Advanced Review with Electronic Data and CDISC Implementation in PMDA

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Advanced Review with Electronic Data Promotion Group
Pharmaceuticals and Medical Devices Agency (PMDA)
Outline

• Outline of Advanced Review with Electronic Data in PMDA
• Notifications and Guide
• PMDA Data Standards Catalog
• CDISC validation in PMDA
• Pilot projects for utilization of electronic data
• Summary
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

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

NDA etc.
e-Submission of study data

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

Data Accumulation

Database
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

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
- Visualization and analysis of data, supported by browsing software
- 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.

Advanced Review with Electronic Data Promotion Group

In recent drug development, the use of data-based quantitative information such as those using modeling and simulation (M&S) methods has been proactively promoted in decision-making process.

Under such circumstances, PMDA recognizes the need for accumulating electronic study data, analyzing the data by advanced methods, and making use of the data in the process of its reviews and consultations. The use of such accumulated data is expected to reduce the workload of regulatory submission for sponsors, improve PMDA’s evidence-based reviews and consultations, and lead to development of new guidelines, which will eventually result in the rise of the success rate of drug development.

http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html
Prospect of e-Study data utilization in Japan

**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

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

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

**J-FY2018**

- Ordinary utilization of e-data in the product review

**J-FY2019 - 2021**

- Establishment of disease models
- Publication of disease-specific guidelines
- Earnest on cross-product analysis and development of disease models

**J-FY2022 -**

- Publication of guidelines to contribute to drug development

**First-class review authority**

**Promotion of paperless operation**

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

**Setup e-data management and utilization**

**Present J-FY2015**

**NDA=New Drug Application**

**Transitional period** are taken until March 31st, 2020
### Timeline for implementation of electronic data submission

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<tbody>
<tr>
<td></td>
<td>5 6 7 8 9 10 11 12 1 2 3</td>
<td>4 5 6 7 8 9 10 11 12 1 2 3</td>
<td>4 5 6 7 8 9 10 11 12 1 2 3</td>
</tr>
<tr>
<td><strong>Guidance and related documents</strong></td>
<td>Issuance of “Basic Principles”</td>
<td>Issue of “Notification on Practical Operations ” and “Technical Conformance Guide”</td>
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<td></td>
<td>Release of related information</td>
<td>Issue of “Notification on the consultation for the clinical e-data submission”</td>
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<tr>
<td><strong>Review</strong></td>
<td>2014 1st Pilot</td>
<td>2015 Pilot</td>
<td>Initiation of e-study data submission</td>
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<tr>
<td></td>
<td>2014 2nd Pilot</td>
<td></td>
<td>3.5 years of Transitional period</td>
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<tr>
<td><strong>Consultation for e-study data submission</strong></td>
<td>Pilot</td>
<td>New Consultation framework</td>
<td></td>
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<tr>
<td><strong>System Development</strong></td>
<td>System Development/Pilot for data submission</td>
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</table>

*Today*
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.

- **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
Major contents of the Practical Operations

• Clinical trial data subject to electronic submission
  • Subject products, trials, data, ISS/ISE
  • Data submission for supplemental NDA (including application for partial changes)

• Format and method of electronic data submission
  • Use of Gateway, process of submission, validation for CDISC data
  • Relationship of electronic data submission and eCTD

• Details on the electronic datasets to be submitted
  • Data that conforms to the CDISC standards and programs
  • Data and programs for clinical pharmacology study/analysis

• Process of consultations concerning electronic data

• Initiation timing of submission of study data and interim measure
  • Initiation date: 1st October, 2016
  • Transitional period: until 31st March, 2020
Initiation timing of submission of e-study data

- The initiation date of submission of e-study data is October 1, 2016.
- There is a transitional period of 42 months from October 1, 2016 to March 31, 2020.

