CDISC Implementation in PMDA

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Advanced Review with Electronic Data Promotion Group
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Advanced workflow of review/consultation

**Analysis by PMDA**
- Giving additional scientific value to submitted data

**Cooperation with Academia**

**Regulatory Science**

**Practical use of Innovative Medical Products**
- More rational & effective evaluation process for regulatory decision

**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

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Guidance and related documents</strong></td>
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<tr>
<td>Issuance of “Basic Principles”</td>
<td>![1Q]</td>
<td>![2Q]</td>
<td>![3Q]</td>
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<tr>
<td>Release of related information</td>
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<tr>
<td><strong>Review</strong></td>
<td>2014 1&lt;sup&gt;st&lt;/sup&gt; Pilot</td>
<td>2015 Pilot</td>
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<td>2014 2&lt;sup&gt;nd&lt;/sup&gt; Pilot</td>
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<td><strong>Consultation for e-study data submission</strong></td>
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<td>Pilot</td>
<td>New Consultation framework</td>
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<tr>
<td><strong>System Development</strong></td>
<td></td>
<td>System Development/Pilot for data submission</td>
<td>Today</td>
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</table>

- 2014 1<sup>st</sup> Pilot
- 2014 2<sup>nd</sup> Pilot
- 2015 Pilot
- New Consultation framework
- System Development/Pilot for data submission

- Issuance of “Basic Principles”
- Issuance of “Notification on Practical Operations” and “Technical Conformance Guide”
- Issuance of “Notification on the consultation for the clinical e-data submission”

3.5 years of Transitional period

Initiation of e-study data submission

Today
# Information and resources for industry

<table>
<thead>
<tr>
<th>Notification/Guide/Workshop</th>
<th>Date</th>
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<tbody>
<tr>
<td>Basic Principles on Electronic Submission of Study Data for New Drug Applications</td>
<td>Jun 20, 2014</td>
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<tr>
<td><strong>Notification on Practical Operations of Electronic Study Data Submissions</strong></td>
<td>Apr 27, 2015</td>
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<tr>
<td>Question and Answer Guide regarding “Notification on Practical Operations of Electronic Study Data Submissions”</td>
<td>Apr 27, 2015</td>
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<tr>
<td>Technical Conformance Guide</td>
<td>Apr 27, 2015</td>
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<tr>
<td>Notification on the consultation for the clinical e-data submission</td>
<td>May 15, 2015</td>
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<tr>
<td>Briefings regarding Notification on Practical Operations</td>
<td>May 28, 2015</td>
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<td>Jun 3, 2015 (Osaka)</td>
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<td><strong>Data Standards Catalog</strong></td>
<td>Jul 30, 2015</td>
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<tr>
<td>Workshop regarding Technical Conformance Guide</td>
<td>Sep 28, 2015</td>
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<tr>
<td><strong>Validation Rules</strong></td>
<td>Autumn, 2015</td>
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<tr>
<td>Portal Site Users Manual</td>
<td>J-FY2015</td>
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<tr>
<td><strong>FAQ Web Page</strong></td>
<td>J-FY2015</td>
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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

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<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Feasibility</td>
<td>Feasibility &amp; utilization of study data in review process</td>
<td>Utilization of study data in review process</td>
<td>Utilization of study data for actual review</td>
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<tr>
<td><strong>Target studies</strong></td>
<td>5 drugs</td>
<td>CDISC: 4 drugs</td>
<td>CDISC: 3 drugs</td>
<td>CDISC: 14drugs</td>
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<tr>
<td></td>
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<td>CP: 3 PPK datasets</td>
<td>CP: 3 PPK/PD datasets</td>
<td>CP: Standard Two-Stage Approach: 4 drugs</td>
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<td>Population Approach</td>
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<td></td>
<td>7 drugs</td>
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<td>PBPK: 2 drugs</td>
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<tr>
<td><strong>Persons in charge</strong></td>
<td>Around 80 reviewers + 20 from promotion group</td>
<td>Around 180 reviewers + 20 from promotion group</td>
<td>Around 190 reviewers + 20 from promotion group</td>
<td>Around 190 reviewers + 20 from promotion group (tentative)</td>
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<tr>
<td><strong>Details</strong></td>
<td>- All the reviewers try to reproduce the several analysis results in CTD</td>
<td>- All the reviewers try to replicate the main analysis results in CTD</td>
<td>- Some reviewers including biostatisticians in each review team are assigned mainly handle the data analysis</td>
<td>- Pilot project which is almost parallel with actual new drug review</td>
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<td>- Team meetings for the discussion on the review process with data analysis</td>
<td>- Team meetings for the discussion on the necessary analyses for the review and the review process with data analysis</td>
<td>- The pilot project will NOT affect the actual regulatory review of the drug</td>
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**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

General analyses for efficacy and safety data
- Simple analyses depending on the characteristics of evaluation variables – continuous/categorical/time-to-event

Relatively complicated analyses
- Analyses with programing (innovative/complicated analyses)
- Simulations

Software: JMP
Datasets: SDTM

Software: JMP, etc.
Datasets: ADaM

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
  - 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

**Present J-FY2015**

**J-FY2016**

Setup e-data management and utilization

**J-FY2018**

Ordinary utilization of e-data in the product review

**J-FY2019 - 2021**

Starting earnest cross-product analysis

**J-FY2019 - 2021**

Preparations of guidelines and related documents

More predictable efficacy/safety

Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

Industries’ workload is reduced gradually while keeping the same review period

**First-class review authority**

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

**Transitional period are taken until March 31st, 2020**

- More predictable efficacy/safety
- Earnest on cross-product analysis and development of disease models

**J-FY2022 -**

Publication of guidelines to contribute to drug development

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

**Setup e-data management and utilization Ordinarily utilize e-data in the product review**

**Promotion of paperless operation**

*NDA=New Drug Application
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

• Basic Principles on Electronic Submission of Study Data for New Drug Applications

• Notification on Practical Operations of Electronic Study Data Submissions

• Technical Conformance Guide on Electronic Study Data Submissions

• PMDA Data Standards Catalog (Japanese and English)
  ▪ https://www.pmda.go.jp/files/000206482.zip

• International Pharmaceutical Regulatory Harmonization Strategy - Regulatory Science Initiative –

• PMDA International Strategic Plan 2015