Electronic Study Data Submission for New Drug Application in Japan

Ken Sakushima (PMDA, FDA/CDER/OSP*), Hiroshi Sakaguchi (PMDA), TJ Chen (FDA/CDER/OSP)

PMDA: Pharmaceuticals and Medical Devices Agency, FDA: U.S. Food & Drug Administration, * Oak Ridge Institution for Science and Education (ORISE) Fellow

Background

Pharmaceuticals and Medical Devices Agency (PMDA) started receiving CDISC electronic clinical study data (e-data) through PMDA's gateway system for NDA in Japan since Oct 2016.

- Standardized electronic submission is voluntary until March 2020, will be mandatory from April 2020.
- PMDA published notifications, technical conformance guide, validation rules, and data standard catalog.
- PMDA provides consultation services for applicants regarding e-data preparation.

Summary

- PMDA pilot project
  - Data Store and Management & Feasibility of Analyses incl. PPK/PD
- Characteristics of PMDA's requirements & recommendations
  - CDISC Standards, Validation Rules, ARM, and Programs
- Difference between FDA and PMDA
  - SEND requirement, Regulatory clock (Deadlines), and SI unit

Efficient utilization of e-data will benefit the public through the enhancement of drug development and predictability of safety and efficacy of the drug.

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

PMDA Pilot Project (2013-2015)

A total of 4 pilots with SDTM dataset ± ADaM dataset (incl. like) and PPK/PD dataset

(*Numbers refer to year-suffix, products for SDTM dataset ± ADaM dataset – products for PPK/PD dataset)

*2013 (5-0)

Submitted data store and management with in-house system
→**Confirmed**
Analysis of the stored data by reviewer with introduced software
→**Skilled reviewers were able to conduct**

*2014-1 (4-3)

Analysis to obtain the necessary for the review using submitted data
→**Succeeded in reproduce the result in CTD**
Population pharmacokinetic data store and management with in-house system
→**Confirmed**

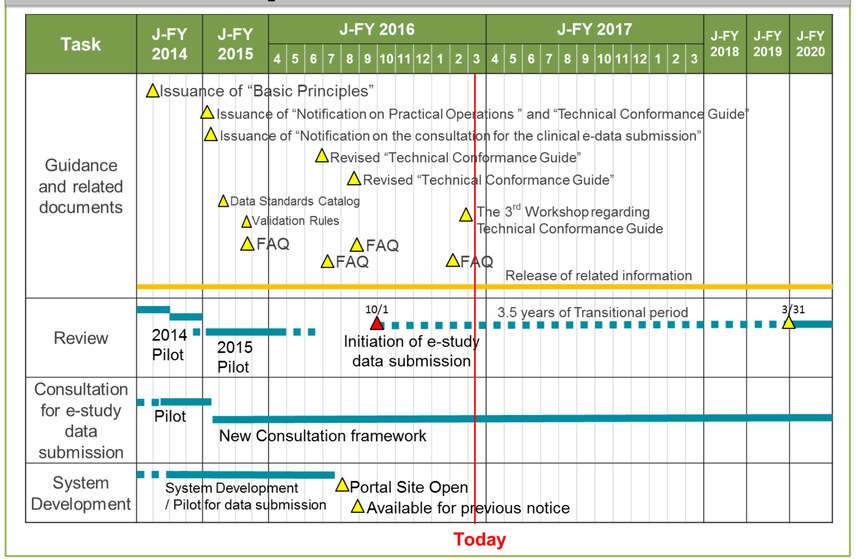
*2014-2 (3-3)

Analysis to obtain the necessary for the review using submitted data
→**Skilled reviewers were able to conduct**
Utilization of submitted data for PPK/PD analyses
→**Skilled reviewers were able to conduct**

