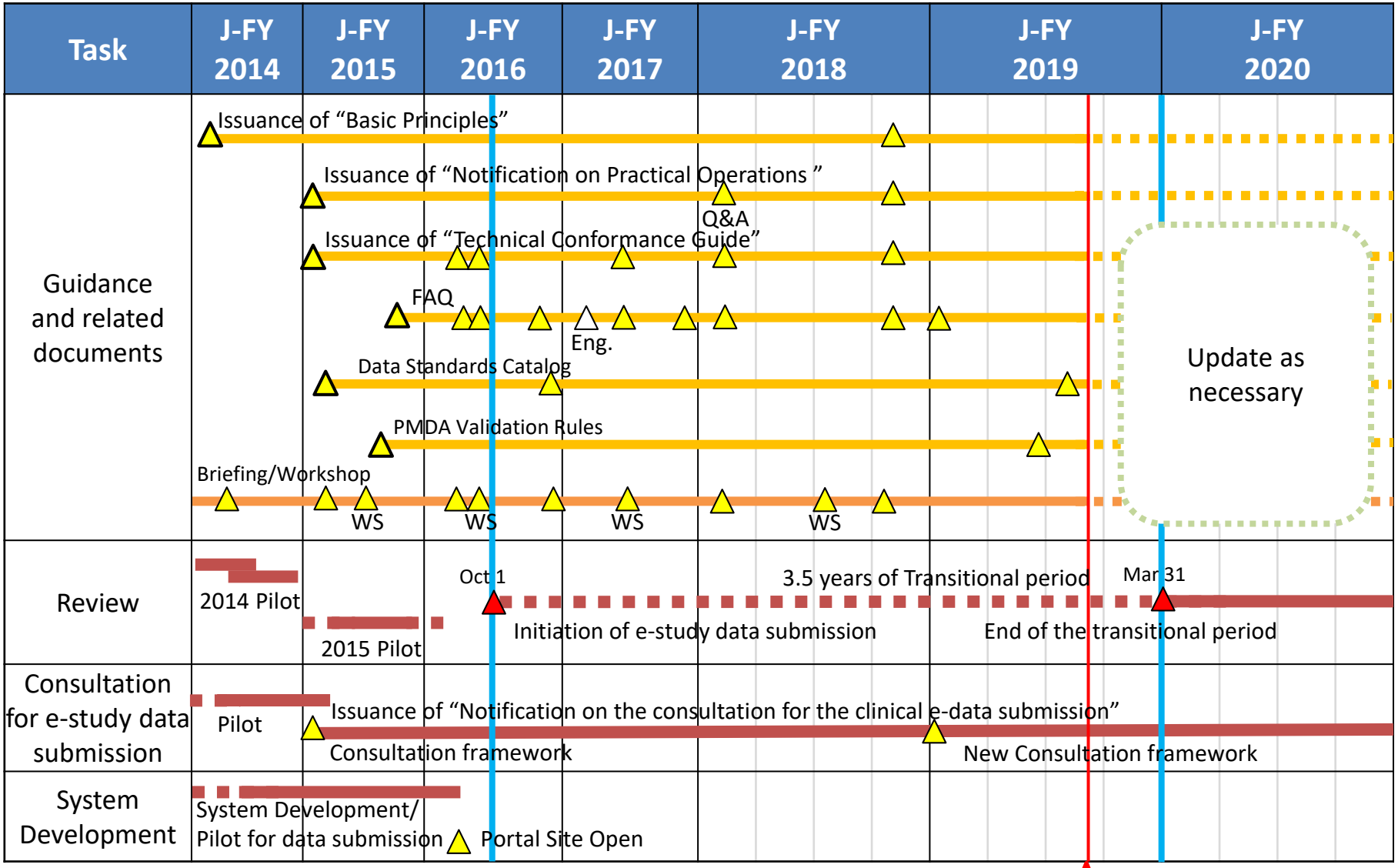
Integration of cross-products information

- 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.

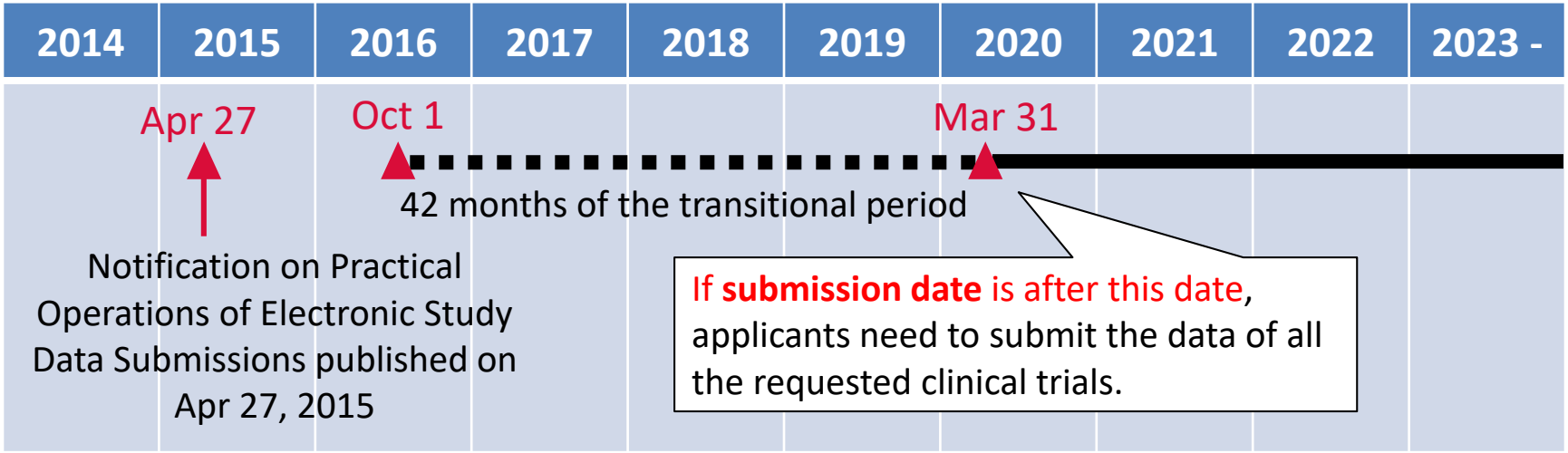
Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Timeline for implementation of e-data submission



Initiation timing and transitional period of submission of e-study data

- The initiation date of submission of e-study data is October 1, 2016.
- There is a transitional period of 42 months from October 1, 2016 to 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.



Notifications, Guide, FAQs, and Standards Catalog

- **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
  - Latest update on Jan 24, 2019
- **Notification on Practical Operations** of Electronic Study Data Submissions and Q&A
  - Practical issues on e-Study data submission
  - Latest update on Jan 24, 2019
- **Technical Conformance Guide** on Electronic Study Data Submissions
  - Technical details on e-Study data submission
  - Latest update on Jan 24, 2019
- **FAQ website** (Latest update on Apr 10, 2019)
  - Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and the guide
- **PMDA Data Standards Catalog** (Latest update on Nov 1, 2019)
  - List of acceptable versions of Data Exchange Standards and Terminology Standards

