Best Practice for e-Study Data Submission to PMDA

CDISC Japan User Group (CJUG) ADaM Team

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PharmaSUG Single Day Event, Japan

September 04, 2018
# Definition of Term

<table>
<thead>
<tr>
<th>Japanese</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>申請</td>
<td>NDA</td>
</tr>
<tr>
<td>申請電子データ提出確認相談</td>
<td>Consultation on data format of the submission of electronic study data</td>
</tr>
<tr>
<td>治験相談</td>
<td>Clinical consultation</td>
</tr>
<tr>
<td>第2相終了後面談</td>
<td>End of Phase II meeting</td>
</tr>
<tr>
<td>申請電子データ提出</td>
<td>e-Study data submission/eData submission</td>
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<tr>
<td>経過措置期間</td>
<td>Transitional period</td>
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<tr>
<td>評価資料</td>
<td>Evaluation data/study</td>
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<tr>
<td>参考資料</td>
<td>Reference data/study</td>
</tr>
<tr>
<td>電子データ提出対象試験</td>
<td>Target data/study</td>
</tr>
<tr>
<td>臨床データパッケージ</td>
<td>Clinical data package</td>
</tr>
<tr>
<td>審査予定事前面談</td>
<td>Pre-consultation meeting on review schedule</td>
</tr>
<tr>
<td>別紙8</td>
<td>Attachment 8</td>
</tr>
</tbody>
</table>
Disclaimer

• The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of our organizations and companies.

• Our organization and company does not guarantee the accuracy or reliability of the information provided herein.
Abstract

• Electronic study data submission (eData submission) to Pharmaceuticals and Medical Devices Agency (PMDA) has started since October 2016 with 3.5 years transitional period and will be mandatory from April 2020. Several sponsors have already experienced eData submission to PMDA during the transitional period and its know-how is gradually accumulated in each sponsor.

• Therefore, CDISC Japan User Group (CJUG) ADaM team has been discussing the best practice and creating a document to summarize useful tips of eData submission to PMDA based on our practical experiences. In this presentation, lessons learned, major considerations and key factors for successful eData submission to PMDA, such as identification of study data to be submitted, consultation on data format of submission of electronic study data, validation of conformance to the CDISC standard and timeline for eData submission, will be provided.
Outline

• **CDISC Japan User Group (CJUG) ADaM Team Theme 1**

• **Background**
  • e-Study Data Submission to PMDA

• **Lessons Learned**
  • Identification of study data and analyses to be submitted
  • Consultation on data format of submission of electronic study data
  • Framework for e-Study data submission within a company
  • Considerations on Global Development

• **Summary**
Outline

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• Summary
# CJUG ADaM team theme 1

## Members

Across regions and companies!

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
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</thead>
<tbody>
<tr>
<td>Ayako Noda</td>
<td>Janssen Pharmaceutical K.K.</td>
</tr>
<tr>
<td>Ayuko Yamamura</td>
<td>Eli Lilly Japan K.K.</td>
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</tr>
<tr>
<td>Yohei Takanami (Lead)</td>
<td>Takeda Pharmaceutical Company, Ltd.</td>
</tr>
<tr>
<td>Yoshifumi Arita</td>
<td>Bayer Yakuhin, Ltd.</td>
</tr>
</tbody>
</table>
CJUG ADaM team theme 1
Deliverable in 2018

has been discussing the best practice and creating a document to summarize useful tips of e-Study data submission to PMDA based on our practical experiences.
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Key date for e-study data submission to PMDA

Oct-2016
Start accepting e-study data

2016 2017 2018 2019 2020

Transitional period (3.5 years)

Apr-2020
To be mandatory

• e-Study data submission during transitional period (as of Mar/30/2018)
  ✓ 41 products (26 companies)
  ✓ Characteristic for products
    ➢ Regardless of Japanese company/foreign company, NDA/sNDA*
    ➢ Several TA, especially oncology area

* sNDA: Supplemental new drug application
(In Japanese)
Huge change for us...

