Technical Guide for Electronic Data Submission in Japan

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Strength *through Collaboration*

Outline

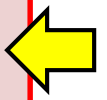
- Contents of Notification and Guide for Industry
  - Data Validation
  - Datasets to be submitted
  - Appended documents
  - Other points to be considered
- Pilot Project in J-FY 2015
- Summary

Notifications and Guide Released for Industry

- **The most recent notification and guide provide practical procedures and technical information** regarding submissions of e-study data for new drug applications.

Focus of today's presentation

Notifications/Guide	Release Date	Issuer	Overview
Basic Principles on Electronic Submission of Study Data for New Drug Applications ("Basic Principles")	June 20, 2014	Ministry of Health, Labour and Welfare	• The first official announcement that MHLW/PMDA will require electronic study data in NDA. • Both of Japanese and English versions are available on PMDA website
Technical Notification on the e-data submission* ("Technical Notification")	April 27, 2015	Ministry of Health, Labour and Welfare	• Explains practical issues regarding the introduction of electronic submissions of study data for new drug applications • States the start date of e-study data submission for NDA
Technical Conformance Guide* ("Technical Guide")	April 27, 2015	PMDA	• Explains technical details regarding e-study data submission • Subject to updates based on the accumulated experience and/or the revisions of the data standards



* An English version is under preparation.

“Technical Notification”: Major Contents

- “Technical Notification on the e-study data submission” mainly covers the following contents;

1. Handling of clinical study data subject to e-study data submission
2. Format and method of e-study data submission ⟸
3. Electronic datasets to be submitted ⟸
4. Process of consultations concerning e-study data
5. Initiation timing of submissions of e-study data and transitional period

Highlights of each content will be explained in the following slides, in combination with the contents of “Technical Guide”

“Technical Guide”: Major Contents

- “Technical Conformance Guide” explains the further technical details of “Technical Notification” and mainly covers the following contents;
  1. System requirements necessary for the e-study data submission of application data
     - Basic system requirements, recommended environment, obtaining portal site account
  2. Electronic Submission of the application data
     - Process of submission, use of portal site, file size, folder structure, validation of CDISC data
  3. Electronic application data to be submitted
     - Details of datasets subject to electronic submission(CDISC compliant data and programs), Data and programs for clinical pharmacology study/analysis
  4. Relationship between the electronic application data and eCTD
     - Submission details of eCTD

Data Validation

“Technical Notification”: 2
Format and Method of e-study Data Submission

- **Data Validation:**
  - PMDA will perform the validation of all submitted electronic data, including the adherence to the CDISC standard using a tool known as the Open CDISC Enterprise.
  - During the validation process, if PMDA identifies a major error that affects the decision on acceptance of the submitted data and no prior consultation or explanation was provided regarding this error, PMDA will immediately inform the applicant of this error. The application review will not be initiated until such errors are corrected.

"Technical Guide": 3.6 Validation of the Electronic Data

- **Validation of CDISC-conformant data:**
  - The PMDA will perform validation of CDISC-conformant data using OpenCDISC Enterprise.

  Validation Rules
  - Validation rules direct next actions based on the severity of errors/violation identified during the validation process and those actions can be categorized as below:
    a) If violated, the review will be suspended until corrections have been made (Reject rule) -- applied to very basic errors such as the absence of necessary datasets for each clinical study.
    b) If violated without any prior explanation, the review will be suspended until corrections have been made.
    c) Violations will not necessarily require any explanation.

“Technical Notification”: 3. Electronic Datasets To Be Submitted(1/2)

- The following datasets and files that conform to the CDISC standards are to be submitted.

Documents/Datasets/Files	Details
SDTM dataset	• SDTM datasets should be submitted after storing the data collected from the CRFs in each domain (where possible) based on the variables designated by the corresponding SDTM and SDTM IG.
ADaM dataset (used for main analyses)	• The datasets to be submitted must have been composed in accordance with ADaM and ADaM IG. • When submitting the electronic data of an integrated analysis (ISS/ISE), the analysis dataset based on ADaM must be submitted (unless an SDTM dataset was used for the analysis)
SDTM and ADaM data definition	• The definitions of variables in SDTM and ADaM datasets (hereinafter referred to as metadata) must be respectively summarized according to the CDISC-specified Define-XML format and submitted together with the style sheet.
Annotated CRF (As an attachment to the dataset)	• An annotated CRF must be submitted demonstrating the relationship between each item of data collected from the CRF and variables included in the dataset and data guide.
Data guide (As an attachment to the dataset)	• The data guide should include an explanation of the points that should be made clear during the review, such as the conformity degree to the CDISC standards (validation results), and particularly the points that do not affect the acceptance of the data but may become a problem when trying to use the data.

"Technical Notification": 3. Electronic Datasets To Be Submitted(2/2)

- **Submission of Programs:**
  - Programs used to create the ADaM dataset and analysis programs must be submitted in order for PMDA to understand the process in which the dataset was created and analyzed.
- **Recommended Controlled Terminology, Code Lists, and Units:**
  - Data may be coded using acceptable codes listed on the PMDA's website (http://www.pmda.go.jp /) .
  - WHO Drug Dictionaries Drug Code (WHO DDs) must be used when coding drugs.
  - Constructing a dataset using common terminology defined by the applicant is acceptable in unavoidable circumstances.
  - The use of SI units is recommended.
- **Versions of CDISC standards:**
  - Several versions of various standards may be used to create the datasets, and the list of acceptable versions is available on the PMDA's website. It is advisable to use the latest version when preparing the data.

“Technical Guide”: 4.1.1. Datasets to be submitted (1/3)

- **SDTM datasets:**
  - The SDTM dataset is to be submitted, basically, after the data collected from the CRF and other records are stored into the domain designated by variables designated by the version of SDTM and SDTM IG.
  - The applicant may manage the clinical study data using their own unique format that includes SDTM, but even in such cases, the dataset to be submitted must be converted into formats that are in accordance with SDTM and SDTM IG.

"Technical Guide": 4.1.1. Datasets to be submitted (2/3)

- **ADaM datasets:**
  - The analysis dataset should be submitted in accordance with ADaM in the CDISC standards.
  - It is not necessary to submit ADaM datasets for all analyses described in the analysis plan.
  - ADaM datasets should be submitted for analyses performed for…
    - Important results on efficacy and safety and study results that provide the rationales for dosage and administration
      - Primary efficacy analyses
      - Secondary efficacy analyses
      - Primary safety analyses
      - Basic analyses of adverse events
      - Analyses to investigate the effect of major factors on efficacy and safety

“Technical Guide”: 4.1.1. Datasets to be submitted (3/3)

- **File formats of datasets:**
  - The SDTM and ADaM datasets that conform to the CDISC standards should be submitted in the SAS XPORT file transport format Version, which is the data transport format released by the SAS Institute, and as one file per dataset.

Appended Documents

“Technical Guide”: 4.1.2. Definition documents and other appended documents of datasets (1/3)

- **Definition documents of datasets:**
  - The definition documents of the SDTM and ADaM datasets in the Define-XML format of CDISC should respectively be summarized into the XML format files containing references to the style sheets that enable their contents to be displayed and stored in the submission folder together with these style sheets prior to submission.
  - The file name of the definition document should be “define.xml.”
  - The definition document should include the definitions of datasets, variables, possible values of variables, and controlled terminologies and codes. The information on controlled terminologies and dictionaries should include their versions.

"Technical Guide": 4.1.2. Definition documents and other appended documents of datasets (2/3)

- **Annotated CRF:**
  - The Annotated CRF shows the link between each item of data collected from the CRF and the variables included in the dataset.
  - For the method of annotating, refer to the SDTM Metadata Submission Guideline (SDTM-MSG) by CDISC.
  - The file format of the Annotated CRF, in principle, should be a PDF, as specified in the eCTD notification and the notification on handling of eCTD, and the file name should be "acrf.pdf." In principle, it should be stored in the same folder as SDTM datasets.

Appended Documents

“Technical Guide”: 4.1.2. Definition documents and other appended documents of datasets (3/3)

- **Data guide:**
  - To promote the understanding of the content and characteristics of the dataset by reviewers during the review and enable the applicant to explain about the utilization status of and adherence to the data standards when creating the datasets, a dataset definition document as well as a data guide must be created for each of the SDTM and ADaM datasets, which, in principle, should be stored in the same folder as their corresponding dataset.

  - Each document, in principle, should be created as a PDF as specified in the eCTD notification and the notification on handling of eCTD, and the files for SDTM and ADaM should preferably be named “study-data-reviewers-guide.pdf” and “analysis-data-reviewers-guide.pdf,” respectively. The data guide may be written in Japanese.

“Technical Guide”: 4.1.3. Version of standards

- **Version of standards to be used:**
  - When creating the dataset and the definition document conforming to the CDISC standards, refer to the PMDA’s website (http://www.pmda.go.jp/) for versions of the CDISC standards, controlled terminologies, and dictionaries that are accepted by the PMDA.
  - It is acceptable to use different versions within the same application, but the same version must be used within the same clinical study.
  - If the applicant had referred to other versions for certain domains within the same clinical study, the version used and the reason for using that version must be explained in the data guide.
  - Datasets of integrated analyses of multiple clinical studies should be created using the same version, even if the version used to create the dataset of each clinical study was different.

“Technical Guide”: 4.1.4. Therapeutic Area Standards

- **Therapeutic area standards:**
  - These standards may be used for diseases for which standards have already been published. However, the standards used must be provided in the definition document of the dataset and the data guide.

Japanese Text

“Technical Guide”: 4.1.5. Handling of data in Japanese Text

- **Handling of data written in Japanese text:**
  - If variables had been collected in Japanese and there is a risk of losing certain information by translating it into English, as long as the descriptions in Japanese are necessary and appropriate, data written in Japanese may be submitted.
  - Examples of variables that may contain Japanese texts are shown in “Technical Guide” (but are not limited to these).
  - The method of storing Japanese data into datasets and the method of submission when a domain contains Japanese items, in principle, will be shown in “Technical Guide” .

“Technical Guide”: 4.1.6. Submission of programs

- **Programs to be submitted:**
  - With respect to the programs related to the electronic application data conforming to the CDISC standards, the programs used to create the ADaM dataset and programs used for analyses must be submitted.
  - The main purposes of requesting the submission of these programs are to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not absolutely necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment.

“Technical Notification”: Q&A12 Required format of the datasets

Types and Submission Formats of Documents Subject to Electronic Submission

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		

Information and Resources for Industry

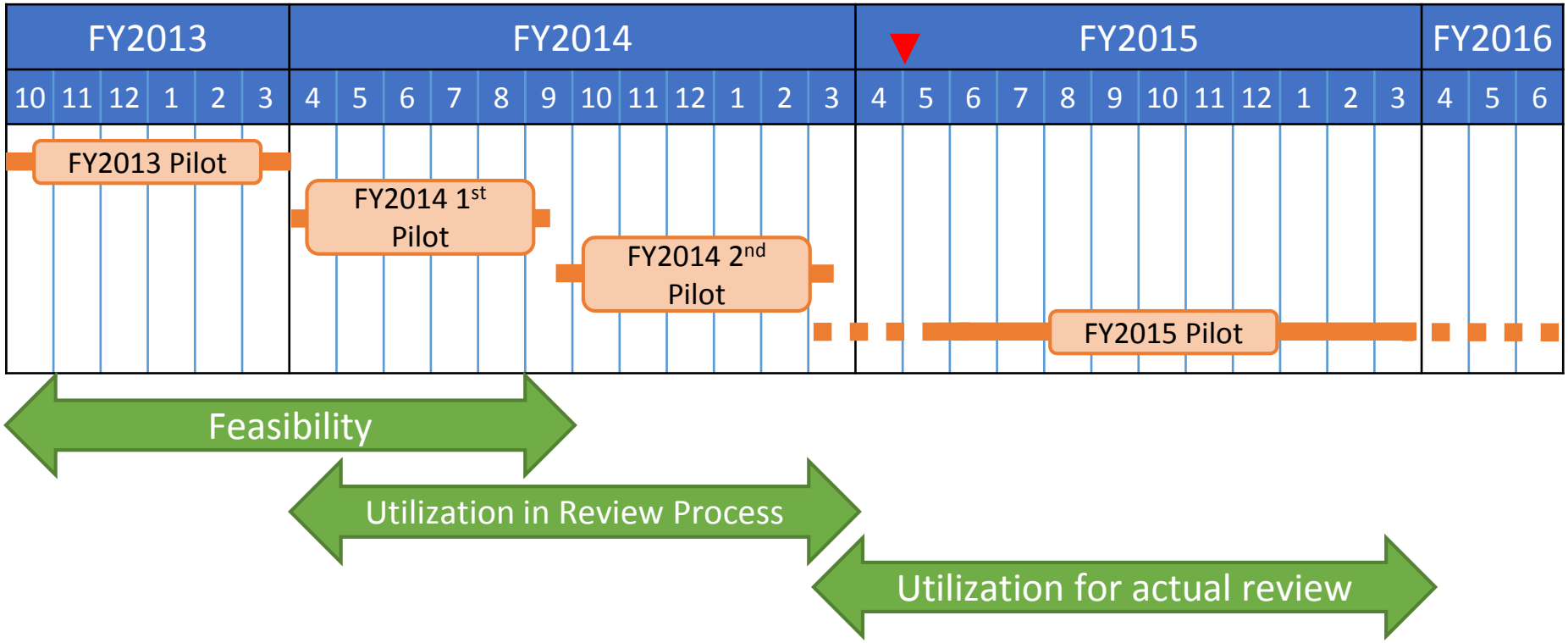
	Notification/Guide/Workshop	Category	Date
1	Basic Principles on Electronic Submission of Study Data for New Drug Applications	Notification	June 20, 2014
2	Question and Answer Guide Regarding “Basic Principles on Electronic Submission of Study Data for New Drug Applications”	Notification	June 20, 2014
3	Technical Notification on the e-study data submission	Notification	April 27, 2015
4	Question and Answer Guide Regarding “Technical Notification on the e-study data submission”	Notification	April 27, 2015
5	Technical Conformance Guide	Guide	April 27, 2015
6	Notification on the consultation for the clinical e-data submission		
7	Briefings Regarding Technical Notification		June 3,)
8	Data Catalog	Guide	July, 2015
9	Validation Rule	Guide	Autumn, 2015
10	Workshop Regarding Technical Conformance Guide	Workshop	Sep, 2015
11	Portal Site Users Manual	Guide	J-FY2015
12	FAQ Web Page	Guide	J-FY2015
13	Revised Technical Conformance Guide	Guide	J-FY2016

Technical details about CDISC standard will be covered.

Scheduled

Pilot projects for utilization of electronic data

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



Overview of the Pilot Projects

Now in Progress

	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: 13drugs CP: Standard Two-Stage Approach: 4 datasets Population Approach : 7 datasets (As of May 29,2015)
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

J-FY2015 Pilot Project

- **The last pilot project before the initiation of e-study data submission**
- Purpose:
  - To confirm that the analysis of the submitted clinical study data for new drugs using introduced software enables the reviewers to obtain the necessary for the review
  - To consider the utilization of the analysis results in the new drug review process in the actual review situation
- Two types of target studies:
  - The pilot conducted using e-study data under the actual situation of regulatory review of new drug application
  - The pilot conducted using e-study data (without considering actual new drug submission)
- **More than ten companies have already applied** for the pilot project.

Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - The Basic Principles, Technical Notification, and Technical Guide have been published.
- Our experiences of reviewing and analyzing electronic study data have been increased through the pilot projects
  - The experiences were reflected in the Technical Notification and Technical Guide.
- Effective utilization of submitted electronic data lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.
- We greatly appreciate your understanding and cooperation.

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

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