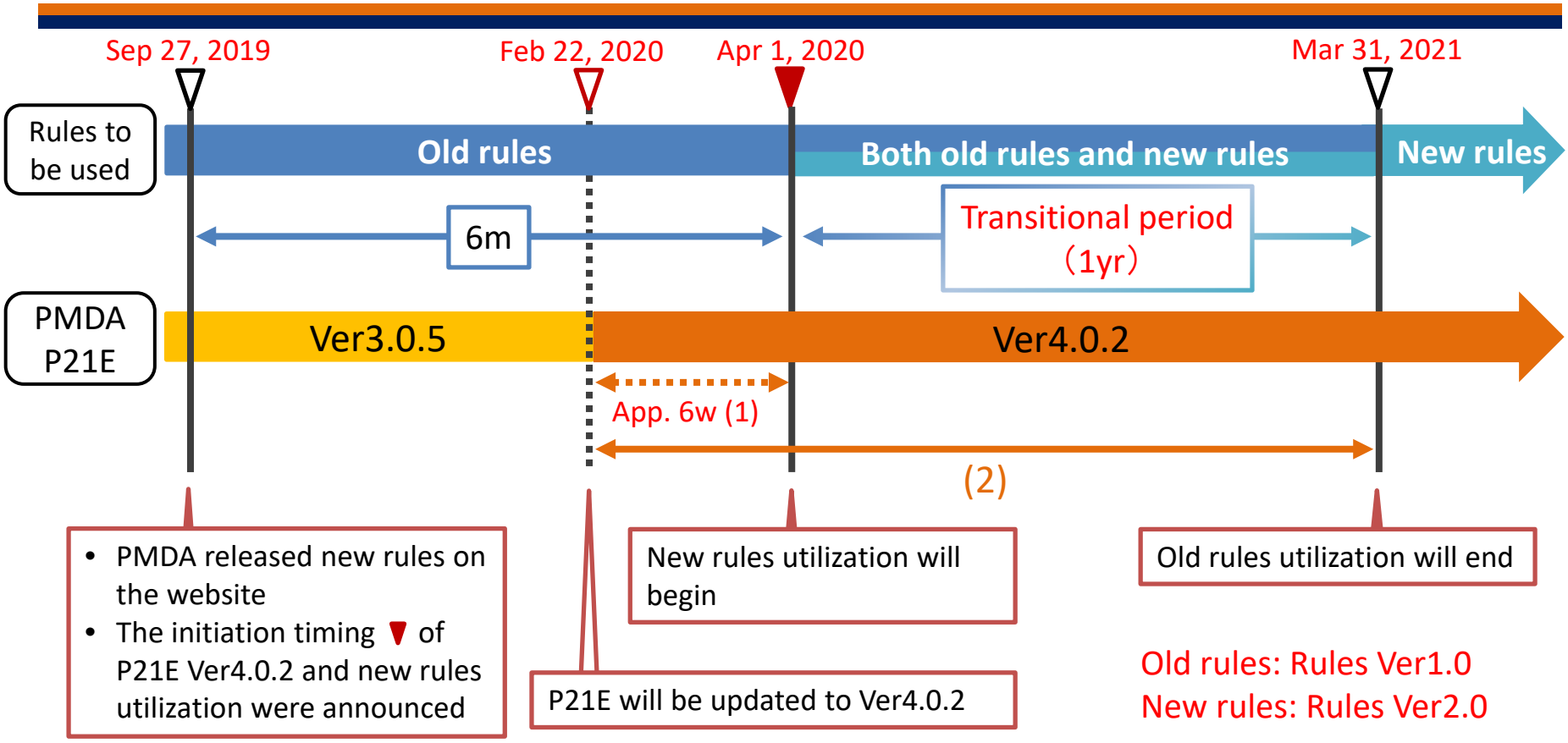
Update of PMDA Data Standards Catalog

- Updated on Nov 1, 2019.
- No major change on the date support begins/ends
  - Corrections of name of the consultation, name of WHODD, and WHODD version description

PMDA Data Standards Catalog (2019-11-01) - Terminology Standards

Terminology Standard	Version(s)	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
CDISC Controlled Terminology	Between 2009-02-17 (inclusive) and 2011-06-10 (exclusive)	2016-10-01	2017-06-30	When using the version indicated in "Version(s)" column, consult PMDA at the consultation on data **preparation** of the submission of electronic study data.
CDISC Controlled Terminology	2011-06-10 or later	2016-10-01		
MedDRA	8.0 or later	2016-10-01		
WHO Drug Dictionary Enhanced/ **WHODrug Global (since 2017 March)**	2008:**4** (2008-12-01) or later	2016-10-01		

