Advanced Review with Electronic Data and CDISC Implementation in PMDA

Yuki Ando

Senior Scientist for Biostatistics

Advanced Review with Electronic Data Promotion Group

Pharmaceuticals and Medical Devices Agency (PMDA)

Outline

- Outline of Advanced Review with Electronic Data in PMDA
- Notifications and Guide
- PMDA Data Standards Catalog
- CDISC validation in PMDA
- Pilot projects for utilization of electronic data
- Summary

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

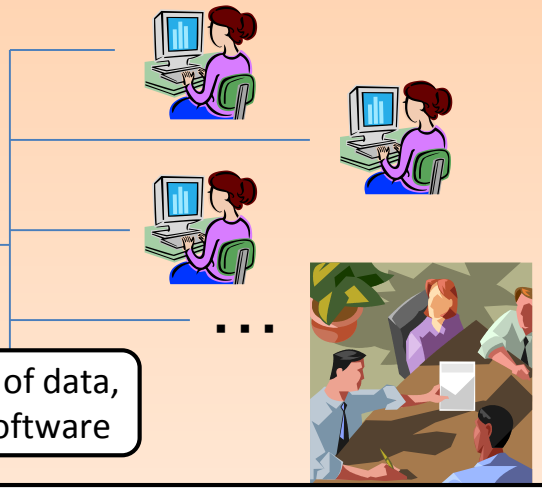
Storage of electronic data in the dedicated server and registration in the database

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

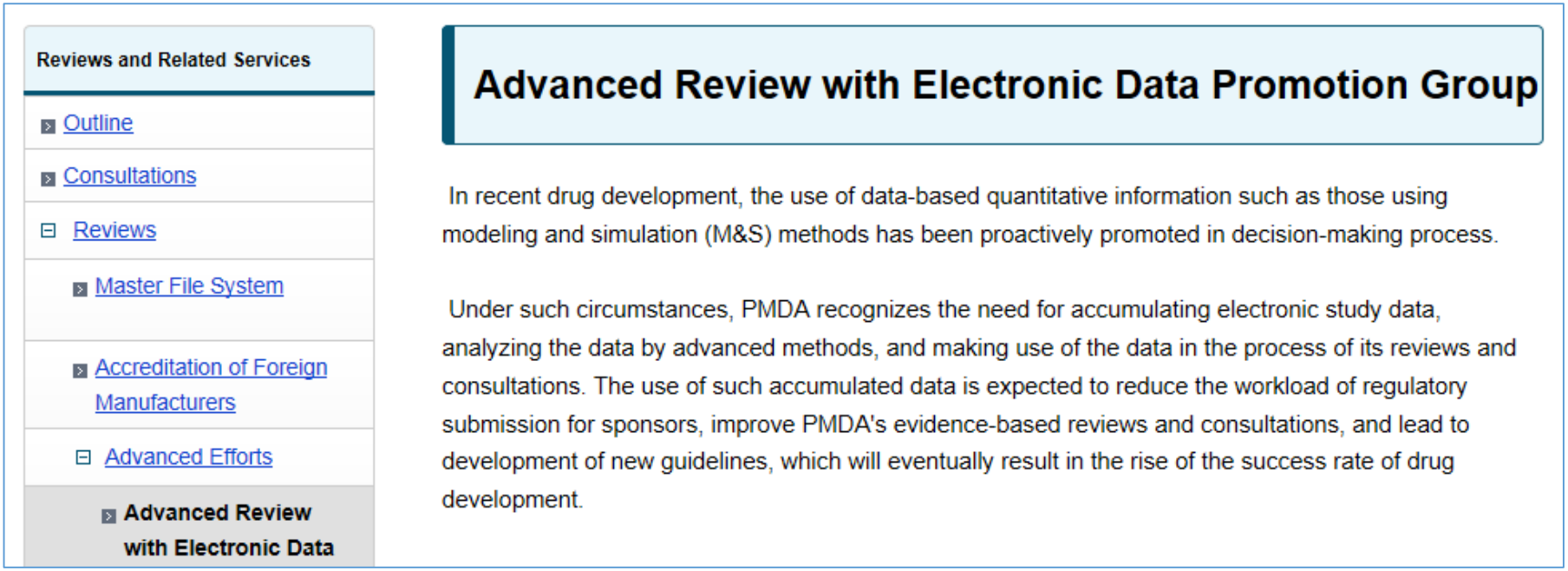
- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

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

Task force for advanced review/consultation

- On April 1st, 2014, "Advanced Review with Electronic Data Promotion Group" was established in PMDA from its precedent tentative group which was setup on Sept 1st, 2013.



http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

Prospect of e-Study data utilization in Japan

Prospect As of June 2015
(Subject to Change)

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

*NDA=New Drug Application

Transitional period are taken until March 31st, 2020

- 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

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

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

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

First-class review authority

Present
J-FY2015

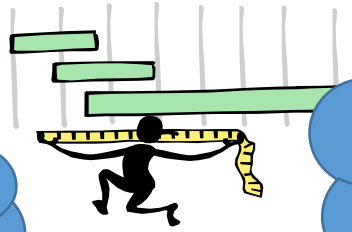
J-FY2016

Setup e-data management and utilization

Promotion of paperless operation

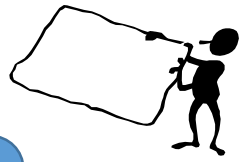
J-FY2018

Ordinary utilization of e-data in the product review



J-FY2019 - 2021

Starting earnest cross-product analysis

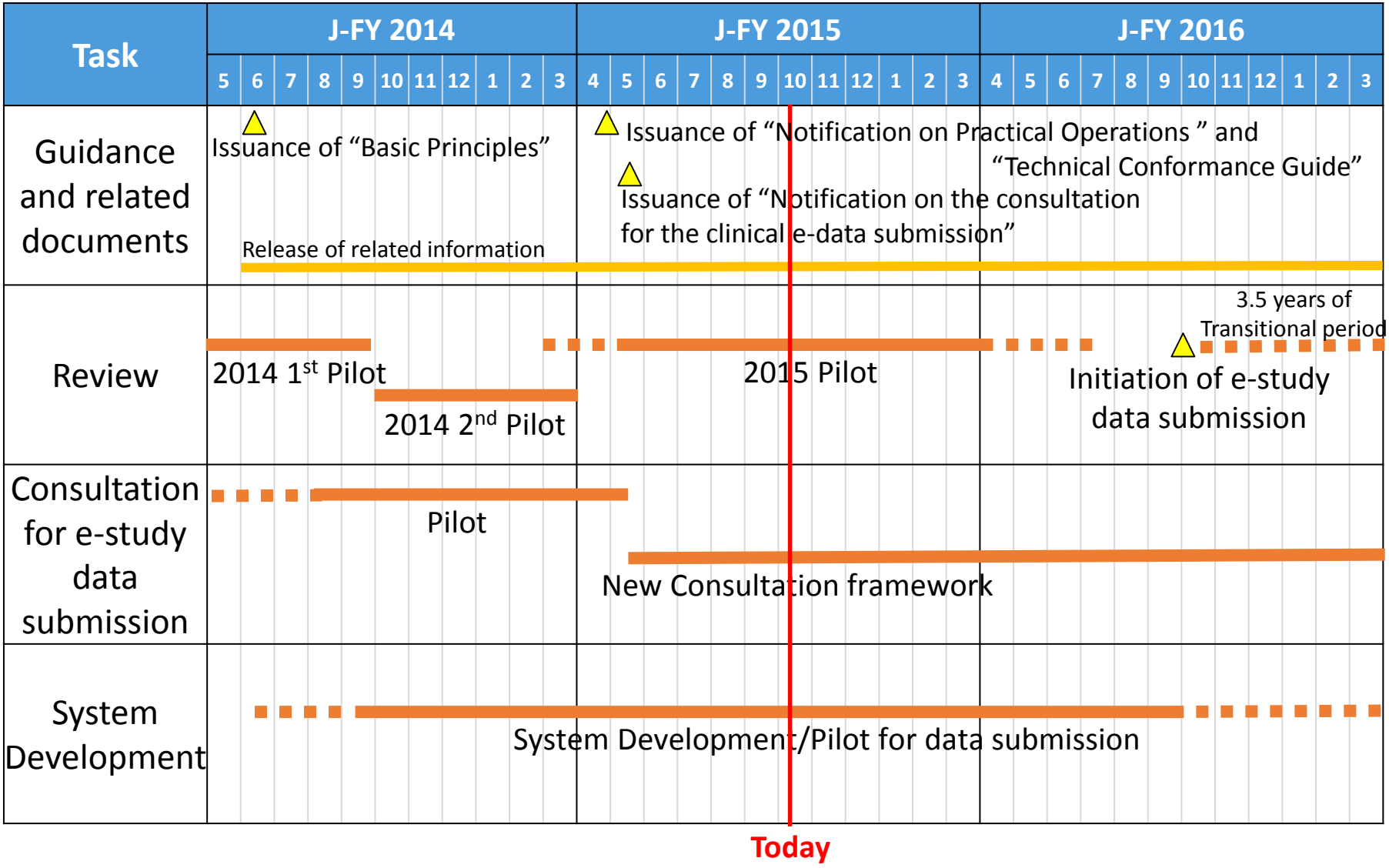


J-FY2022 -

Publication of guidelines to contribute to drug development

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

Timeline for implementation of electronic data submission



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

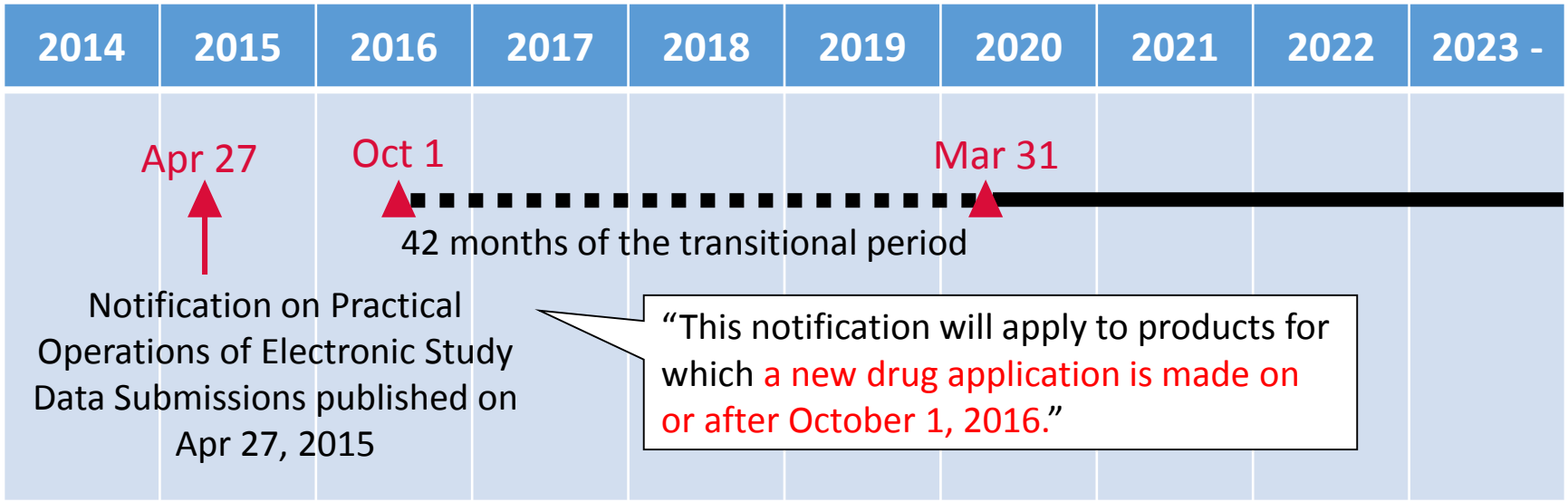
- Technical Conformance Guide on Electronic Study Data Submissions
  - Published on April 27, 2015, by PMDA
  - Technical details
  - Possibility of updates based on the accumulated experience and/or the revisions of the data standards

Major contents of the Practical Operations

- Clinical trial data subject to electronic submission
  - Subject products, trials, data, ISS/ISE
  - Data submission for supplemental NDA (including application for partial changes)
- Format and method of electronic data submission
  - Use of Gateway, process of submission, validation for CDISC data
  - Relationship of electronic data submission and eCTD
- Details on the electronic datasets to be submitted
  - Data that conforms to the CDISC standards and programs
  - Data and programs for clinical pharmacology study/analysis
- Process of consultations concerning electronic data
- Initiation timing of submission of study data and interim measure
  - Initiation date: 1st October, 2016
  - Transitional period: until 31st March, 2020

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.



Major contents of the Technical Conformance Guide

- System requirements for the submission of electronic study data
- Submission of electronic data
  - Process, use of portal site, file size, folder structure, validation of the study data
- Electronic study data to be submitted (details)
  - CDISC-conformant electronic study data and relevant documents
    - SDTM, ADaM, Define-XML, Results Metadata, Annotated CRF, Reviewer's Guides, etc., and points to be considered
    - Handling datasets with Japanese characters
    - Versions of standards
    - Submission of programs
  - Electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses
    - Directions for clinical pharmacology data package
    - Submission data details by analysis type
- Relationship between the electronic study data and eCTD

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
- Programs
  - Analysis programs
  - Programs for creating ADaM datasets
- Annotated CRF
- Reviewer's Guide
  - Study Data Reviewer's Guide
  - Analysis Data Reviewer's Guide

Final work packages of Study Data Reviewer's Guide and Analysis Data Reviewer's Guide by **PhUSE** are mentioned as references in PMDA's Technical Conformance 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

- The lists that were mentioned as "… and the list of acceptable versions is available on the PMDA's website (http://www.pmda.go.jp/)" in the Notification on Practical Operations
  - Data Exchange Standards
  - Terminology Standards
- Now you can download PMDA Data Standards Catalog.
  - 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.

PMDA Data Standards Catalog – 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	1.4	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	1.0	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		
Documents	PDF	1.4-1.7	-	PDF	2016-10-01		In principle, eCTD PDF specification should be referenced for details.

PMDA Data Standards Catalog – Terminology Standards

Terminology Standard	Version(s)	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
CDISC Controlled Terminology	2009-02-17 or later	2016-10-01		
MedDRA	8.0 or later	2016-10-01		
WHO Drug Dictionary Enhanced	2008:3 (2008-12-01) or later	2016-10-01		

- 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.

CDISC validation in PMDA

- We plan to use OpenCDISC Enterprise for CDISC validation
  - Apply to SDTM, ADaM, CT, and Define-XML
  - PMDA validation rules will be provided 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)

- 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 must have a value that is Y(/N) or Null
  - --FN, --RFN, --PFN 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

Tentative
Still under discussion

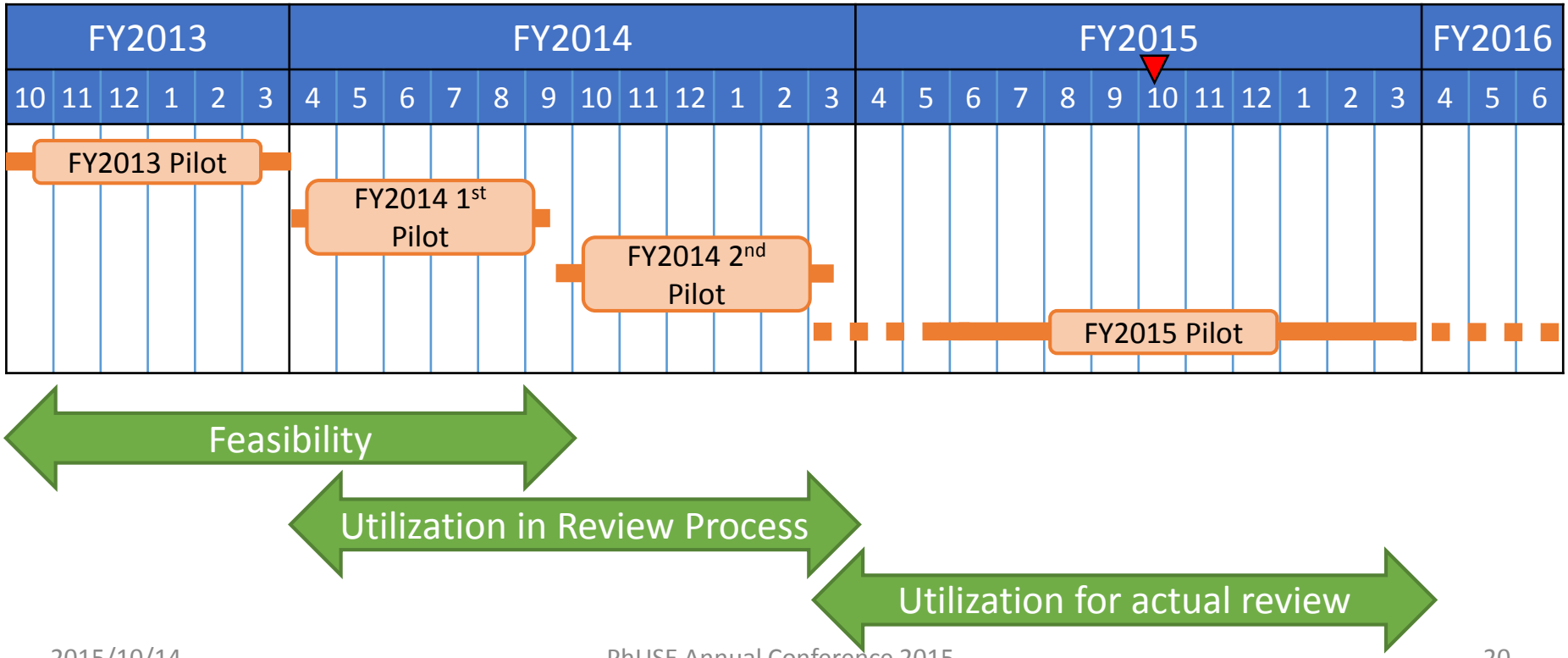
Information and resources for industry

Notification/Guide/Workshop	Date
Basic Principles on Electronic Submission of Study Data for New Drug Applications	Jun 20, 2014
Question and Answer Guide regarding “Basic Principles on Electronic Submission of Study Data for New Drug Applications”	Jun 20, 2014
Notification on Practical Operations of Electronic Study Data Submissions	Apr 27, 2015
Question and Answer Guide regarding “Notification on Practical Operations of Electronic Study Data Submissions”	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	Autumn, 2015
Portal Site Users Manual	J-FY2015
FAQ Web Page	J-FY2015
Revised Technical Conformance Guide	J-FY2016

Scheduled

Pilot projects for utilization of electronic data

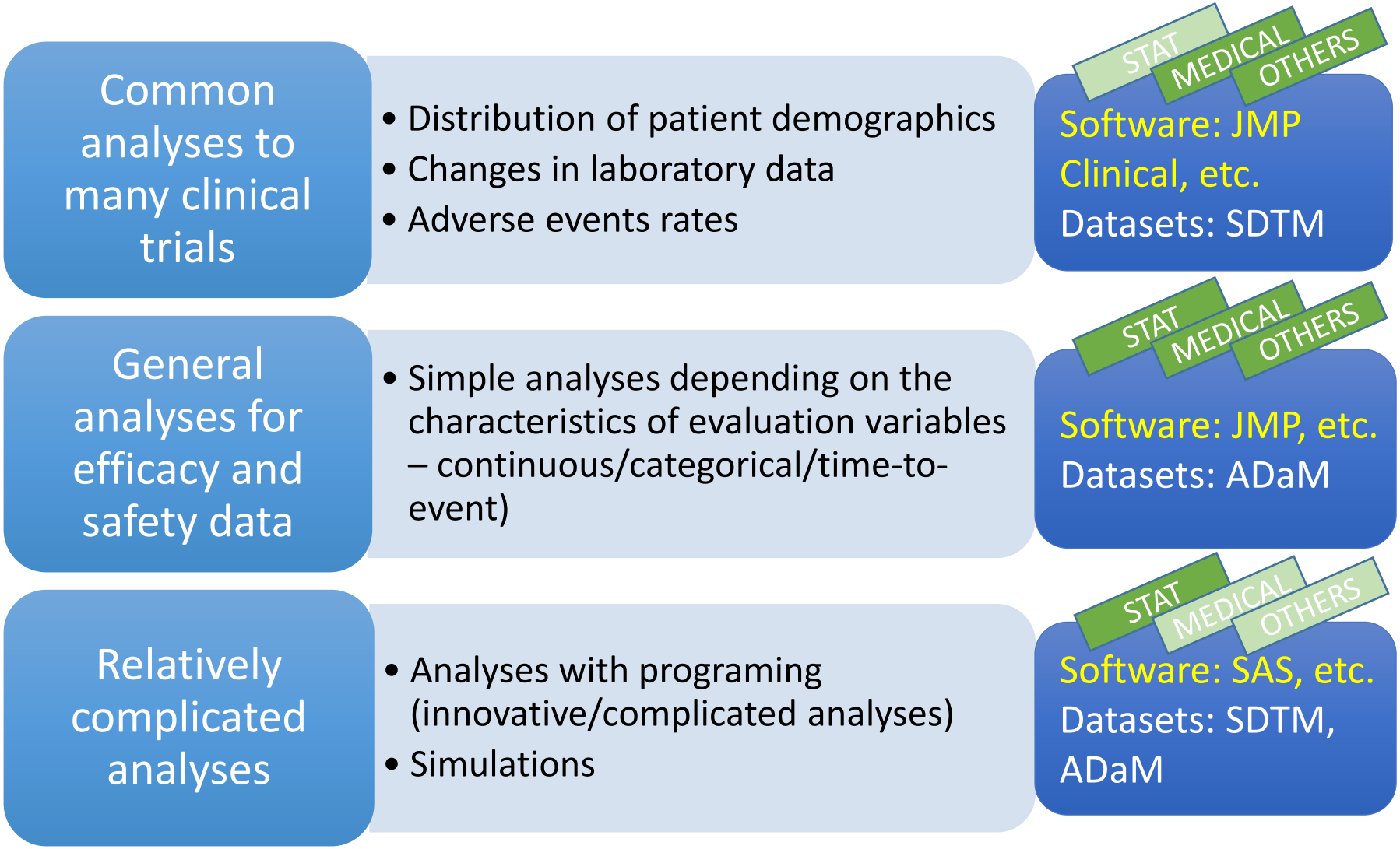
- Step-by-step implementation of pilot projects
  - Confirmation of feasibility
  - Consideration of data utilization in the review process
  - Pilot intended for actual new drug review



Overview of the pilot projects

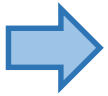
	J-FY2013	J-FY2014-1	J-FY2014-2	J-FY2015
Purpose	Feasibility	Feasibility & utilization of study data in review process	Utilization of study data in review process	Utilization of study data for actual review
Target studies	5 drugs	CDISC: 4 drugs CP: 3 PPK datasets	CDISC: 3 drugs CP: 3 PPK/PD datasets	CDISC: 14drugs CP: Standard Two-Stage Approach: 4 drugs Population Approach : 7 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 Now in Progress

Expected analyses in review teams



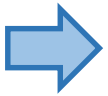
Experience based on the pilot projects

- 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

Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - The Basic Principles, Notification on Practical Operations, and Technical Conformance Guide, and PMDA Data Standards Catalog 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.
- Compliance with CDISC and quality of the submitted electronic data will be the key in future review process, and we would like to have active discussion about practical issues of data submission with industry.
- 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