- Sponsor has to implement streamlined process for e-Study data submission because it greatly affects **timeline and cost for NDA**
- Data science dept. has to lead e-Study data submission and discuss it with stakeholders (e.g. other dept. and PMDA)

**Hard skill**
- CDISC, Programming, Statistics, Clinical Pharmacology

**Soft skill**
- Discussions/Collaborating with internal and external stakeholders
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## Consultations with PMDA on e-Study data submission

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Discussion topics on e-Study data submission</th>
<th>Timing (recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical consultation (e.g. End of Phase II meeting)</td>
<td>• To agree with PMDA about <a href="#">target data/studies and analyses</a> of e-Study data submission</td>
<td>A couple of years to 6 months before NDA</td>
</tr>
</tbody>
</table>
| Consultation on data format of submission of e-Study data (Consultation on data format) | • To discuss [technical issues/concerns](#) for data format  
• To share [validation issues](#) on Pinnacle 21 | Several months before NDA |
| Pre-consultation meeting on review schedule | • To confirm finalized submission package and application date  
• To submit [finalized Attachment 8](#) to PMDA beforehand | 6 weeks before NDA |
General milestones for e-study data submission to PMDA

- Phase II Study
- Phase III Study
- Pre-consultation meeting on review schedule
- Consultation on data format of submission of e-Study data
- Creation of Submission Package of e-Study data
- NDA

Lessons Learned
Identification of data/studies and analyses

Discussions at Clinical Consultation

- **Target data/studies** should be identified and agreed with PMDA based on clinical data package **at clinical consultation (e.g. End of phase II meeting)**
  - Target analyses (**ADaM-related materials**) per study as well

- Data science dept. (e.g. Stat, DM, CP) is heavily involved in the preparation of **e-Study data submission section in Briefing Book** as well as the discussion with PMDA at the consultation
  - **NOT** to discuss general questions/topics related to other products

- **To confirm at Preliminary consultation when wondering at which consultation a question has to be discussed**
  - Additional consultation may be needed to identify the target data/studies

**Clinical data package**

- Study 001
- Study 002
- Study 003
- Study 004
- ISS
- PPK

**Target data/study**

- Study 001
- Study 002
- Study 003
- Study 004
- ISS
- PPK

**Target analyses**

- PK, LB, AE
- Primary efficacy endpoint, Key secondary efficacy endpoint, AE, LB, EG
Identification of data/studies and analyses

Target data/studies

• To identify target data/studies according to PMDA requirements (e.g. Notification, FAQ)
• To confirm the clinical data package, **evaluation or reference**

- Evaluation data/study
  - A data/study used for main evaluation of drug

- Reference data/study
  - A data/study which is positioned as supplement of evaluation studies

• Which data/studies should be submitted?
  • Even for reference data/studies?
### Identification of data/studies and analyses

**Notification on Practical Operations of Electronic Study Data Submissions**

- **a.** 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 dose and administration

- **b.** Study data from phase I studies and clinical pharmacology studies listed right

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Relevant Studies</th>
</tr>
</thead>
</table>
| a. 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 dose and administration | **Phase I studies of oncology drugs**  
**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**)  
**QT/QTc studies** based on ICH E14 Guideline |
| Study data from phase I studies and clinical pharmacology studies listed right | **Clinical studies where standard pharmacokinetic analysis was Performed** (Standard CP study)  
**Population analyses (PPK)**  
**Physiologically based pharmacokinetic sufficient model analyses (PBPK)** |
| Phase I and clinical pharmacology studies **other than a and b**, which were deemed necessary by PMDA | **References other than a and b, which were deemed necessary by PMDA**  
**Integrated summary of safety and efficacy (ISS/ISE)** |

Q5-6: When a sponsor conducts clinical trials to evaluate the effect of intrinsic or extrinsic factors such as age, sex, weight, genetic factors, severity of disease, disease complications, or dietary, alcohol or smoking habits on the pharmacokinetics of an investigational drug, are these study data subject to submission even if the study result indicates negative effect of these factors on the pharmacokinetics of the drug?

A: It is not necessary to submit study data in that case. The 0.8 - 1.25 range on the geometric mean ratio of pharmacokinetic parameters (when pharmacokinetic parameters are log-normally distributed) can be used as one of the criteria for assessing a “negative effect” in deciding whether the study data need to be submitted. In some cases, study data might not need to be submitted even though the ratio is not within the range of 0.8 - 1.25. To ensure the necessity of submission of study data evaluating the effect of intrinsic or extrinsic factors, we recommend using a clinical trial consultation if necessary.
Q4-4: When is it necessary to submit electronic datasets of integrated analyses (ISS/ISE)? What is the scope of electronic data on ISS/ISE that must be submitted?