P21 Enterprise version up schedule

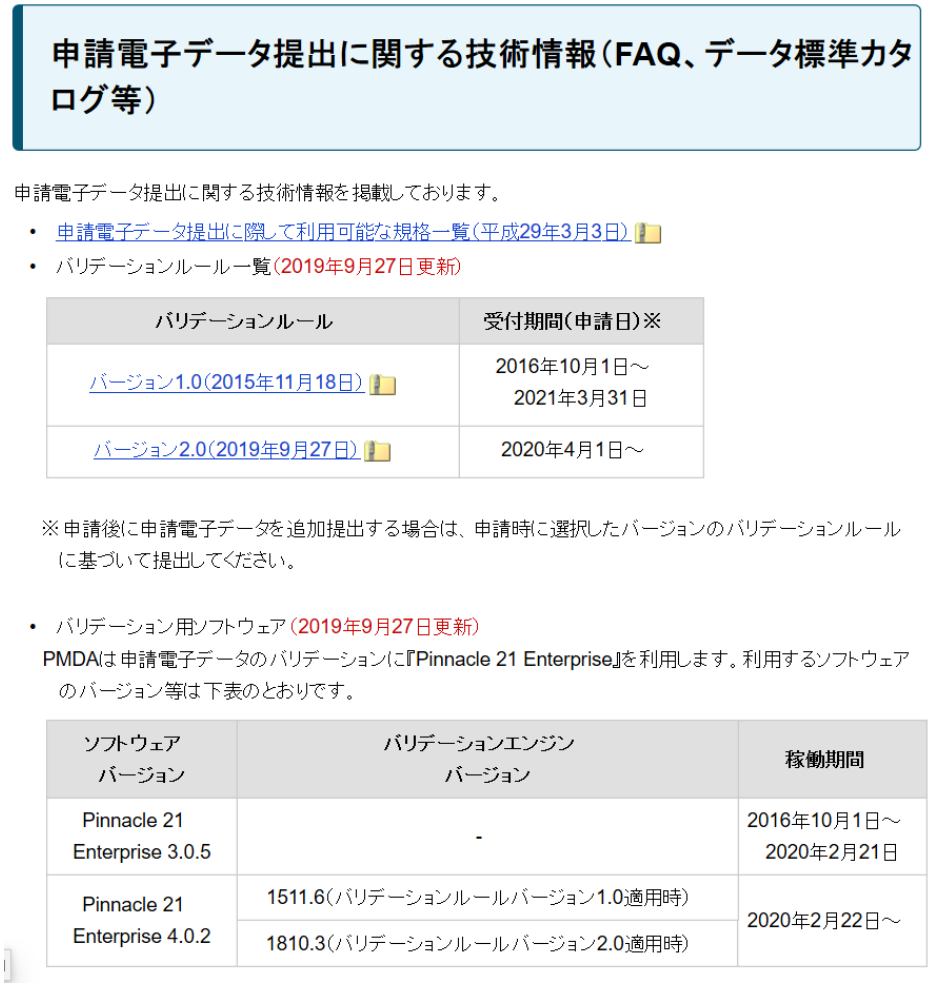


(1) : PMDA will update P21E to Ver4.0.2 ahead of time because the data of the new drug applications can be submitted from 5 weeks in advance of the application date.

(2) : In case of that the data with validation using Ver3.0.5 (old rules) is submitted, the difference of the results caused by the difference of versions of P21E will be ignored.

Announcement on the PMDA website

- The update schedule was announced on Sep 27, and we are working on the announcement on the website in English.
- The validation rules Ver 2.0 are available at
  - http://www.pmda.go.jp/files/000231624.zip
- We would like to proceed the updating work so as not to interfere with the submission and receipt of data.



申請電子データ提出に関する技術情報（FAQ、データ標準カタログ等）

申請電子データ提出に関する技術情報を掲載しております。

- 申請電子データ提出に際して利用可能な規格一覧（平成29年3月3日）
- バリデーションルール一覧（2019年9月27日更新）

バリデーションルール	受付期間（申請日）※
バージョン1.0（2015年11月18日）	2016年10月1日～ 2021年3月31日
バージョン2.0（2019年9月27日）	2020年4月1日～

※申請後に申請電子データを追加提出する場合は、申請時に選択したバージョンのバリデーションルールに基づいて提出してください。

- バリデーション用ソフトウェア（2019年9月27日更新）

PMDAは申請電子データのバリデーションに『Pinnacle 21 Enterprise』を利用します。利用するソフトウェアのバージョン等は下表のとおりです。

ソフトウェア バージョン	バリデーションエンジン バージョン	稼働期間
Pinnacle 21 Enterprise 3.0.5	-	2016年10月1日～ 2020年2月21日
Pinnacle 21 Enterprise 4.0.2	1511.6（バリデーションルールバージョン1.0適用時）	2020年2月22日～
	1810.3（バリデーションルールバージョン2.0適用時）	

New versions of CDISC standards

- PMDA plan to include the new versions of CDISC standards in the PMDA Data Standards Catalog after the investigation of whether the impact will be acceptable and preparation for the validation rules.

Standards	Status
SDTM v1.7 & SDTM IG v3.3	• Under review in PMDA
ADaM IG v1.1	• Updated contents have been reviewed • Validation rules will be considered based on ADaM Conformance Rules 2.0
ADaM IG v1.2	• Will be reviewed after the implementation of v1.1
Define-XML v2.1	• Updated contents and impact on the Electronic Submission Gateway will be reviewed

SEND

- Utilization of non-clinical study data and the standard (SEND) are discussed under the funded research project which includes PMDA toxicology reviewers as main researchers.
  - For example, recently they discuss utilization of viewer software of SEND dataset.
- They will summarize their discussions as the research group in early 2021, so please wait for their announcement.

New categorization of consultation meetings

- We divided the previous “Consultation on data format of submission of electronic study data” into two categories,
  - “Consultation on preparation of submission of electronic study data” for methods of storing data and/or submission
  - “Consultation on data format of submission of electronic study data” for validation results
- We added new category “Consultation on exemption of submission of electronic study data” based on the revision of the notifications.

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

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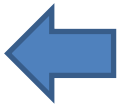


Consultation for clinical e-data submission

- 302 consultation meetings have been conducted as of Oct 31, 2019.

