PMDA Update

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Pharmaceuticals and Medical Devices Agency
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

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

NDA etc.
e-Submission of study data

Data Accumulation

Database

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

**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

Visualization and analysis of data, supported by browsing software

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

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
Prospect of e-Study data utilization in Japan

Prospect As of April 2016 (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

*NDA=New Drug Application

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

Establishment of disease models
Publication of disease-specific guidelines

J-FY2022 - Publication of guidelines to contribute to drug development

J-FY2019 - 2021
Starting earnest cross-product analysis

J-FY2018
Ordinary utilization of e-data in the product review
Promotion of paperless operation

First-class review authority

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

Present
### Timeline for implementation of electronic data submission

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<td>Guidance and related documents</td>
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<td>△Issuance of “Basic Principles”</td>
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<td>△Validation Rules</td>
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<td>Data Standards Catalog</td>
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<td>Release of related information</td>
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<tr>
<td>Review</td>
<td>2014 Pilot</td>
<td>2015 Pilot</td>
<td>10/1</td>
<td>3.5 years of Transitional period</td>
<td>3/31</td>
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<tr>
<td>Consultation for e-study data submission</td>
<td>Pilot</td>
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<td>New Consultation framework</td>
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<td>System Development</td>
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<td>Summer</td>
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<td>System Development / Pilot for data submission</td>
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<td>Portal Site Open</td>
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Today
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.
  - During the period, applicants will be able to submit the data of at least one clinical trial included in their clinical data packages. (After the period, they need to submit the data of all the requested clinical trials.)

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<td>Notification on Practical Operations of Electronic Study Data Submissions published on Apr 27, 2015</td>
<td>42 months of the transitional period</td>
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<td>May 1</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.”
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

Now we are working on the revision of Technical Conformance Guide
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 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
### Study/analysis types and submission formats

<table>
<thead>
<tr>
<th>Section in notification of the Basic Principles</th>
<th>Content</th>
<th>Individual clinical study data</th>
<th>Analysis dataset Concerning efficacy and safety analysis</th>
<th>Analysis dataset Concerning PK or PK/PD analysis</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>
<td>ADaM</td>
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<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>
<td>ADaM</td>
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<td>Phase I studies of oncology drugs</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
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<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>
<td>In principle, ADaM, but other formats may be acceptable in certain cases</td>
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<tr>
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<td>QT/QTc studies based on ICH E14 guideline</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td>2. (2) 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>
<td>ADaM is preferable, but other formats are acceptable</td>
</tr>
<tr>
<td></td>
<td>Clinical studies where standard pharmacokinetic analysis was performed</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM is preferable, but other formats are acceptable</td>
</tr>
<tr>
<td></td>
<td>Population analysis</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM is preferable, but other formats are acceptable</td>
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<tr>
<td></td>
<td>Physiologically-based pharmacokinetic model analysis</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM is preferable, but other formats are acceptable</td>
</tr>
<tr>
<td>2. (2) References other than a and b, which were deemed necessary by PMDA</td>
<td>May be submitted in formats other than CDISC standard</td>
<td>SDTM</td>
<td>ADaM</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>
<td>ADaM</td>
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</table>

*Q&A No.12 of Notification on Practical Operations*
PMDA Data Standards Catalog

• PMDA Data Standards Catalog was published on Jul 30, 2015

• The list of acceptable versions
  • Data Exchange Standards (SAS Transport, SDTM, ADaM, Define, PDF)
  • Terminology Standards (CDISC CT, MedDRA, WHO DD Enhanced)

• Available on the PMDA website
  • 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.

• 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.

Now we are considering the process to start accepting new version of standards (e.g. ADaM IG 1.1) and to stop accepting old version of standards.
CDISC validation in PMDA

• PMDA validation rules was published on Nov 18, 2015
• We plan to use Pinnacle 21 Enterprise for CDISC validation
  • Apply to SDTM, ADaM, CT, and Define-XML
  • PMDA validation rules are provided on the PMDA website 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) “Reject”

- **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, ABLFL, ANLzzFL must have a value that is Y(/N) or Null
  - --FN, --RFN, --PFN, ABLFN, ANLzzFN 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

Because we will use the information in define.xml when we conduct CDISC validation, the validation rules of Define-XML are very important.
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.

• New FAQs will be released periodically.

• FAQs are provided only in Japanese.  Sorry…

Now we are working on the revision of FAQs
## 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 + Q&amp;A</td>
<td>Jun 20, 2014</td>
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<tr>
<td>Notification on Practical Operations of Electronic Study Data Submissions + Q&amp;A</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>
</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>
</tr>
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<td>Validation Rules</td>
<td>Nov 18, 2015</td>
</tr>
<tr>
<td>FAQ Web Page</td>
<td>Nov 27, 2015</td>
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# Information and resources for industry - Scheduled

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<tr>
<th>Notification/Guide/Workshop</th>
<th>Date</th>
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<tr>
<td>FAQ (2\textsuperscript{nd} release)</td>
<td>Jun 2016</td>
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<tr>
<td>Briefings regarding Portal Site</td>
<td>Jul 14, 2016</td>
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<tr>
<td>The 2\textsuperscript{nd} Workshop regarding Technical Conformance Guide</td>
<td>Aug 31 and Sep 1, 2016</td>
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<tr>
<td>- Clinical Pharmacology data</td>
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<td>- CDISC standard data</td>
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### Overview of the pilot projects

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<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 CP: 3 PPK datasets</td>
<td>CDISC: 3 drugs CP: 3 PPK/PD datasets</td>
<td>CDISC: 16 drugs CP: Standard Two-Stage Approach: 6 drugs Population Approach: 9 drugs PBPK: 2 drugs</td>
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<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 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>
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Completed
Experience based on the previous 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
- Annotated CRF
- Reviewer’s Guide (SDRG, ADRG)
- ADaM datasets
- Analysis Results Metadata
- Establishment of validation rules and severity in PMDA
- Review of validation results
Experience based on the pilot project 2015

• Clinical trial data of 6/16 drugs were provided with actual New Drug Applications.
  • The reviewers experienced actual relationship between the review process and the time required for analyzing the data.

• Reviewers insisted the importance of Analysis Results Metadata.
  • We will strongly recommend to submit ARM.

• The relationship between the information included in define file and that in SDRG/ADRG should be discussed.

• As a result of trial implementation of validation, there were several errors categorized as “Reject”.
  • Because the data were prepared before the release of the PMDA validation rules.
  • Please review the data and the define file carefully before data submission.
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 programming (innovative/complicated analyses)
  - Simulations

**Software and Datasets**
- **Software**: JMP
  - **Datasets**: SDTM
- **Software**: JMP, etc.
  - **Datasets**: ADaM
- **Software**: SAS, etc.
  - **Datasets**: SDTM, ADaM
Future implementation of CDISC in Japan

• Therapeutic Area Standards
  • PMDA, JPMA and medical societies have decided to review TA standards in cooperation.

• 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
• Advanced Review with Electronic Data Project is being executed successfully so far.
  • The Basic Principles, Notification on Practical Operations, Technical Conformance Guide, PMDA Data Standards Catalog, and PMDA Validation Rules 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.
  • Accumulated experiences will be reflected in the future Technical Conformance Guide and FAQs.

• 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
- Technical Conformance Guide on Electronic Study Data Submissions
- PMDA Data Standards Catalog (Japanese and English)
  - https://www.pmda.go.jp/files/000206482.zip