Electronic Data Submission and Utilization in Japan

Hiromi Sugano
Biostatistics Reviewer
Office of New Drug II / Office of Advanced Evaluation with Electronic Data
Pharmaceuticals and Medical Devices Agency
Outline

• Current situation of e-data submission
• Preparation for the end of the transitional period
• Practical case for utilization of submitted data in review process
• Utilization of accumulated data
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

Scientific discussion and decision making on the basis of internal analysis result

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

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

Submission of electronic clinical study data has started since Oct 1st 2016!
Timeline for implementation of e-data submission

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guidance and related documents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issuance of “Basic Principles”</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Issuance of “Notification on Practical Operations”</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Issuance of “Technical Conformance Guide”</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>FAQ</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Data Standards Catalog</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>PMDA Validation Rules</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Briefing/Workshop</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Portal Site Open</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td><strong>Review</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>2014 Pilot</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>2015 Pilot</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>WS</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>Oct 1</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>3.5 years of Transitional period</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>Mar 31</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td><strong>Consultation for e-study data submission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Issuance of “Notification on the consultation for the clinical e-data submission”</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>New Consultation framework</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td><strong>System Development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>System Development / Pilot for data submission</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>Portal Site Open</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
</tbody>
</table>

- **Preparation for the end of transitional period**
  - Revision of the notifications, etc.

- **Regular Update**

Date: 2018/09/04

PharmaSUG SDE Japan 2018
Consultation for clinical e-data submission

- 169 consultation meetings have been requested by 49 companies as of July 31, 2018.

<table>
<thead>
<tr>
<th>Year</th>
<th>N of request</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
</tr>
</tbody>
</table>

- Multiple meetings have been held for some products.
- The number of consultation for NDA after transitional period is increasing.
- Various characteristics
  - With/without official minutes
  - Japanese/foreign company
  - Oncology and other therapeutic areas
Data submitted with new drug applications

- 51 NDAs were submitted with electronic study data by 27 companies as of July 31, 2018.
  - Although several issues below have occurred during data transmission, all the submitted data are successfully received.
    - System issues
    - Validation failure because of violations categorized “Reject”.
    - Lack of explanations for “Error” issues.
  - Various characteristics on the NDAs
    - Domestic/global company
    - Oncology holds majority, but submissions in other areas are also increasing
    - Initial application / application for partial changes (supplemental application)
    - Clinical pharmacology study
Explanation on electronic data for reviewers

So far, we have not received major questions/concerns about the submitted data or data format during new drug review period.

• PMDA requests applicants to submit various information for explanation on study data, and they are very useful for reviewers.
  – Analysis Results Metadata
  – Reviewer’s Guide (SDRG, ADRG)
  – Define.xml
  – Programs for creating ADaM datasets

• Analysis Results Metadata will be the key in their review with electronic data.
  – Most reviewers usually start with confirming the reproducibility of the primary results in CTDs, and Analysis Results Metadata is very useful for reviewers for their quick access to the analysis datasets used.

We strongly recommend that you include “Creating ARM” in your plan of organizing submission datasets.
Transitional period will be ended...

- The transitional period will be ended on March 31, 2020.
  - During the transitional period, applicants can submit the data of at least one clinical trial included in their clinical data packages.
  - After the period, applicants need to submit the data of all the requested clinical trials.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apr 27</td>
<td>Oct 1</td>
<td>42 months of the transitional period</td>
<td>Mar 31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notification on Practical Operations of Electronic Study Data Submissions published on Apr 27, 2015

If submission date is after this date, applicants need to submit the data of all the requested clinical trials.
Preparation for the end of transitional period

We have already revised notifications and clarification, for example,

• Revision of notifications with considering situation when applicants can not use Electronic Submission Gateway
• Clarification of relationship between
  – Electronic study data submission
  – Submission of eCTD
  – Use of Electronic Submission Gateway

We are considering revision of notifications and clarification, for example,

• Clarification of timing of data submission for special situation
  – Ex. New drug applications for anti-HIV drugs

We will proceed the project with continual discussion with industry for the smooth transition to the next phase.
### Process of starting to analyze data

<table>
<thead>
<tr>
<th>Data Submission</th>
<th>Clinical trial consultations</th>
<th>Discussion about which study should be included in e-study data submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Submission</td>
<td>Consultation for electronic study data submission</td>
<td>Discussion about technical issues of e-study data submission</td>
</tr>
<tr>
<td>Data Submission</td>
<td>Pre-application meeting on procedures for new drug review</td>
<td>Confirmation of the e-study data submission and the schedule of the NDA</td>
</tr>
<tr>
<td>Data Submission</td>
<td>Validation</td>
<td>Check the result based on “Exhibit 8”</td>
</tr>
<tr>
<td>NDA</td>
<td>Confirmation of submitted data sufficiency</td>
<td>Check whether submitted data are sufficient based on “Exhibit 8”</td>
</tr>
<tr>
<td>NDA</td>
<td>Start to analyze data</td>
<td></td>
</tr>
</tbody>
</table>