Year		Number 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 – Oct 31, 2019)	Consultation on data format	57	76
	Consultation on preparation	18	
	Consultation on exemption	1	
Total			302

Recent contents for “Consultation of preparation”

- Issues related to legacy data conversion
  - Approaches of legacy data conversion and explanation of the traceability
  - Creation of ADaM datasets
  - Relationship between the analysis results by newly created datasets and those in clinical study report
  - Necessity of conversion or update of Controlled Terminology
  - Issues when the original versions of standards are unknown
  - Submission of programs or specification documents
- How to address “Reject” and/or “Error” in the CDISC validation

  Explanations of validation results are discussed at Consultation on **data format** of submission of electronic study data
- Submission of study datasets from multiple cutoff dates
- Explanation of custom domains

Data submitted with new drug applications

- 94 NDAs were submitted with electronic study data as of Oct 31, 2019.

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 – Oct 31, 2019)	20
Total	94

Data submitted with new drug applications

- We have sent letters of requesting data correction and/or additional explanation of the data at the initial submission of 34/94 NDAs (36%) as of Oct 31, 2019.

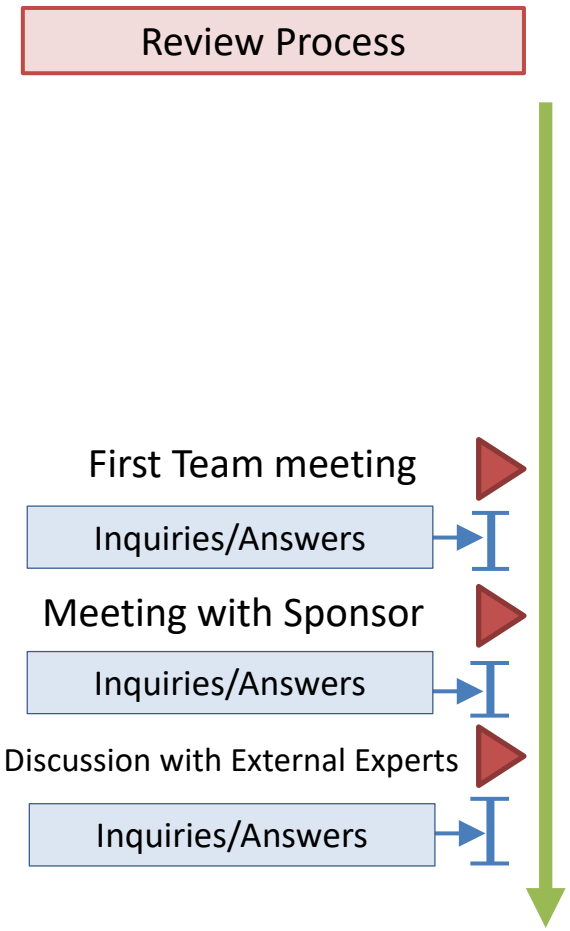
Year	N of NDAs/Total
J-FY 2016 (Oct 1, 2016 – Mar 31, 2017)	7/10
J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)	13/31
J-FY 2018 (Apr 1, 2018 – Mar 31, 2019)	10/33
J-FY 2019 (Apr 1, 2019 – Oct 31, 2019)	4/20
Total	34/94

- Reasons of sending letters was detection of non-compliance with the PMDA validation rules categorized “Error” without pre-explanation or “Reject”.

Points to be considered for data submission

- Confirm types of CDISC validation prior to the submission
  - Whether they cover the validations described in FAQ1-24
- Confirm descriptions and their consistency between
  - Attachment 8 for consultation meeting
  - reviewer's guides
  - define.xml
  - information to be input on Electronic Submission Gateway
- Confirm file names and folder names
- Confirm consistency of the datasets on the list in Attachment 8 and actual datasets to be submitted

Review process and data analysis



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 External Expert Discussion	• Additional analysis taking comments from external experts into account • Indication, dosage, special population