A: ..., submission of electronic data for ISS/ISE will be requested when integrated analyses of multiple clinical studies were performed for the assessment of specific efficacy or safety, such as assessments in special populations or of rare adverse events, and when the results are considered to be relevant to the assessment of efficacy, safety, and dosage and administration of the product. In order to confer with the PMDA on the scope of the submission of electronic data of integrated analyses, applicants must use the clinical trial consultation, not the “consultation on data format of submission of electronic study data,” because a decision on the scope of the submission accompanies scientific evaluations. At the submission of data, ...
It is not necessary to submit ADaM datasets for all analyses described in the statistical analysis plan. However, ADaM datasets should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as primary efficacy analysis and secondary efficacy analyses (secondary analyses of primary variable and analyses of key secondary variables), primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety. The applicant should preferably consult the PMDA beforehand on the sufficiency of the datasets to be submitted.

With respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration.

- To identify the important ADaM datasets/programs and programs used for analyses that should be submitted.
- To agree them with PMDA at clinical consultation.
### Identification of data/studies and analyses

**Target analyses for e-study data submission on clinical data package**

<table>
<thead>
<tr>
<th>Protocol No</th>
<th>Phase</th>
<th>Evaluation/Reference</th>
<th>e-Study data submission</th>
<th>Notes</th>
<th>Target analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>I</td>
<td>Evaluation</td>
<td>Yes</td>
<td>To meet condition to be submitted e-study data for CP study on FAQ (e.g. TQT study, BE study)</td>
<td>PK, AE, LB</td>
</tr>
<tr>
<td>002</td>
<td>I</td>
<td>Evaluation</td>
<td>Yes</td>
<td>PK, AE, EG</td>
<td></td>
</tr>
<tr>
<td>003</td>
<td>I</td>
<td>Reference</td>
<td>Yes</td>
<td>PK, AE</td>
<td></td>
</tr>
<tr>
<td>004</td>
<td>I</td>
<td>Reference</td>
<td>No</td>
<td>NOT to meet condition to be submitted e-study data for CP study on FAQ (e.g. Within the 0.8 - 1.25 range on the geometric mean ratio in Food Effect and DDI studies)</td>
<td>-</td>
</tr>
<tr>
<td>005</td>
<td>I</td>
<td>Reference</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>006</td>
<td>II</td>
<td>Evaluation</td>
<td>Yes</td>
<td>Studies that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration</td>
<td>Key efficacy endpoint, AE, LB, Biomarker</td>
</tr>
<tr>
<td>007</td>
<td>II</td>
<td>Evaluation</td>
<td>Yes</td>
<td>Key efficacy endpoint, AE, LB, EG</td>
<td></td>
</tr>
<tr>
<td>008</td>
<td>III</td>
<td>Evaluation</td>
<td>Yes</td>
<td>Key efficacy endpoint, AE, LB</td>
<td></td>
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<tr>
<td>009</td>
<td>III</td>
<td>Evaluation</td>
<td>Yes</td>
<td>Key efficacy endpoint, AE, LB, EG</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>-</td>
<td>Evaluation</td>
<td>Yes</td>
<td>Analyses were performed to assess rare adverse events</td>
<td>AE</td>
</tr>
</tbody>
</table>
Consultation on data format

General information

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Purpose</th>
<th>Timing (recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation on data format</td>
<td>• To discuss technical issues/concerns for data format</td>
<td>Several months before NDA</td>
</tr>
<tr>
<td></td>
<td>• To share validation issues on Pinnacle 21</td>
<td></td>
</tr>
</tbody>
</table>

• Might be held **more than once**
  • Depends on the volume of clinical package, situation etc.

• **Data science dept. has to mainly lead to create a document in the "Attachment 8" format and to discuss with PMDA at the consultation**
  • Adjust a schedule with stakeholders (e.g. Regulatory Affairs)
  • Summarize the discussion points
Consultation on data format

What kind of technical issues/concerns can we ask PMDA?

Lessons Learned

- Timeline
- Folder structure
- Media to be submitted
- Difficulty in creating CDISC-compliant e-Study data due to specific reasons
- File size
- How to create CDISC standard dataset
- Dataset not in English
- How to submit e-Study data without eCTD
- Custom domain
- Additional e-Study data submission after NDA
- SUPPQUAL that includes variables related to primary analyses
Consultation on data format
Attachment 8 (Supporting Document for Consultation on Data Format)