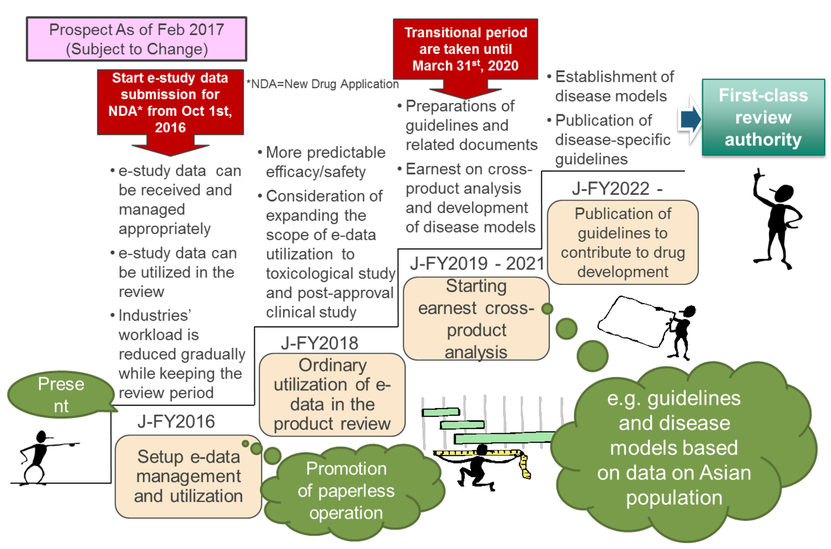
*2015 (14-7)

Analysis to obtain the necessary for the review using submitted data in the actual review situation
→**Conducted by most reviewers**
Utilization of submitted data for conformity inspection
→**Progressed the feasible procedures**

Timeline for Implementation of e-data Submission



Prospect of e-Study data Utilization in Japan



PMDA's Characteristics & Difference between FDA and PMDA

Characteristics of PMDA's requirements & recommendations

General

- CDISC Standards
- Data Standards Catalog
- New Drugs (Incl. Biologics)

Validation Rules

- CDISC validation of e-data for acceptance
- PMDA will perform validation using Pinnacle 21 Enterprise

ARM

- Define.xml for ADaM datasets preferably includes Analysis results metadata (ARM)

Programs

- Programs used to create the ADaM datasets and analysis programs (if difficult, specifications showing the analysis algorithm) must be submitted

Comparison on some differences between U.S.FDA and PMDA

Item	U.S.FDA	PMDA
Electronic data to be submitted	• Electronic data standards are listed in the Data Standards Catalog (SEND, SDTM, ADaM, etc.) • All phases of clinical studies	• All phase II and phase III studies that are generally regarded to be the major evidence for evaluation (see below for the details) • Certain Phase I studies and QT/QTc studies • SEND data is not required as of March 2017 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. b. For study results from phase I studies and clinical pharmacology studies, results from studies listed below are required to be electronically submitted. - Phase I studies of oncology drugs. - Phase I studies that have been conducted on both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies). - QT/QTc studies based on ICH E14 guideline. Basic Principles on Electronic Submission of Study Data for New Drug Applications
Regulatory clock for standardized submission	• Required for studies start after Dec. 17, 2016 in NDAs, BLAs, ANDAs • For Com. IND, the requirement starts after Dec. 17, 2017	• Study data of all the studies requiring electronic submission (NOT based on study start date) will need to be electronically submitted - Transitional period (- March 31, 2020), then mandatory from April 1, Eventually, study data of all the studies requiring electronic submission will need to be electronically submitted. However, until March 31, 2020, there will be a transitional period during which the data from some of the studies for which electronic submission is possible may be electronically submitted. Notification on Practical Operations of Electronic Study Data Submissions
SI unit	• Sponsors are expected to discuss SI unit issues with U.S.FDA before the start of Phase III trials.	• The use of SI unit is recommended • Store both the original data and the converted data in SI units The use of SI units is recommended. If data were collected in units that are commonly used in guidelines for diagnosis, treatment, and therapeutic evaluation for various diseases where conversion of the data to those in SI units is possible, separately store the converted data in SI units in the SDTM dataset as data in the standard units and submit them. Notification on Practical Operations of Electronic Study Data Submissions

Disclaimer

The contents of this poster represent the view of the presenters only, and do not represent the views and/or policies of PMDA and FDA.

Acknowledgement

We thank Mina Hohlen and Stephen Wilson for her support and encouragement in organizing this poster. We also thank all of the members of Advanced Review with Electronic Data Promotion Group, PMDA.

Pharmaceuticals and Medical Devices Agency 独立行政法人 医薬品医療機器総合機構

U.S. FOOD & DRUG ADMINISTRATION