Completion of Review

Utilization of submitted data -1/3

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

First Team meeting

Inquiries/Answers

Meeting with Sponsor

Inquiries/Answers

Discussion with External Exper

Inquiries/Answers

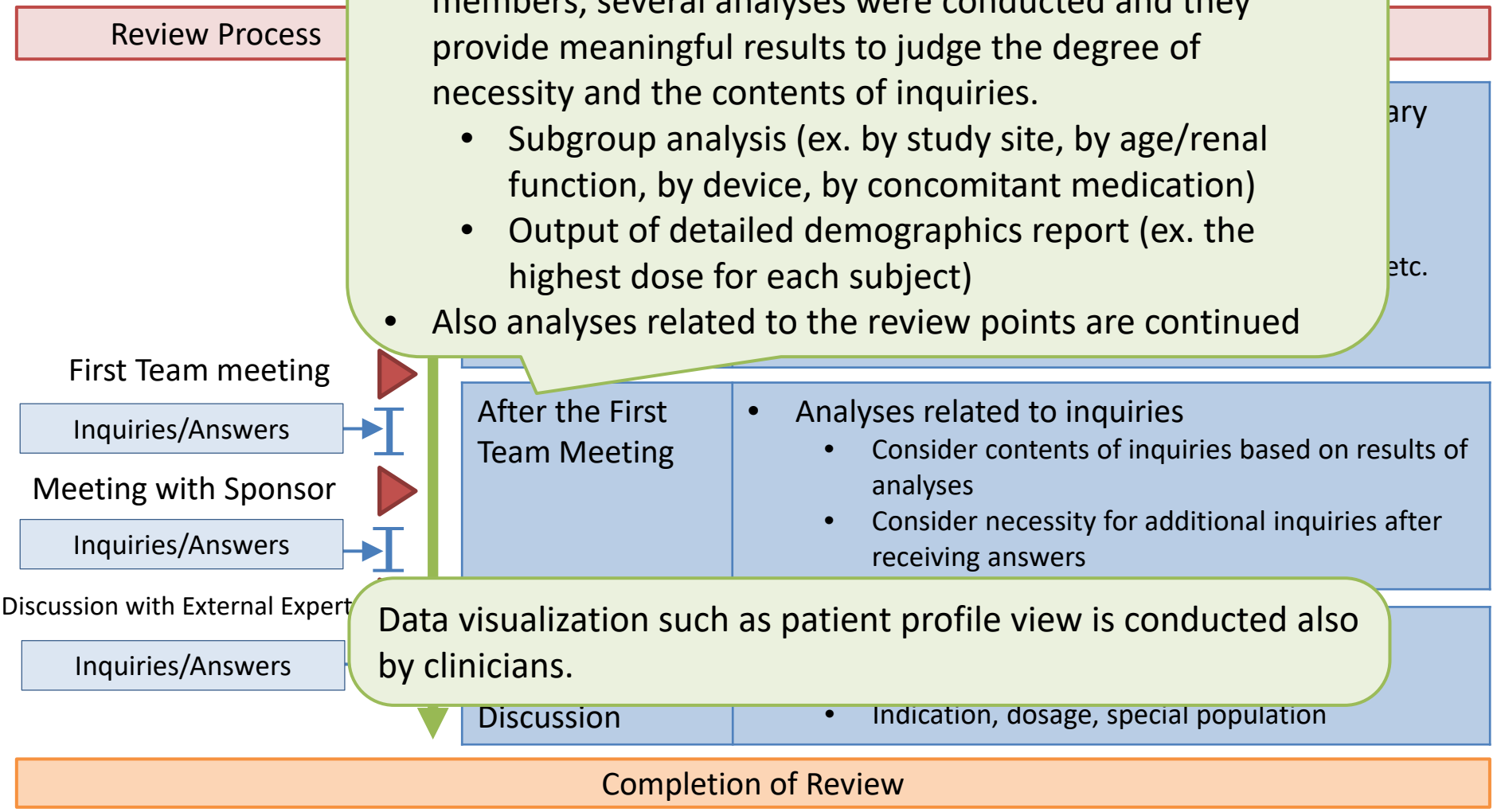
ults of

after

- (Biostatistics) Reviewers initially conduct the primary analysis to confirm the reproducibility of the main results.
- Supplementary analyses (based on several analysis populations, different models, several imputation methods) will be performed to check the robustness of the primary result.
- If time allows, the reviewers will conduct several analyses for review points based on their review experiences