- Preparation of Attachment 8

- To be submitted to PMDA for Consultation on data format
  - Should be finalized and submitted at the Pre-consultation meeting on review schedule
- Examples of standardization and streamlining of the process for Attachment 8 creation in an organization
  - To create a template with instruction
    - To clarify R&R for each section
    - To annotate references and points to consider (e.g. refer to information at PMDA workshop, options of the contents)
    - To prepare English version in order to share with global team (Only Japanese version is available as of Jul., 2018)
  - To create tools to compare the list of datasets in Attachment 8 with that of actual datasets to be created
    - To keep the consistency of materials to be submitted to PMDA
### Lessons Learned

#### Consultation on data format

**Quality of Attachment 8**

**Case 1: Explanation of validation errors should be more specific**

<table>
<thead>
<tr>
<th>Store the data according to CRF</th>
<th>Store the data according to CRF. If actual amount of dose of concomitant medication was unknown, &quot;UNK&quot; is entered in Dose Description (CMDOSTXT) field and Dose Units (CMDOSU) is not provided.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not modify because analyses are not affected</td>
<td>There are some records of which PARAMCD/PARAM are empty. Alternatively, there are equivalent variables EGTESTCD/EGTEST. Statistical analyses and data summary were performed using them.</td>
</tr>
<tr>
<td>Implemented as per company’s standards.</td>
<td>In addition to variables of IDVAR and IDVARVAL, COGRPID and COSPID were also populated per company’s standard. COGRPID provides the traceability of where the comment came from, while COSPID is the sequence order within each subject.</td>
</tr>
<tr>
<td><strong>In case validation errors are detected in PMDA validation</strong></td>
<td>In this trial, subjects were expected to receive multiple treatments. Therefore, period start date time (i.e. TRxxSDT &amp; TRxxSDTM where xx=01, 02 …etc.) were used in place of TRTSDT/TRTSDTM to avoid confusion.</td>
</tr>
<tr>
<td><strong>In case validation errors are detected in PMDA validation</strong></td>
<td>All records of “LBSTRESN does not equal LBSTRESC” are subjective tests. Subjective results reported in LBORRES and also in LBSTRESC values, but LBSTRESN is set to null. So LBSTRESN does not equal LBSTRESC.</td>
</tr>
</tbody>
</table>
Consultation on data format

Quality of Attachment 8

Case 2: Inconsistency between Attachment 8 and Reviewer’s Guide (RG can be attached in validation result section)

- Explanation of validation errors also has to be described in RG
- Need to **keep consistency between Attachment 8 and RG**
  - PMDA points out the inconsistency (e.g. version of CDISC standards, list of CDISC-compliant data)
- RG can be attached to Attachment 8 to explain data issues/errors
  - To reduce the workload to copy the results of validation tool to Attachment 8 and RG (and QC)
Framework for e-Study Data Submission within a company

- Examples in each organization
  - To assign **a CDISC Expert** in each CTD team
    - Without organization changes
  - To establish **an e-Study Data Submission Committee**
    - Input not only compound-specific issues, but general topics
    - From Stat, DM, CP, RA etc.
  - To create **a new department**
    - With organization changes

- To manage whole the process and promote good governance of e-Study Data Submission (e.g. PMDA consultation, timeline, budget etc.)
Considerations on Global Development

- Differences on requirements between FDA and PMDA
  - Target data/studies
    - PMDA: Submission level <=> FDA: Study level
  - Validation Rules
    - PMDA has "Reject" criteria
    - Validation has to be conducted for both FDA and PMDA
      - The reasons of errors should be described in Reviewer's Guide
  - SI unit
    - Specific requirements to Japan NDA
    - Data might be modified for submission to PMDA

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Rule ID</th>
<th>Diagnostic Message</th>
<th>FDA Severity</th>
<th>PMDA Severity</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

*Image of RG to describe results of validation for both FDA and PMDA
Considerations on Global Development

• Timeline/Schedule for US and Japan NDA
  • To streamline the process for submission to PMDA
  • To take into consideration PMDA requirements beforehand
  • To continuously communicate with global team

Creation of e-Study Data

Need to meet both FDA and PMDA requirements under the tight schedule especially for simultaneous NDA

Lessons Learned
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• Summary
Summary

• For successful e-Study data submission
  • Important to collaborate across companies and share the knowledge and experiences towards the fast-approaching mandatory phase

• New role for Data Science department
  • To improve hard and soft skill for e-Study data submission
  • Deeply involved in the discussions with stakeholders especially for clinical consultation and consultation on data format

• Global Development
  • To understand the differences between regions and meet both the requirements of FDA and PMDA on e-Study Data Submission
Reference


[6] PMDA: FAQs on Electronic Study Data Submission (Excerpt)