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<td>Apr 27</td>
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<tr>
<td>Notification on Practical Operations of Electronic Study Data Submissions published on Apr 27, 2015</td>
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<td>42 months of the transitional period</td>
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<td>Mar 31</td>
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“This notification will apply to products for which a new drug application is made on or after October 1, 2016.”
Major contents of the Technical Conformance Guide

• System requirements for the submission of electronic study data
• Submission of electronic data
  • Process, use of portal site, file size, folder structure, validation of the study data
• Electronic study data to be submitted (details)
  • CDISC-conformant electronic study data and relevant documents
    • 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
    • Submission of programs
  • Electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses
    • Directions for clinical pharmacology data package
    • Submission data details by analysis type
• Relationship between the electronic study data and eCTD
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
- Programs
  - Analysis programs
  - Programs for creating ADaM datasets
- Annotated CRF
- Reviewer’s Guide
  - Study Data Reviewer’s Guide
  - Analysis Data Reviewer’s Guide

Final work packages of Study Data Reviewer’s Guide and Analysis Data Reviewer’s Guide by PhUSE are mentioned as references in PMDA’s Technical Conformance Guide.
<table>
<thead>
<tr>
<th>Section in notification of the Basic Principles</th>
<th>Content</th>
<th>Individual clinical study data</th>
<th>Analysis dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. (2) a</td>
<td>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</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>For study results from phase I studies and clinical pharmacology studies, results from studies listed right are required to be electronically submitted.</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>Phase I studies of oncology drugs</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>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)</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>QT/QTc studies based on ICH E14 guideline</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>Clinical studies where standard pharmacokinetic analysis was performed</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>Population analysis</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>Physiologically-based pharmacokinetic model analysis</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) b Note</td>
<td>May be submitted in formats other than CDISC standard</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) References other than a and b, which were deemed necessary by PMDA</td>
<td>*If necessary, consult beforehand</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) Integrated summary of safety and efficacy (ISS/ISE)</td>
<td>**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</td>
<td>SDTM</td>
<td>ADaM</td>
</tr>
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</table>

Q&A No.12 of Notification on Practical Operations
The lists that were mentioned as “... and the list of acceptable versions is available on the PMDA’s website (http://www.pmda.go.jp/)” in the Notification on Practical Operations

- Data Exchange Standards
- Terminology Standards

Now you can download PMDA Data Standards Catalog.

- [http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.html](http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.html)
- Both Japanese version and English version are included in one ZIP file.
<table>
<thead>
<tr>
<th>Use</th>
<th>Data Exchange Standard</th>
<th>Supported Version(s)</th>
<th>Implementation Guide Version</th>
<th>Exchange Format</th>
<th>Date Support Begins (YYYY-MM-DD)</th>
<th>Date Support Ends (YYYY-MM-DD)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Clinical study datasets - Transport</td>
<td>SAS Transport (XPORT)</td>
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<td>-</td>
<td>XPT</td>
<td>2016-10-01</td>
<td></td>
<td>In principle, eCTD PDF specification should be referenced for details.</td>
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<td>3.2</td>
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<td>3.1.3</td>
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<td>3.1.2 Amendment1</td>
<td>XPT</td>
<td>2016-10-01</td>
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<td>3.1.2</td>
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<td>Clinical study datasets</td>
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<td>1.0</td>
<td>XPT</td>
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<td>Clinical study data definition files</td>
<td>Define</td>
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<tr>
<td>Clinical study data definition files</td>
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<td>XML</td>
<td>2016-10-01</td>
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<tr>
<td>Documents</td>
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<td>-</td>
<td>PDF</td>
<td>2016-10-01</td>
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</table>
### Terminology Standards

<table>
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<tr>
<th>Terminology Standard</th>
<th>Version(s)</th>
<th>Date Support Begins (YYYY-MM-DD)</th>
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</thead>
<tbody>
<tr>
<td>CDISC Controlled Terminology</td>
<td>2009-02-17 or later</td>
<td>2016-10-01</td>
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<tr>
<td>MedDRA</td>
<td>8.0 or later</td>
<td>2016-10-01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Drug Dictionary Enhanced</td>
<td>2008:3 (2008-12-01) or later</td>
<td>2016-10-01</td>
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</tr>
</tbody>
</table>

- We will consider the beginnings and endings of support of the versions in consideration of the usage in Japan and other countries.
- “Date support ends” will be noticed with sufficient margin.
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
## Information and resources for industry

### Notification/Guide/Workshop

<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>
</tr>
<tr>
<td>Notification on Practical Operations of Electronic Study Data Submissions</td>
<td>Apr 27, 2015</td>
</tr>
<tr>
<td>Question and Answer Guide regarding “Notification on Practical Operations of Electronic Study Data Submissions”</td>
<td>Apr 27, 2015</td>
</tr>
<tr>
<td>Technical Conformance Guide</td>
<td>Apr 27, 2015</td>
</tr>
<tr>
<td>Notification on the consultation for the clinical e-data submission</td>
<td>May 15, 2015</td>
</tr>
<tr>
<td>Briefings regarding Notification on Practical Operations</td>
<td>May 28, 2015 (Tokyo)</td>
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<td>Jun 3, 2015 (Osaka)</td>
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<tr>
<td>Data Standards Catalog</td>
<td>Jul 30, 2015</td>
</tr>
<tr>
<td>Workshop regarding Technical Conformance Guide</td>
<td>Sep 28, 2015</td>
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<tr>
<td>Validation Rules</td>
<td>Autumn, 2015</td>
</tr>
<tr>
<td>Portal Site Users Manual</td>
<td>J-FY2015</td>
</tr>
<tr>
<td>FAQ Web Page</td>
<td>J-FY2015</td>
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</tbody>
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2015/10/14 PhUSE Annual Conference 2015
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

<table>
<thead>
<tr>
<th>FY2013</th>
<th>FY2014</th>
<th>FY2015</th>
<th>FY2016</th>
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<tbody>
<tr>
<td>10 11 12 1 2 3</td>
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<td>4 5 6 7 8 9 10 11 12 1 2 3</td>
<td>4 5 6</td>
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</tbody>
</table>

- FY2013 Pilot
- FY2014 1st Pilot
- FY2014 2nd Pilot
- FY2015 Pilot

Feasibility
Utilization in Review Process
Utilization for actual review

2015/10/14 PhUSE Annual Conference 2015
# 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>
</tr>
<tr>
<td><strong>Target studies</strong></td>
<td>5 drugs</td>
<td>CDISC: 4 drugs CP: 3 PPK datasets</td>
<td>CDISC: 3 drugs CP: 3 PPK/PD datasets</td>
<td>CDISC: 14 drugs CP: Standard Two-Stage Approach: 4 drugs Population Approach: 7 drugs PBPK: 2 drugs</td>
</tr>
<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>
</tr>
<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 Team meetings for the discussion on the review process with data analysis</td>
<td>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</td>
<td>Pilot project which is almost parallel with actual new drug review The pilot project will NOT affect the actual regulatory review of the drug</td>
</tr>
</tbody>
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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
- SAS

Datasets:
- SDTM
- ADaM
Experience based on the pilot projects

• Importance of standardized analysis datasets and the relationship to the results
  • Most reviewers review the submission materials (analysis results) first.
  • “Which dataset should be used for additional analysis for the results?”

• Importance of understanding the datasets and variables
  • “Which variable/records we should use?”

• Importance of CDISC conformity
  • The reviewers could use their experience of previous pilot data.
  • Using/understanding standardized variables make the review easier and faster, regardless of the software.

Request for
  • ADaM datasets
  • Analysis Results Metadata

Request for
  • Annotated CRF
  • Reviewer’s Guide (SDRG, ADRG)

• Establishment of validation rules and severity in PMDA
  • Review of validation results

2015/10/14
PhUSE Annual Conference 2015
Summary

• Advanced Review with Electronic Data Project is being executed successfully so far.
  • The Basic Principles, Notification on Practical Operations, and Technical Conformance Guide, and PMDA Data Standards Catalog have been published.

• Our experiences of reviewing and analyzing study data have been increased through the pilot projects.
  • The experiences were reflected in the Notification on Practical Operations and Technical Conformance 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.
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
  • English: https://www.pmda.go.jp/files/000206451.pdf

• Technical Conformance Guide on Electronic Study Data Submissions
  • English: https://www.pmda.go.jp/files/000206449.pdf

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