**At any time during the development, multiple times**
# Review process and data analysis

## Review Process

### Analysis Timing

<table>
<thead>
<tr>
<th>Before the First Team Meeting</th>
<th>After the First Team Meeting</th>
<th>After Expert Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contents of Analyses</strong></td>
<td><strong>Contents of Analyses</strong></td>
<td><strong>Contents of Analyses</strong></td>
</tr>
<tr>
<td>• Confirmation of reproducibility of the primary analysis</td>
<td>• Analyses related to inquiries</td>
<td>• Additional analysis taking comments from external experts into account</td>
</tr>
<tr>
<td>• Analyses for review points</td>
<td>• Consider contents of inquiries based on results of analyses</td>
<td>• Indication, dosage, special population</td>
</tr>
<tr>
<td>• Indication, dosage, etc.</td>
<td>• Consider necessity for additional inquiries after receiving answers</td>
<td></td>
</tr>
<tr>
<td>• Consistency, AE, individual patient profile, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Analysis for exploring review points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Factors affecting efficacy and safety</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Analysis Timing

- **First Team meeting**
  - Inquiries/Answers
  - Discussion with Experts
  - Inquiries/Answers

- **Meeting with Sponsor**
  - Inquiries/Answers

- **Inquiries/Answers**

- **Completion of Review**
## Analyses of CDISC data in review team

### 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, etc.

**Datasets**: SDTM, ADaM

**Note**: STAT, MEDICAL, OTHERS
Practical case for utilization of submitted data in review process (1)

• To check the appropriateness of applicant’s idea that dosage adjusted according to patient’s weight, reviewer/stat performed subgroup analysis and searched other factors which affect efficacy/safety of the product.

➤ Inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary)
Practical case for utilization of submitted data in review process(2)

• To check the consistency of efficacy among subjects in the trial, reviewer(stat) confirmed a relationship between inclusion/exclusion criteria and endpoint outcome (ex. subgroup analysis by baseline status).

➢ No need for inquiries from PMDA
Practical case for utilization of submitted data in review process (3)

- To check the robustness of the primary result which used value transformation, or assumption of distribution, or model for the primary analysis, reviewer (stat) performed supplementary analysis.

- Be able to quickly and efficiently cope with a point from the external expert, and prepared review report without delay
Practical case for utilization of submitted data in review process(4)

• To check whether PPK analysis result from multinational trial was valid for Japanese or not, reviewer(CP) checked goodness of fit and performed predictive check for Japanese.

• To check the impact of the result from *in vitro*, reviewer(CP) checked other scenarios by clinical trial simulation using PBPK model. (ex. worst case scenario prediction).

- Inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary), or no need for inquiries from PMDA
- Sometimes outlier is specified
Practical case for utilization of submitted data in review process(5)

• It often becomes an issue that how is the relationship between dose and efficacy/safety outcome in the optional titration (ex. based on response) design trial.

➢ It is favorable that some variable about dose change (ex. when and how much) is prepared in ADaM dataset for the supplementary analysis.
Summary of e-data review so far (1)

• Reviewers can develop an understanding about the e-data, trial design, and the product than ever.
• The timeline of review process isn’t change.
• Sometimes inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary) or no need for inquiry.
• It becomes possible to quickly and efficiently cope with a point from the external expert.
• It often needs e-data analysis plan meeting before first team meeting, and even after that, needs to take time to analyze timely, so schedule management and business efficiency improvement are important than ever.

• It is necessary for reviewers to cooperate among their specialties (ex. stat and clinical) more than ever from an early stage.
Regulatory Science Center established on Apr 1

- Review Offices
- Office of Advanced Evaluation with Electronic Data (former Advanced Review with Electronic Data Promotion Group)
- Office of Research Promotion
- Office of Medical Informatics and Epidemiology
- Safety Offices
- MID-NET etc.
- e-study database

PharmaSUG SDE Japan 2018
Regulatory Science Center established on Apr 1

Review Offices
- E-Study data accumulate
  - utilize
  - NDA review
  - PMDA reviewers analyze e-Study data

Database
- MID-NET, etc.
  - utilize
  - Medical Records
  - DPC
  - Receipt
  - cooperate
  - Study on advanced analysis methods such as Modeling & Simulation
    - Cross-product analysis
      - Disease Models
      - Biomarkers etc.
  - Study on advanced Pharmacoepidemiological analysis methods
    - Benefit/Risk assessment of each product

Safety Offices
- Spontaneous reports, Post-marketing surveillance
  - utilize
  - Risk assessment
  - Risk assessment based on accumulated reports

Enhancement of practical use of Innovative Products
- More Effective and High Quality Review and Consultation
- More Predictable efficacy and safety
  - Quick and rational regulatory decision

Regulatory Science Research based on data analysis
- Publication of Guidelines
- Epoch-making Proposal leading the world

Benefit the Public

2018/09/04 PharmaSUG SDE Japan 2018
PMDA initiatives for quantitative science

- Several initiatives/activities for quantitative science are established and are in execution for new drug/device development and review in Japan.
- We are considering how we can efficiently use those data that we will obtain in each stage of clinical development.

Use of data standards is the key for all the initiatives.
Utilization of study data in the future

Utilization of study data for new drug review
- Improvement of predictability of efficacy and safety
- Reviewing M&S results
- Reviewing novel evaluation methods
- Swift and effective decision-making

Utilization of accumulated study data
- Information from cross-product analysis
- Active use of M&S
- Evaluation of innovative analysis methods based on the accumulated data
- Experiences of meta-analytic approach

Efficient new drug development
- Use of consultation meeting based on the cross-product information by PMDA
- Active use of M&S
- Use of innovative and appropriate methods for the purpose

Use of various data sources in the future
- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources
Summary

• Advanced Review with Electronic Data Project is being achieved successfully so far.

• PMDA will continue to provide information on the e-data submission for industries with considering the end of transitional period.
  – The transitional period will be ended on Mar 31, 2020.

• We appreciate continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug.