Our Way to CDISC Submissions – An Update 12 Months Later

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Strength *through Collaboration*

Outline

- Outline of Advanced Review with Electronic Data in PMDA
- Update of PMDA activity
  - Notifications and Guide
  - Pilot projects
- 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

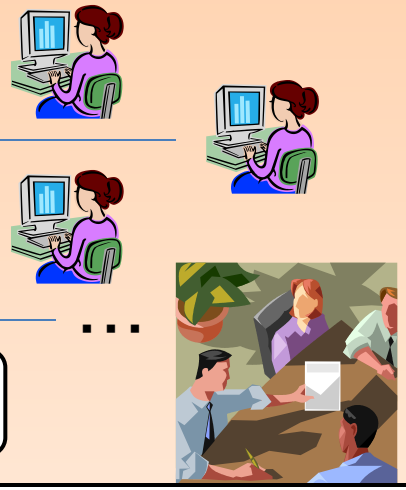
Storage of electronic data in the dedicated server and registration in the database

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

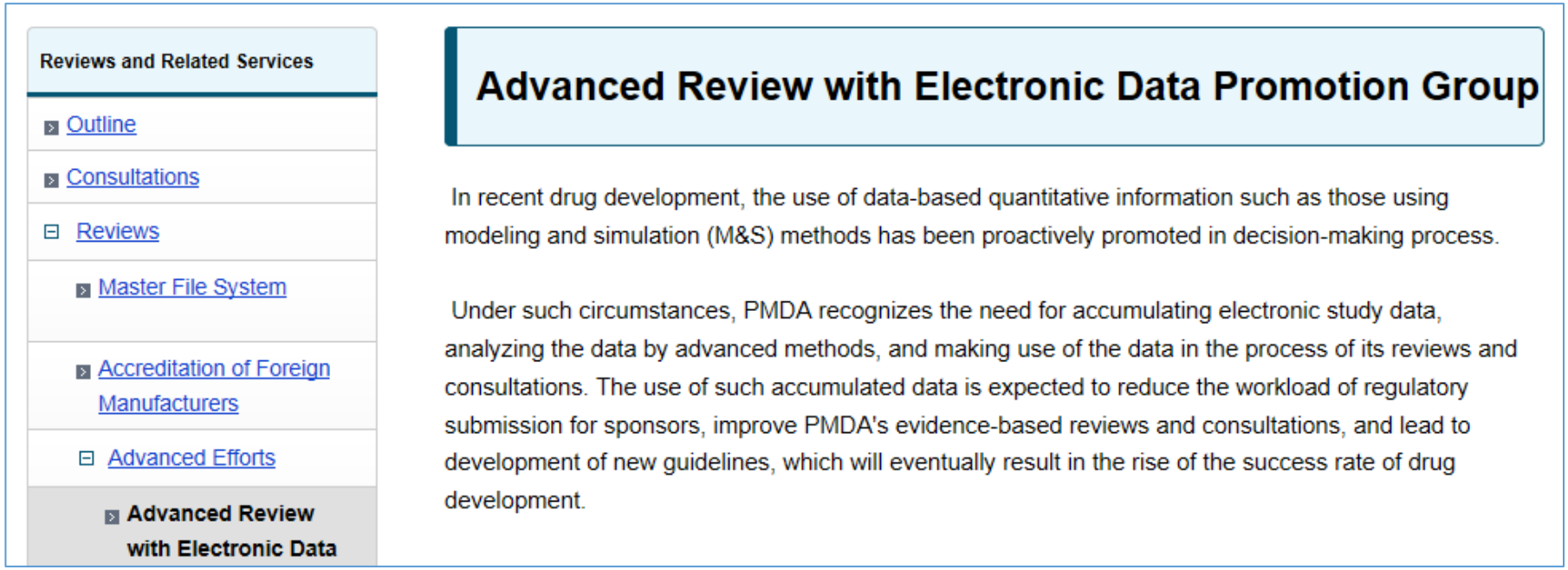
- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

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

Medium- and long-term Prospect

Tentative assumption and expectation

Present
FY2015

- e-data can be received and managed appropriately
- e-data can be utilized in the review
- without extension of review period, industries' workload would decrease gradually

FY2016

Setup e-data management and utilization

FY2018

Ordinary utilization of e-data in the product review

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

FY2019 - 2021

Starting earnest cross-product analysis

- Develop guidance and related documents
- Earnest cross-product analysis, development of disease models

FY2022 - 2023

Publication of guidance to contribute to drug development

- Establishment of disease model
- Publication of disease-specific guidance

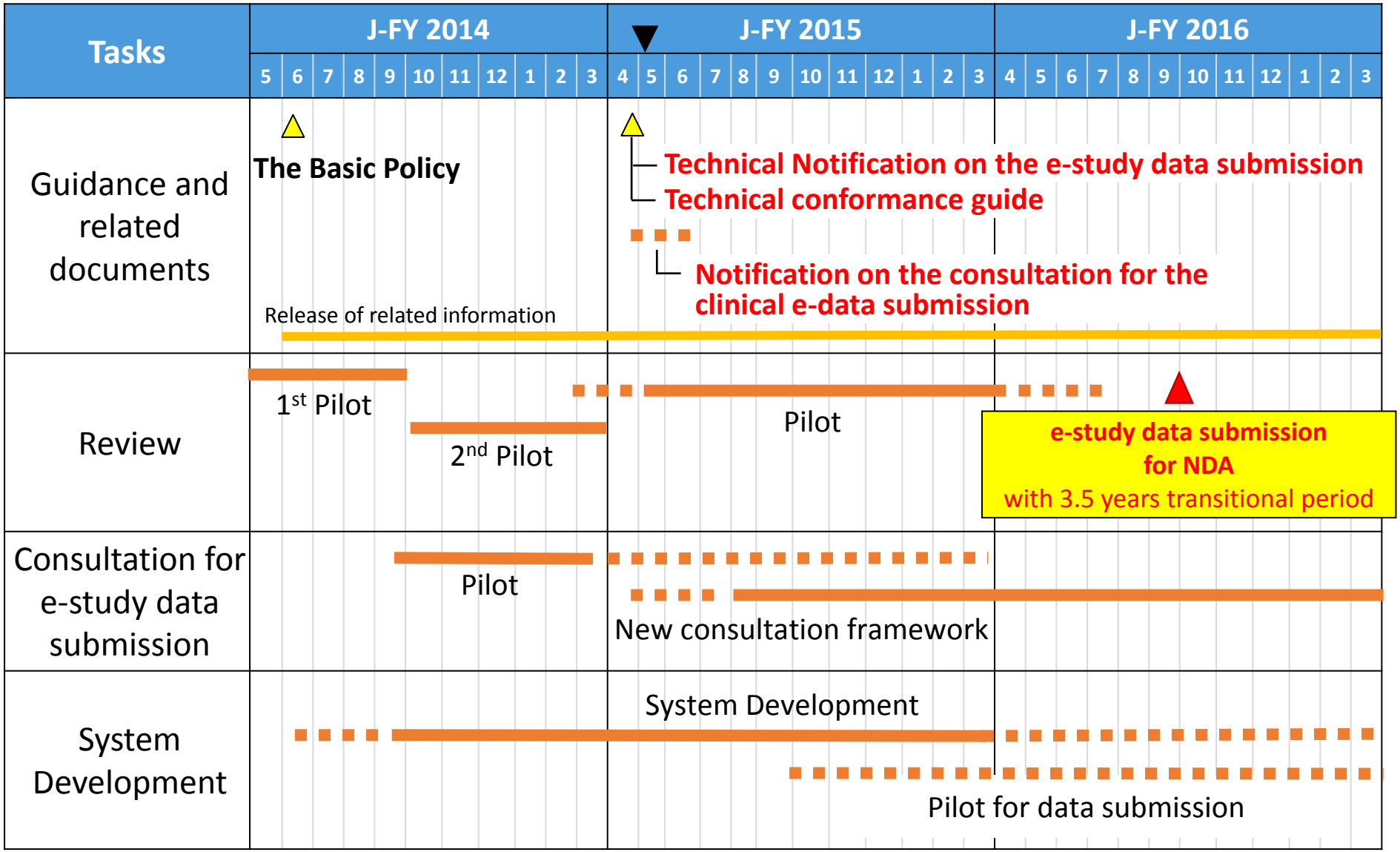
First-class review authority

Promotion of paperless offices

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

FY in Japan is from Apr to Mar in the next year

Proposed Timeline for Constructing the Framework for Utilization of Electronic Study Data



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.
  - Both of Japanese and English versions are available on PMDA homepage.

- Technical Notification
  - 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
  - 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

They are currently being translated into English

Major contents of the Technical Notification

- Clinical trial data subject to electronic submission
  - Subject products, trials, data, ISS/ISE
  - Data submission of supplemental NDA
  - Data submission of NDA with interim analysis results
- Methods of data submission
  - Use of Gateway, process of submission, validation for CDISC data
  - Relationship of electronic data submission and eCTD
- Details of datasets subject to electronic submission
  - CDISC compliant data and programs
  - Data and programs for clinical pharmacology study/analysis
- Consultation process regarding electronic data
- Initiation timing of electronic data submission and transitional period
  - Initiation date: 1st October, 2016
  - Transitional period: until 31st March, 2020

Tentative Translation

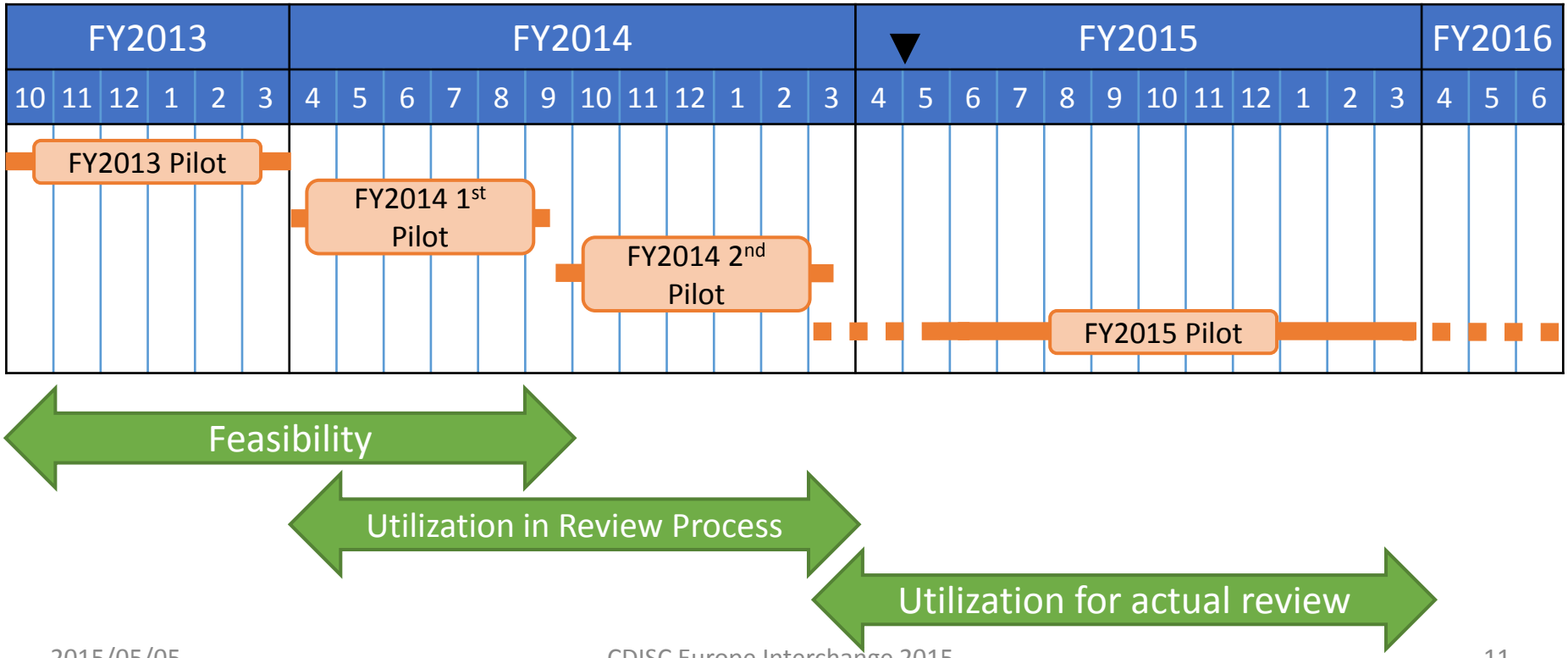
Major contents of the Technical Conformance Guide