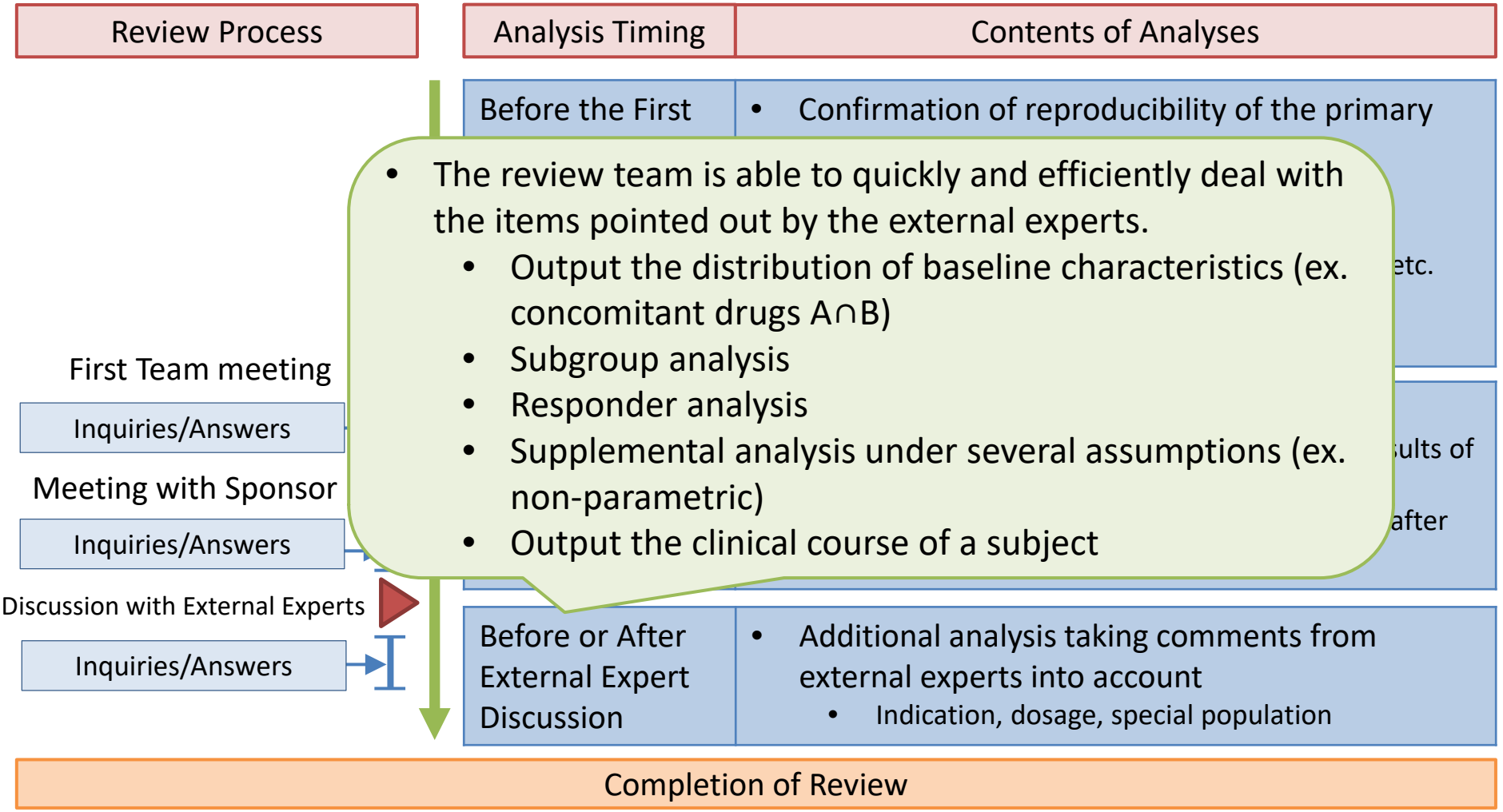
Utilization of submitted data -2/3

- Based on the discussions between the review team members, several analyses were conducted and they provide meaningful results to judge the degree of necessity and the contents 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)
- Also analyses related to the review points are continued



Data visualization such as patient profile view is conducted also by clinicians.

Utilization of submitted data -3/3



Summary of utilization of submitted data

- Reviewers can understand the trial design, and the efficacy and safety of the drug than ever.
- The timeline of review process is not changed even in the recent environment with increasing complex development/design/ analysis issues.
- Inquiries from PMDA can possibly be more reasonable.

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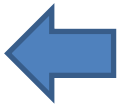

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NDA submission

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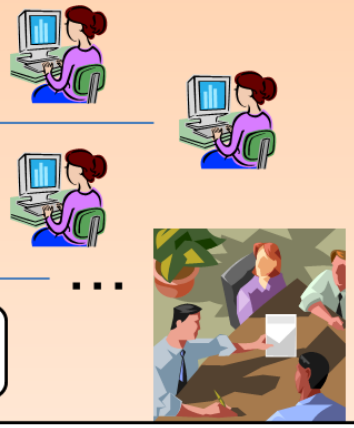

Scientific discussion and decision making on the basis of internal analysis result

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
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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

Examples of utilization of accumulated e-study 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.

Research project supported by AMED

- “Utilization of cross-product analyses of clinical study data and analyses of patient registry data for drug development”
- One of the activities of Office of Advanced Evaluation with Electronic Data, with using submitted and accumulated clinical study data
- Research project by Biostatisticians (in New Drug Review Offices) and Pharmacometricians (in Office of Advanced Evaluation with Electronic Data)
- From J-FY2018 to J-FY2020
- Supported by AMED under Grant Number JP19mk0101123

Objectives of the research project

- Provision of information on advanced technology to domestic stakeholders
  - In addition to internal training in PMDA, seminars by invited overseas experts will be provided to industry and academia
    - “Frontline of utilization of modeling & simulation in disease research and therapeutic development” (3 Sep, 2019)
    - Internal seminars on PBPK modeling, QSP modeling, and Model Based Meta-Analysis (MBMA)
- Research based on the submitted clinical trial data with new drug applications
  - Use of cross-product analysis/data
    - Evaluation of Bayesian methods for MRCT
    - Modeling & Simulation
  - Use of disease registry for drug development
    - Ex. analysis methods of using registry data as control
    - Supportive information for CIN activities in PMDA
- Development of guidance or points to be consider based on the research

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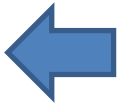
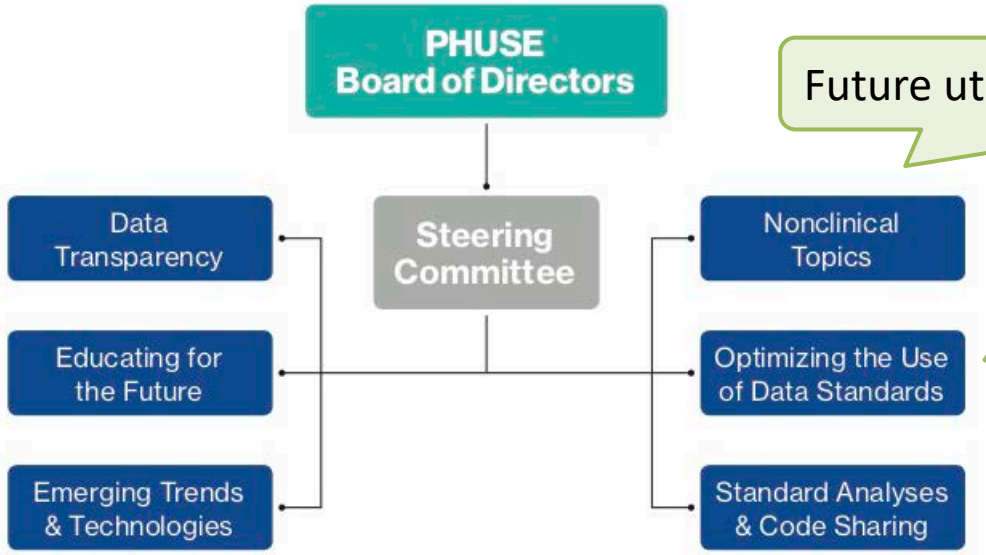


Expectations on PhUSE activities

- We have already mentioned the PhUSE activities as existence of available format of SDRG and ADRG in the PMDA Technical Conformance Guide.
- Now the Biostatisticians in PMDA actively analyze submitted clinical study data and are more interested in data structure, data standards, and analysis methodologies.
- Reflecting growing interest in the future possibility of use of various data sources for drug development and application, there is increasing interest in capturing, processing, and analyzing data.

Expectations on PhUSE WG



Future utilization of SEND data in PMDA

- Utilization of CDISC standardized data in PMDA
- Optimization of the request to sponsors regarding the data standardization and validation
- Optimization of the contents of metadata and other explanations of the data

Utilization of and/or support for emerging technologies for drug development, such as trial design, data sources and evaluation

Standardization of programs, analyses, and their interpretations

Utilization of e-study data in the future

Utilization of study data for new drug review

- Improvement of predictability of efficacy and safety
- Reviewing M&S results
- Reviewing novel evaluation methods
- Swift and effective decision-making

- Data accumulation
- Experiences of data evaluation

Utilization of accumulated study data

- Information from cross-product analysis
- Active use of M&S
- Evaluation of innovative analysis methods based on the accumulated data
- Experiences of meta-analytic approach

Submission of standardized study data

- Consultation based on the cross-product information
- Guidance for therapeutic areas
- Issuance of points to considers for methodology

- Consultation/guidance about innovative analysis methods
- Contribution to data standardization

Efficient new drug development

- Use of consultation meeting based on the cross-product information by PMDA
- Active use of M&S
- Use of innovative and appropriate methods for the purpose

Use of various data sources in the future

- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources