PMDA Update

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Strength *through Collaboration*

Advanced workflow of review/consultation

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

More rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Data Accumulation

Database

Sophisticated review

- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis

- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - ➢ Disease model
  - ➢ Objective B/R assessment
  - ➢ Identifying AE-related factors etc.

Sophisticated Consultation

- More evidence-based consultation

More effective and high quality Review

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

More efficient and Successful Development

- Epoch-making proposal leading the world
- Proactive publication of guideline

Accumulation and utilization of data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

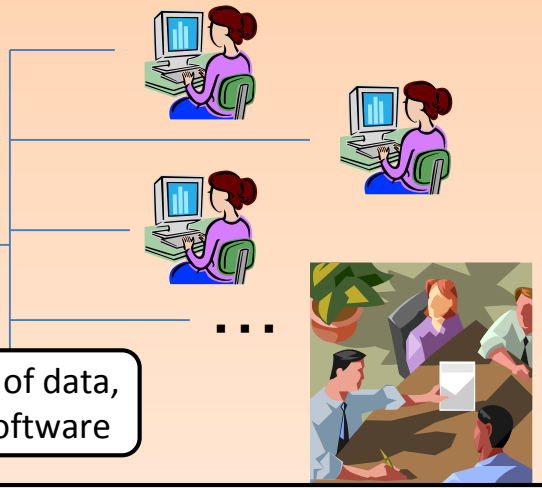
Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

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

Prospect of e-Study data utilization in Japan

Prospect As of April 2016
(Subject to Change)

Start e-study data submission for NDA* from Oct 1st, 2016

*NDA=New Drug Application

- e-study data can be received and managed appropriately
- e-study data can be utilized in the review
- Industries' workload is reduced gradually while keeping the same review period

Present

J-FY2016

Setup e-data management and utilization

- More predictable efficacy/safety
- Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

J-FY2018

Ordinary utilization of e-data in the product review

Promotion of paperless operation

Transitional period are taken until March 31st, 2020

- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

J-FY2019 - 2021

Starting earnest cross-product analysis

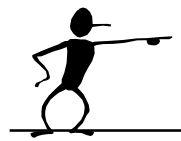
- Establishment of disease models
- Publication of disease-specific guidelines

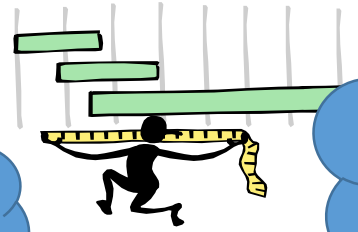
J-FY2022 -

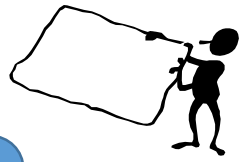
Publication of guidelines to contribute to drug development

First-class review authority

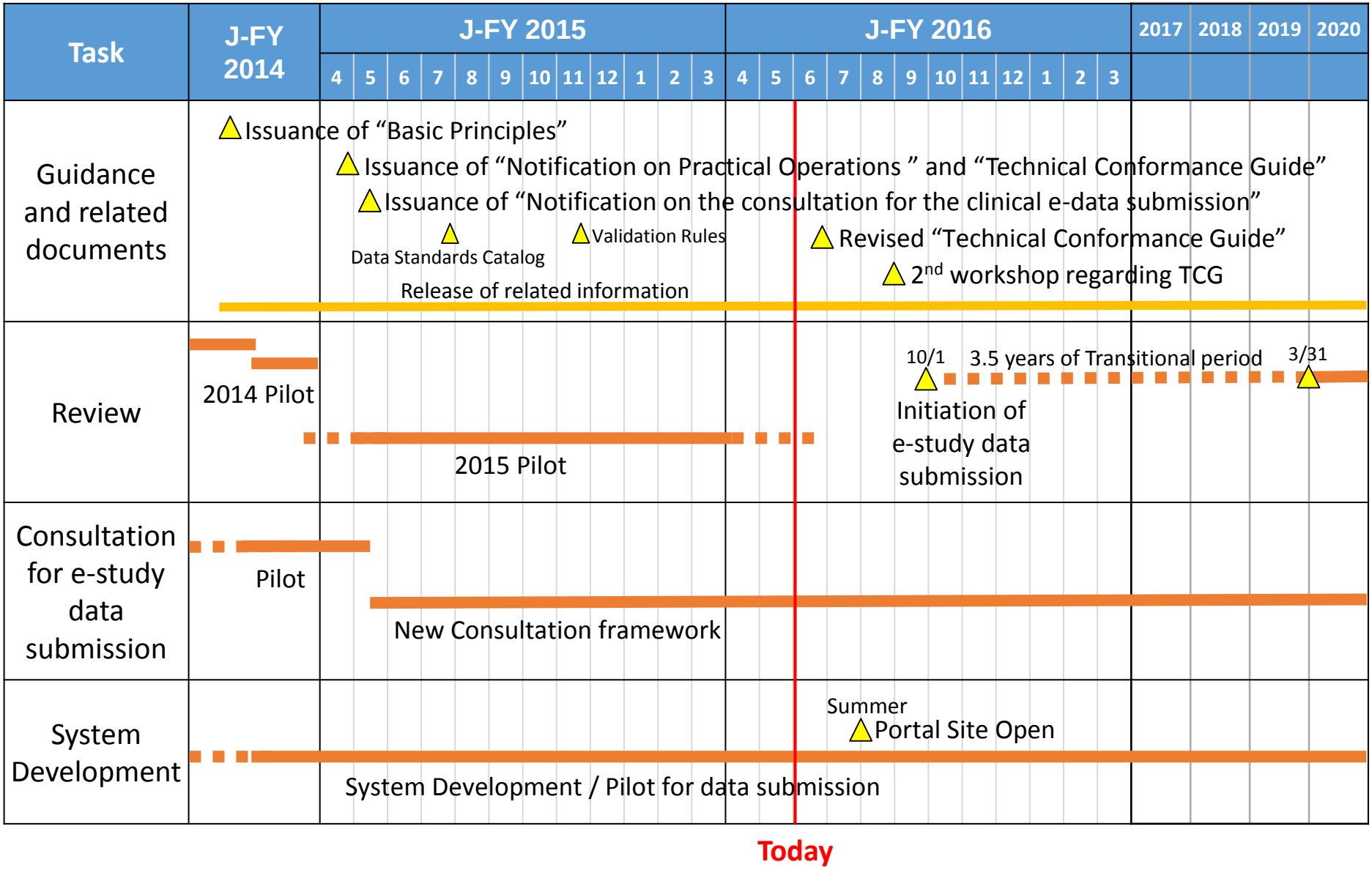
e.g. guidelines and disease models based on data on Asian population





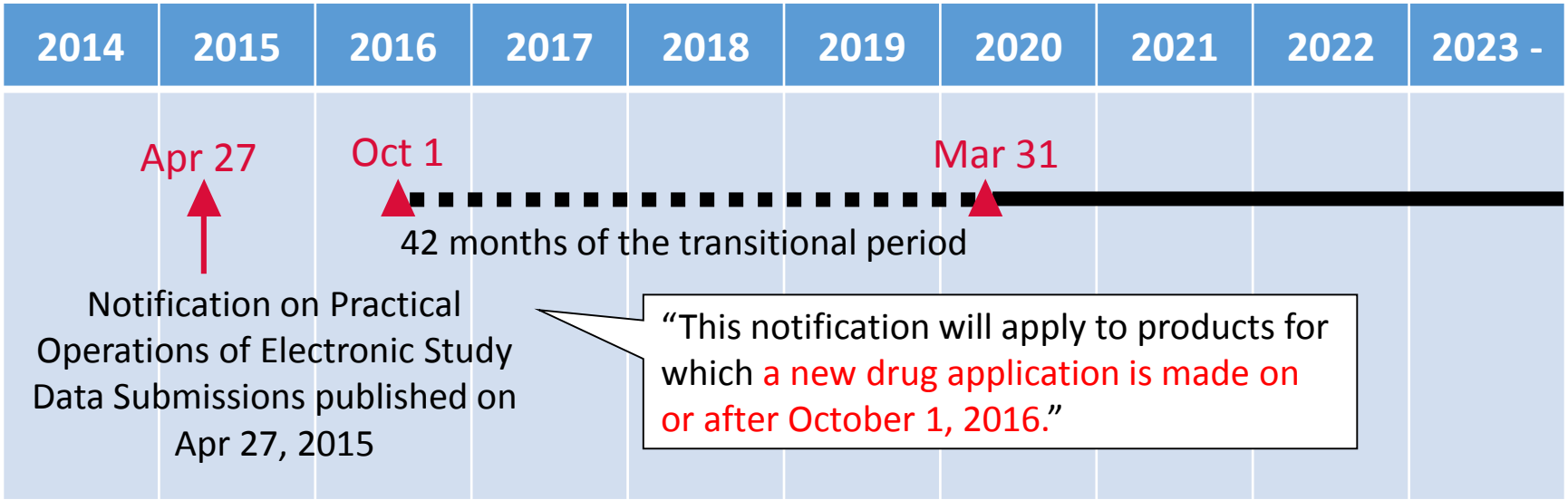


Timeline for implementation of electronic data submission



Initiation timing 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 period, applicants will be able to submit the data of at least one clinical trial included in their clinical data packages. (After the period, they need to submit the data of all the requested clinical trials.)



Notifications and Guide

- Basic Principles on Electronic Submission of Study Data for New Drug Applications
  - Published on June 20, 2014, by Ministry of Health, Labour and Welfare
  - The first official announcement that MHLW/PMDA will require electronic study data in NDA.
- Notification on Practical Operations of Electronic Study Data Submissions
  - Published on April 27, 2015, by Ministry of Health, Labour and Welfare
  - Practical issues
  - Start date of e-study data submission for NDA
- Technical Conformance Guide on Electronic Study Data Submissions
  - Published on April 27, 2015, by PMDA
  - Technical details
  - Possibility of updates based on the accumulated experience and/or the revisions of the data standards

Now we are working on the revision of Technical Conformance Guide

Electronic datasets to be submitted (CDISC)

- Datasets
  - SDTM datasets
  - ADaM datasets
- Definition files in Define-XML format
  - Define.xml for SDTM datasets
  - Define.xml for ADaM datasets with Analysis Results Metadata
- Programs
  - Analysis programs
  - Programs for creating ADaM datasets
- Annotated CRF
- Reviewer's Guide
  - Study Data Reviewer's Guide
  - Analysis Data Reviewer's Guide

Study/analysis types and submission formats

Section in notification of the Basic Principles	Content		Individual clinical study data	Analysis dataset	
				Concerning efficacy and safety analysis	Concerning PK or PK/PD analysis
2. (2) a	Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dosage and administration		SDTM	ADaM	ADaM
2. (2) b Note	For study results from phase I studies and clinical pharmacology studies, results from studies listed right are required to be electronically submitted.	Phase I studies of oncology drugs	SDTM	ADaM	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	ADaM	In principle, ADaM, but other formats may be acceptable in certain cases
		QT/QTc studies based on ICH E14 guideline	SDTM	ADaM	ADaM
2. (2) Note	Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA	Clinical studies where standard pharmacokinetic analysis was performed	SDTM	ADaM	ADaM is preferable, but other formats are acceptable
		Population analysis	May be submitted in formats other than CDISC standard		
		Physiologically-based pharmacokinetic model analysis			
2. (2)	References other than a and b, which were deemed necessary by PMDA		SDTM	ADaM	ADaM
			*If necessary, consult beforehand		
2. (2)	Integrated summary of safety and efficacy (ISS/ISE)		SDTM	ADaM	ADaM
			**In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset had been used for analysis, submission of SDTM study data is acceptable		

Q&A No.12 of Notification on Practical Operations

PMDA Data Standards Catalog

- PMDA Data Standards Catalog was published on Jul 30, 2015
- The list of acceptable versions
  - Data Exchange Standards (SAS Transport, SDTM, ADaM, Define, PDF)
  - Terminology Standards (CDISC CT, MedDRA, WHO DD Enhanced)
- Available on the PMDA website
  - http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.html
  - Both Japanese version and English version are included in one ZIP file.
- We will consider the beginnings and endings of support of the versions in consideration of the usage in Japan and other countries.
  - “Date support ends” will be noticed with sufficient margin.

Now we are considering the process to start accepting new version of standards (e.g. ADaM IG 1.1) and to stop accepting old version of standards.

CDISC validation in PMDA

- PMDA validation rules was published on Nov 18, 2015
- We plan to use Pinnacle 21 Enterprise for CDISC validation
  - Apply to SDTM, ADaM, CT, and Define-XML
  - PMDA validation rules are provided on the PMDA website for sponsor's use.
  - Sponsors should use the same validation rules and check the results in advance.
- Three levels of severity of the errors
  - Reject (a) Rules which, if violated, will cause the review to be suspended until corrections have been made
  - Error (b) Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made
  - Warning (c) Rules which, even when violated, will not necessarily require any explanation

Examples of rules categorized as (a) “Reject”

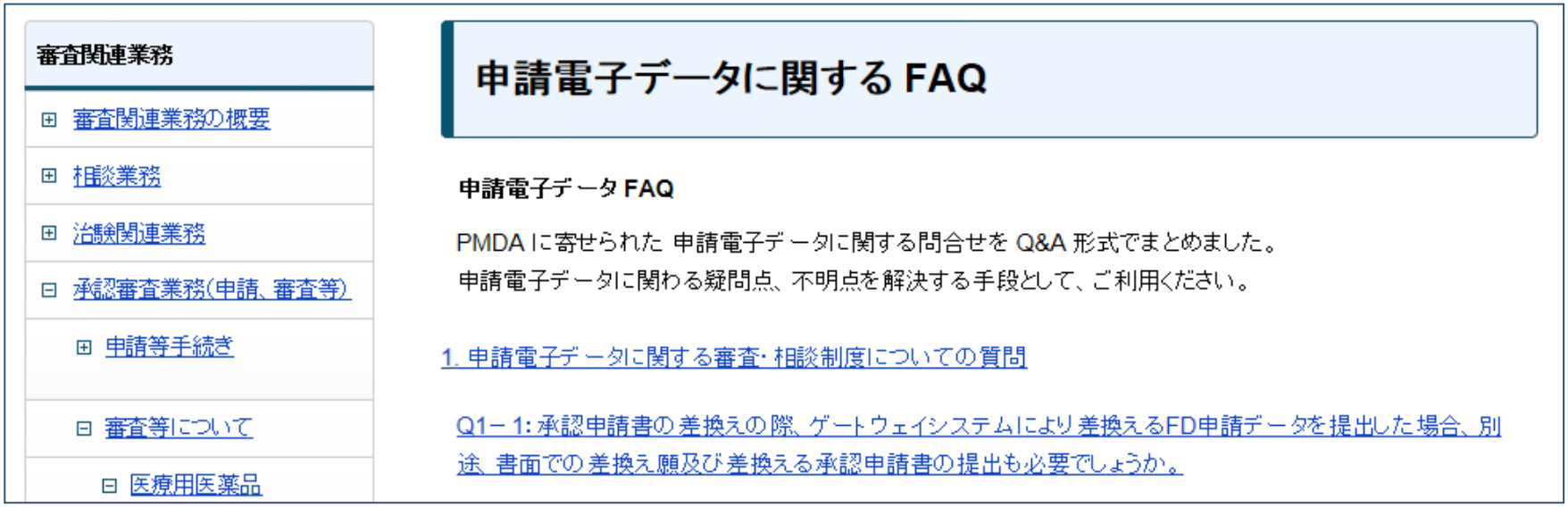
- SDTM
  - Conformity of specific variables to the non-extensible codelists (ex. AGEU, COUNTRY, IECAT, RELTYPE, SEX, NY, ND)
  - Existence of “Required” variables and the values
  - File format (xpt)
  - Existence of DM domain
  - All subjects are included in DM domain
  - Variables described in IG as inappropriate for usage must be not included
  - Variables designed only for SEND must be not included in the SDTM dataset
- ADaM
  - Existence of ADSL
  - --FL, --RFL, --PFL, ABLFL, ANLzzFL must have a value that is Y(/N) or Null
  - --FN, --RFN, --PFN, ABLFN, ANLzzFN must have a value that is 1(/0) or Null
  - Conformity of specific variables to the non-extensible codelists (ex. SEX, NY)
- Define-XML
  - Existence of specific information (ex. versions of IG)
  - Valid against CDISC Define-XML schemas

Because we will use the information in define.xml when we conduct CDISC validation, the validation rules of Define-XML are very important.

FAQ Home Page

- Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and guide
- Some of the Q&As may be included in the future update of Technical Conformance Guide.
- New FAQs will be released periodically.
- FAQs are provided only in Japanese. Sorry…

Now we are working on the revision of FAQs



Information and resources for industry

Notification/Guide/Workshop	Date
Basic Principles on Electronic Submission of Study Data for New Drug Applications + Q&A	Jun 20, 2014
Notification on Practical Operations of Electronic Study Data Submissions + Q&A	Apr 27, 2015
Technical Conformance Guide	Apr 27, 2015
Notification on the consultation for the clinical e-data submission	May 15, 2015
Briefings regarding Notification on Practical Operations	May 28, 2015 (Tokyo) Jun 3, 2015 (Osaka)
Data Standards Catalog	Jul 30, 2015
Workshop regarding Technical Conformance Guide	Sep 28, 2015
Validation Rules	Nov 18, 2015
FAQ Web Page	Nov 27, 2015
Portal Site Users Manual + Video	Mar 28, 2016

Information and resources for industry - Scheduled

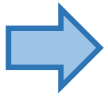
Notification/Guide/Workshop	Date
Revised Technical Conformance Guide	Jun 2016
FAQ (2nd release)	Jun 2016
Briefings regarding Portal Site	Jul 14, 2016
The 2nd Workshop regarding Technical Conformance Guide - Clinical Pharmacology data - CDISC standard data	Aug 31 and Sep 1, 2016

Overview of the pilot projects

	J-FY2013	J-FY2014-1	J-FY2014-2	J-FY2015
Purpose	Feasibility	Feasibility & utilization of study data in review process	Utilization of study data in review process	Utilization of study data for actual review
Target studies	5 drugs	CDISC: 4 drugs CP: 3 PPK datasets	CDISC: 3 drugs CP: 3 PPK/PD datasets	CDISC: 16 drugs CP: Standard Two-Stage Approach: 6 drugs Population Approach : 9 drugs PBPK: 2 drugs
Persons in charge	Around 80 reviewers + 20 from promotion group	Around 180 reviewers + 20 from promotion group	Around 190 reviewers + 20 from promotion group	Around 190 reviewers + 20 from promotion group (tentative)
Details	- All the reviewers try to reproduce the several analysis results in CTD	- All the reviewers try to replicate the main analysis results in CTD - Team meetings for the discussion on the review process with data analysis	- Some reviewers including biostatisticians in each review team are assigned mainly handle the data analysis - Team meetings for the discussion on the necessary analyses for the review and the review process with data analysis	- Pilot project which is almost parallel with actual new drug review - The pilot project will NOT affect the actual regulatory review of the drug Completed

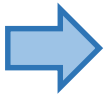
Experience based on the previous pilot projects

- Importance of standardized analysis datasets and the relationship to the results
  - Most reviewers review the submission materials (analysis results) first.
  - “Which dataset should be used for additional analysis for the results?”
- Importance of understanding the datasets and variables
  - “Which variable/records we should use?”
- Importance of CDISC conformity
  - The reviewers could use their experience of previous pilot data.
  - Using/understanding standardized variables make the review easier and faster, regardless of the software.



Request for
- ADaM datasets
- Analysis Results Metadata

Request for
- Annotated CRF
- Reviewer’s Guide (SDRG, ADRG)



- Establishment of validation rules and severity in PMDA
- Review of validation results

Experience based on the pilot project 2015

- Clinical trial data of 6/16 drugs were provided with actual New Drug Applications.
  - The reviewers experienced actual relationship between the review process and the time required for analyzing the data.
- Reviewers insisted the importance of Analysis Results Metadata.
  - We will strongly recommend to submit ARM.
- The relationship between the information included in define file and that in SDRG/ADRG should be discussed.
- As a result of trial implementation of validation, there were several errors categorized as “Reject”.
  - Because the data were prepared before the release of the PMDA validation rules.
  - Please review the data and the define file carefully before data submission.

Expected analyses in review teams

Common analyses to many clinical trials

- Distribution of patient demographics
- Changes in laboratory data
- Adverse events rates

STAT MEDICAL OTHERS

Software: JMP Clinical, etc.
Datasets: SDTM

General analyses for efficacy and safety data

- Simple analyses depending on the characteristics of evaluation variables – continuous/categorical/time-to-event)

STAT MEDICAL OTHERS

Software: JMP, etc.
Datasets: ADaM

Relatively complicated analyses

- Analyses with programing (innovative/complicated analyses)
- Simulations

STAT MEDICAL OTHERS

Software: SAS, etc.
Datasets: SDTM, ADaM

Future implementation of CDISC in Japan

- Therapeutic Area Standards
  - PMDA, JPMA and medical societies have decided to review TA standards in cooperation.
- SEND
  - Submission of non-clinical studies (toxicological studies) has been included in the scope of Advanced Review with Electronic Data.
  - We are discussing on practical issues and the timeline.
- Use of data standards for various data
  - Post approval clinical study/investigation, disease registry system
  - Regulatory Science Initiative by MHLW and future establishment of Regulatory Science Center in PMDA

Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - The Basic Principles, Notification on Practical Operations, Technical Conformance Guide, PMDA Data Standards Catalog, and PMDA Validation Rules have been published.
- Our experiences of reviewing and analyzing study data have been increased through the pilot projects.
  - The experiences were reflected in the Notification on Practical Operations and Technical Conformance Guide.
  - Accumulated experiences will be reflected in the future Technical Conformance Guide and FAQs.
- Effective utilization of submitted electronic data lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.

Thank you for your attention!

- PMDA Advanced Review with Electronic Data Promotion Group HP
  - http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html
- Secretariat of PMDA Advanced Review with Electronic Data Promotion Group
  - E-mail: jisedaiPT@pmda.go.jp

References

- Basic Principles on Electronic Submission of Study Data for New Drug Applications
  - Japanese: http://www.pmda.go.jp/files/000159962.pdf
  - English: http://www.pmda.go.jp/files/000160019.pdf
- Notification on Practical Operations of Electronic Study Data Submissions
  - Japanese: http://www.pmda.go.jp/files/000204726.pdf
  - English: https://www.pmda.go.jp/files/000206451.pdf
- Technical Conformance Guide on Electronic Study Data Submissions
  - Japanese: http://www.pmda.go.jp/files/000204728.pdf
  - English: https://www.pmda.go.jp/files/000206449.pdf
- PMDA Data Standards Catalog (Japanese and English)
  - https://www.pmda.go.jp/files/000206482.zip