CDISC standards and data management – The essential elements for Advanced Review with Electronic Data

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Advanced workflow of review/consultation

Analysis by PMDA
- Giving additional scientific value to submitted data

NDA etc.
- e-Submission of study data

Data Accumulation

Database

Sophisticated review
- Each reviewer utilizes innovative assessment techniques

Sophisticated Consultation
- More evidence-based consultation

Cross-Products Analysis
- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Cooperation with Academia

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
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
Medium- and long-term Prospect

Tentative assumption and expectation

- 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

First-class review authority

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

FY2022 - 2023
Publication of guidance to contribute to drug development

FY2019 - 2021
Starting earnest cross-product analysis

FY2018
Ordinary utilization of e-data in the product review

FY2016
Setup e-data management and utilization

Present
FY2014
Promotion of paperless

- More predictable efficacy/safety
- Consideration of expanding scope to toxicological study and post-approval clinical study
- Develop guidance and related documents
- Earnest cross-product analysis, development of disease models

E.g. guidance and disease models based on data on Asian population
Importance of data standard

• PMDA
  • For fast access and easy handling of submitted clinical trial data in many new drug applications
  • For future use of accumulated clinical trial data for cross-products analysis

• Industry/Sponsor
  • For efficient and qualified process to make submission materials
  • For efficient use of medical records of medical institutes for clinical trials
  • For promotion of participating global development and using Japanese clinical trial data for submission to foreign regulatory authorities

PMDA will request patient level clinical trial data in electronic format which complies CDISC standards
Using submitted electronic data for drug review

- CDISC conformant data
  - SDTM
    - Data visualization and analysis by using software for standardized data
    - Statistical analysis by using analysis software
  - ADaM
    - Primary analysis and its sensitivity analysis
    - Other analysis by using analysis software

- Analysis program
  - Confirmation of analysis algorism
  - Utilization for sensitivity analysis and subgroup analysis if possible

- Programs for creating ADaM
  - Understanding of variables in the datasets

- Definition files
  - Understanding of the datasets and the variables
  - Relationship between analysis results and datasets

- Reviewer’s Guide
  - Understanding of the datasets and related issues
  - Prior information of CDISC conformity of the datasets
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

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

Feasibility
Utilization in Review Process
Utilization for actual review
Experiences of the pilot projects

• Importance of understanding the datasets and variables
  • There are inter-company or inter-product difference even among CDISC conformant datasets.
  • Differences between therapeutic areas and/or characteristics of the drug are understandable.

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

• The depth of reviewers’ understanding of the data will be increased
  • Relationship between analysis sets - exclusion criteria - missing data, calculation of values of primary endpoint
Experiences of the pilot projects

• 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.

Review of validation results and review of preliminary explanation of errors
Experiences of the pilot projects

- Datasets for analysis and analysis results
  - The feature of “analysis ready” is critical.
  - In most cases, reviewers review submission materials (CTD = analysis results), then use the data.
  - Relationship between the analysis results and the datasets should be clear.

Request for analysis results metadata
Overview of utilization of electronic study data

**Final** system

- **A** Study data in standardized format (CDISC)
- **B** Evaluation of electronically submitted data (Gateway + validation)
- **C** Storage of original data in one place (storage)
- **D** Data processing for easy analysis (data reduction system)
- **E** Analysis (data analysis/viewing system)
- **F** Effective use of the “final system” (trained experts)

**Objective**
- Improvement of regulatory review/consultation quality
- Support to increase drug development efficiency

Statistics
ADME
Clinical
Other reviewer
CDISC validation in PMDA

• We plan to use OpenCDISC for 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.
  • There will be the critical errors that can not be accepted.
  • Non-conformity to important rules (errors) should be explained in advance.

• Validation results will be reviewed by PMDA reviewers before they start to review.
  • As a consequence, both CDISC conformity and data quality will be reviewed.
## Proposed Timeline for Constructing the Framework for Utilization of Electronic Study Data

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- **e-study data submission for NDA (start date to be announced)**
Technical Notification and Technical Conformance Guide

• Technical Notification
  • Details about the electronic submission which were not described in “Basic Principles on Electronic Submission of Study Data for New Drug Applications” issued on June 20, 2014

• Technical Conformance Guide
  • Technical details which will not be included in the Technical Notification
  • May be updated based on the accumulated experience and/or the revisions of the data standards
Submission and review in the near future

- The details of e-data submission will be described in the notification and guide.

- But in practical situation, there will be remaining issues to be solved on a case-by-case basis.
  - They should be discussed at the consultation for the clinical e-data submission.
  - Function of data management and statistical analysis will be the key in such consultation.

- And for new drug review, clear explanation of the issues and the characteristics of the data will be critical.

Communication and mutual understanding between the reviewers and the person in charge of data management and statistical analysis should be enhanced.
Summary

• Advanced Review with Electronic Data Project being executed successfully so far, and our experience of reviewing and analyzing CDISC-conformant data is accumulating through multiple pilot projects.

• We have drafted the technical notification and technical conformance guide, so the details of the electronic submission will be provided in the near future.

• Conformity to the data standards, quality of the submitted electronic data and quality of the documentation about the data will be the key in future review process.

• Study data, programs, and also the function of data management and statistical analysis in industry/CROs will be more of interest to PMDA reviewers.

• Effective utilization of submitted electronic data will lead to more efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.

• We appreciate your understanding and would like to proceed the project in collaboration with all who are related to the data.