- System requirements for electronic data submission
- Submission of electronic data
  - Process, use of portal site, file size, folder structure, validation of CDISC data
- Details of datasets subject to electronic submission
  - CDISC compliant data and programs
    - 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
  - Data and programs for clinical pharmacology study/analysis
    - Directions for clinical pharmacology data package
    - Submission data details by analysis type
- Relationship of electronic data submission and eCTD
  - Submission details of eCTD

Tentative Translation

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

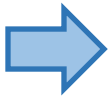


Pilot projects for CDISC compliant data

	FY2013	FY2014-1	FY2014-2
Purpose	- Feasibility	- Feasibility - Utilization of data in review process	- Utilization of data in review process
Number of products	5	4	3
Person in charge	Around 80 reviewers + 20 members from Promotion Group	Around 180 reviewers + 20 members from Promotion Group	Around 190 reviewers + 20 members from Promotion Group
Implementation details	The reviewers conducted some data visualization/ statistical analyses.	The reviewers conducted data visualization/ statistical analysis of primary and related data. The review teams considered the review process with using electronic data.	
Note			Initial consideration of utilization of the data for conformity inspection

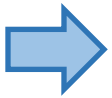
Experience based on the pilot projects -1

- Importance of understanding the datasets and variables
  - Understanding of variation by company, therapeutic area, or product, even among CDISC compliant datasets.



Request for Annotated CRF, Study Data Reviewer's Guide, Analysis Data Reviewer's Guide

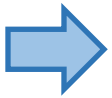
- Relationship between analysis datasets and the results
  - The feature of "analysis ready" is critical.
  - Reviewers review submission materials (CTD = analysis results), then use the data.
  - Information of the relationship between analysis datasets and the results is very useful



Request for analysis results metadata

Experience based on the pilot projects -2

- Importance of CDISC conformity
  - The reviewers could use their experience of previous pilot data to review current pilot data.
  - Using/understanding standardized variables make the review with electronic data easier and faster, regardless of the software.
  - On the other hand, seemingly-minor non-conformity can require great care in some cases.



- Establishment of validation rules and severity in PMDA
- Review of preliminary explanation of errors by the sponsors and the validation results in PMDA

CDISC validation in PMDA

- We plan to use OpenCDISC for CDISC validation.
- The validation rules will be based on general rules and opened to public for sponsor's use.
  - Sponsors should use the same validation rules and check the results in advance.
- We have three levels for severity of the errors
  - Need to be corrected in advance
  - Need to be explained in advance
  - Others
- Validation results will be reviewed by PMDA reviewers before they start to review.

More details are described in the Technical Conformance Guide

FY2015 pilot project

- The last pilot project before the initiation of electronic 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 electronic study data under the actual situation of regulatory review of new drug application
  - The pilot conducted using electronic 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 Conformance 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.
- 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.
- 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

Strength *through Collaboration*

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
- Technical Notification
  - Japanese: http://www.pmda.go.jp/files/000204726.pdf
  - English: (Currently being translated)
- Technical Conformance Guide
  - Japanese: http://www.pmda.go.jp/files/000204728.pdf
  - English: (Currently being translated)