CDISC Implementation in PMDA

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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

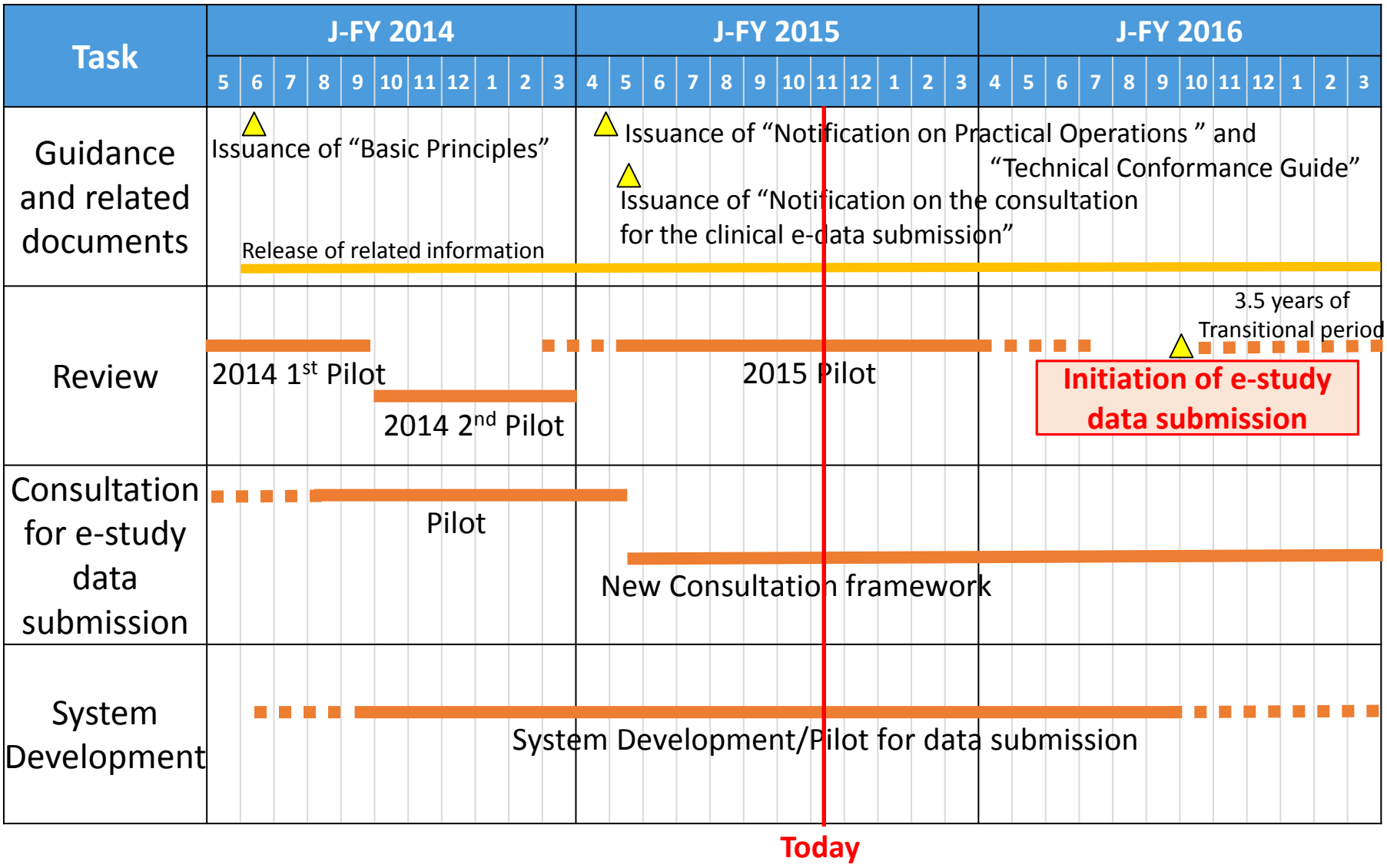
More effective and high quality Review

- 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

Timeline for implementation of electronic data submission



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

Notifications, Guide, and PMDA Data Standards Catalog

- 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
- PMDA Data Standards Catalog
  - The lists of **available standards and the versions**
  - Data Exchange Standards and Terminology Standards

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 recommendation of submitting 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

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

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

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

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

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

First-class review authority

Present
J-FY2015

J-FY2016

Setup e-data management and utilization

- 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

Promotion of paperless operation

J-FY2018

Ordinary utilization of e-data in the product review

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

J-FY2019 - 2021

Starting earnest cross-product analysis

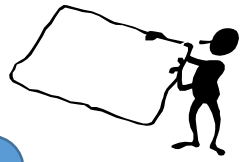
- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

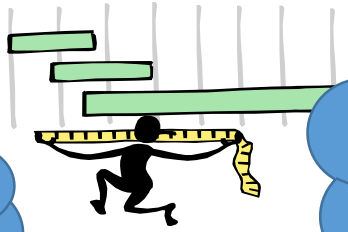
J-FY2022 -

Publication of guidelines to contribute to drug development

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

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



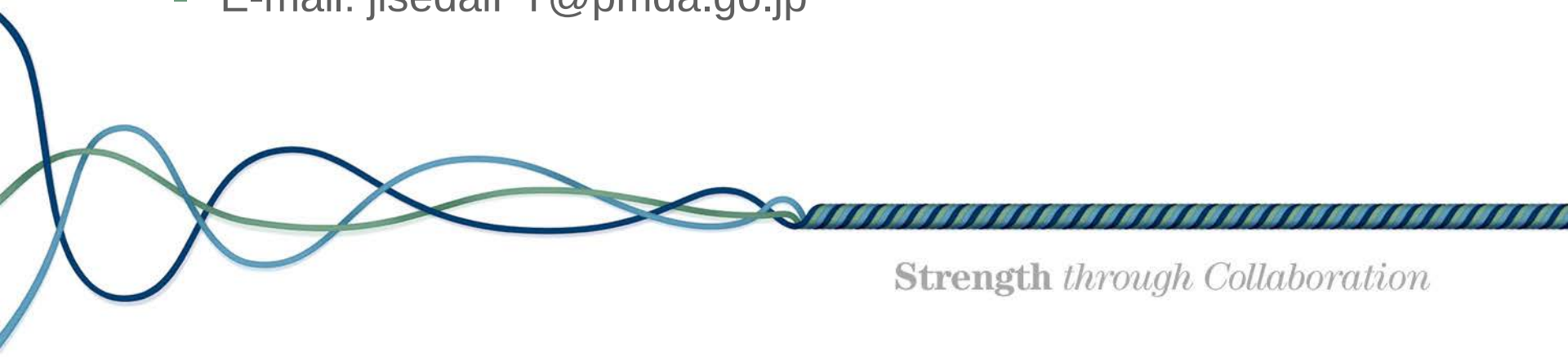


Future implementation of CDISC in Japan

- Therapeutic Area Standards
  - “These standards may be used for diseases for which standards have already been published.” (Technical Conformance Guide by PMDA, 4.1.4)
  - Further investigations of the applicability to clinical environment in Japan will be needed.
- 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

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

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  - 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
- International Pharmaceutical Regulatory Harmonization Strategy - Regulatory Science Initiative –
  - http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/150827-01.html
- PMDA International Strategic Plan 2015
  - https://www.pmda.go.jp/english/int-activities/outline/0017.html