Efficient preparation of eData submission to both PMDA and FDA

CDISC Japan User Group (CJUG) ADaM Team
PharmaSUG Single Day Event, Japan
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Disclaimer

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• 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 began in 1st October 2016 with a 3.5-year transitional period, and will be mandatory starting in 1st April 2020. On the other hand, eData submission to Food and Drug Administration became effective as of 17th December 2016 for all studies that start after this date for New Drug Application. Although both Heath authorities (HAs) require to submit eData, there are some differences in their requirements. Under the circumstance, industries would like to file NDA to both HAs as simultaneous as possible to maximize value of its product. Thus, it is important for us to know and manage these differences.

• Therefore, CDISC Japan User Group ADaM team has been creating a document to summarize differences in the requirements between both HAs and suggestion on streamlined process to achieve simultaneous submission. In this presentation, major important differences in the requirements and the timeline, tips of streamlined process and the internal team organization to prepare eData submission will be provided.
Outline

• CDISC Japan User Group (CJUG) ADaM Team Theme 5&6

• Background

• Efficient preparation of eData submission which meets requirements for both FDA and PMDA

• Summary
Outline

• CDISC Japan User Group (CJUG) ADaM Team Theme 5&6
  • Background
  • Efficient preparation of eData submission which meets requirements for both FDA and PMDA
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## CJUG ADaM team theme 5&6 Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akira Kurisu</td>
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<td>Sanofi K.K.</td>
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<tr>
<td>Ataru Nogawa</td>
<td>intellim Corporation</td>
<td>Yasuhiro Iijima</td>
<td>Novartis Pharma K.K.</td>
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<td>Maruho Co., Ltd.</td>
</tr>
<tr>
<td>Takashi Kitahara</td>
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<tr>
<td>Tomotaro Shiraishi</td>
<td>A2 Healthcare Corporation</td>
<td>Yoshiyuki Kuriya</td>
<td>TAIHO PHARMACEUTICAL CO., LTD.</td>
</tr>
</tbody>
</table>
CJUG ADaM team theme 5&6 Activities

Deliverable in Japanese

Team building

FDA 及び PMDA の申請における
効率的な電子データ準備と申請

CDISC Japan User Group (CJUG) ADaM Team Theme 5

発行日：yyyy/mm/dd
Outline

• CDISC Japan User Group (CJUG) ADaM Team Theme 5&6

• Background

• Efficient preparation of eData submission which meets requirements for both FDA and PMDA

• Summary
Key date for eData submission to both PMDA and FDA

**2016**

**PMDA**
Start accepting eData submission for all studies included in eData submission package from 1st Oct 2016

**2017**

**Transitional period (3.5 years)**

**2018**

**Mandatory period (1st Apr 2020-)**

**2019**

**NDA**
Start requiring eData with CDISC standards for all studies that start after 17th Dec 2016

**2020**

**IND**
Start requiring eData with CDISC standards for all studies that start after 17th Dec 2017
Aim to streamlined process

One common deliverables which meet the requirements for both FDA/PMDA should be created for simultaneous submission.
Outline

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• Summary
## Summary of differences/common points between FDA and PMDA in the requirement

<table>
<thead>
<tr>
<th>Item</th>
<th>FDA</th>
<th>PMDA</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>*** ADaM ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADaM IG</td>
<td>V1.1</td>
<td>V1.0</td>
<td>FDA accepts v1.0 for IND until 03/15/2020</td>
</tr>
<tr>
<td>Dataset</td>
<td>XPT</td>
<td>XPT</td>
<td></td>
</tr>
<tr>
<td>Analysis data reviewer’s guide</td>
<td>Filename: adrg.pdf</td>
<td>Filename: adrg.pdf / analysis-data-reviewers-guide.pdf</td>
<td>PMDA: file should be named so that the contents are identifiable</td>
</tr>
<tr>
<td>Define.XML</td>
<td>V2.0</td>
<td>V1.0/V2.0</td>
<td>Have to submit stylesheet FDA: Define.pdf should be submitted if Define.XML cannot be printed</td>
</tr>
<tr>
<td>.......</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Flow on this presentation

Information sharing about eData submission to PMDA

Consideration of timing of consultation meeting
### Build a team

**Example**

#### Submission team in Japan

<table>
<thead>
<tr>
<th>Working contents</th>
<th>Main person</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of target study/analysis</td>
<td>RA, DM, CP, Stat, Prog</td>
</tr>
<tr>
<td>SDTM</td>
<td>DM, (Stat, Prog)</td>
</tr>
<tr>
<td>ADaM</td>
<td>Stat, Prog</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>CP</td>
</tr>
<tr>
<td>Operations to submit eData</td>
<td>RA-ops</td>
</tr>
<tr>
<td>Overall timeline</td>
<td>RA</td>
</tr>
<tr>
<td>Communication with PMDA</td>
<td>RA</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Clarification of Role & Responsibility!

Information sharing, especially PMDA requirements
Confirmation with team

**important point**

- NDA timeline
- eData submission package
- Policy of creating deliverables
- Resource management
- Current situation per study (next slide)
- Budget
- Overall timeline of eData submission preparation
Confirmation of current situation of eData per study important point

still ongoing?

Possibility of Waiver/Exemption
- Are there enough electronic datasets?
- When did the study start?
- Is the product “Orphan drug”?

Necessity of Legacy data conversion

Has eData for the study already been submitted to either HAs?

Are there any issues in datasets?
## Preparation of eData Validation rule

<table>
<thead>
<tr>
<th>Conformance rule (CDISC standards) (Pinnacle 21)</th>
<th>Conformance rule (Pinnacle 21) based on PMDA validation rule</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Reject</em>/Error/Warning</em>*</td>
<td><strong>Reject/Warning</strong></td>
</tr>
<tr>
<td>* Based on Rejection criteria for study data</td>
<td></td>
</tr>
</tbody>
</table>

* Based on Rejection criteria for study data
**Preparation of eData**

**Validation rule**

<table>
<thead>
<tr>
<th>Rule ID</th>
<th>Publisher ID</th>
<th>Message</th>
<th>Description</th>
<th>FDA Severity</th>
<th>PMDA Severity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD0001</td>
<td>1</td>
<td>Missing ADSL dataset</td>
<td>ADaM Subject level (ADSL) dataset should be included in every submission.</td>
<td>Reject</td>
<td>Reject</td>
<td>X</td>
</tr>
<tr>
<td>AD0005</td>
<td>5</td>
<td>‘FL value is not Y, N or null</td>
<td>A variable with a suffix of FL must have value that is Y, N or null (exception 1: RFL, PFL, ABLFL, ANLzzFL. Exception 2: Population flags COMPLFL, FASFL, ITTFL, PPOTFL, SAFFL, RANDFL, ENRLFL cannot be null and at least 1 must be included in ADSL).</td>
<td>Error</td>
<td>Reject</td>
<td>X</td>
</tr>
<tr>
<td>AD0006</td>
<td>6</td>
<td>‘FN value is not 0, 1 or null</td>
<td>A variable with a suffix of FN has a value that is not 0, 1 or null (exception: RFN, PFN, ABLFN, ANLzzFN and population flags Numeric COMPLFN, FASFN, ITTFN, PPOTFN, SAFFN, RANDFN, ENRLFN cannot be null and at least 1 must be included in ADSL).</td>
<td>Error</td>
<td>Reject</td>
<td>X</td>
</tr>
<tr>
<td>AD0033</td>
<td>33</td>
<td>*RFL value is not Y or null</td>
<td>A variable with a suffix of RFL must have a value that is Y or null (R = record level flag variable)</td>
<td>Error</td>
<td>Reject</td>
<td>X</td>
</tr>
</tbody>
</table>
Preparation of eData
Validation rule (Cont’d)

Conformance rule (CDISC standards) (Pinnacle 21)
Reject*/Error/Warning
* Based on Rejection criteria for study data
Conformance rule (Pinnacle 21) based on PMDA validation rule

Rejection criteria for study data
1. **A dataset named ts.xpt with information on SSD must be present** for each study.
2. The correct STF file-tags must be used for all XPT file.
3. **For SEND/SDTM data, a DM dataset and define.xml must be submitted Module 5. For ADaM data, an ADSL dataset and define.xml must be submitted.**
4. In a new submission include an STF and use the “Replace” operator to replace previously submitted documents which were not referenced in an STF
## Preparation of eData

### Legacy data conversion (LDC)

<table>
<thead>
<tr>
<th>Target study</th>
<th>NDA: non-CDISC standard study starting after Dec17 2016</th>
<th>NDA: non-CDISC standard study included in eData submission package for product applied for after 1st Apr 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-target study</td>
<td>NDA: non-CDISC standard study starting before Dec17 2016</td>
<td>Exemption such as orphan drug application, anti-HIV drug</td>
</tr>
<tr>
<td>Key point</td>
<td>Create <strong>Legacy data conversion plan &amp; Report (LDCP)</strong> in RG as Appendix (PhUSE has recently released ADRG version 1.2 including LDCP)</td>
<td>Consult with PMDA and describe Reviewer’s guide if there are any issues</td>
</tr>
</tbody>
</table>

Create internal template for Reviewer’s guide including LDCP
Submission of eData

Timeline of around NDA (Example: very tight timeline)

• FDA: timeline varies from project to project in real life
• PMDA: there are some key consultations and dates based on the guidance
Submission of eData

**eData submission except for NDA**

- Post-marketing clinical trials
- Products for which the evaluation of study results is practically carried out before NDA
  - Sakigake designation system
  - Anti-HIV drug

**Commercial IND**
- Submit eData for a study which starts after 17Dec2017

**Flowchart**

- Preparation of eData
- Preparation of SDSP
- Pre-IND meeting
- IND
  - Can consult about eData submission for IND
  - Submit SDSP
  - Submit eData
Submission of eData

*eData submission except for NDA (cont’d)*

- Real-Time Oncology Review
  - Pilot-project

https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
Information sharing about eData submission to PMDA

Japan team/Organization level

Global team

Japan team/Project level
Information sharing about eData submission to PMDA

Japan team/Organization level

Provide Training/Build Task force team
Important information
- Overall of requirements for eData submission to PMDA
- Differences between FDA and PMDA
- Role & Responsibility
- Standard timeline
- Several consultation with PMDA

Japan team/Project level

- eData submission package
- Overall milestone*/timeline
* Milestone: Consultation with PMDA/start date of preparation/date of submission of eData

Global team

Share information at project level?
- Can share more project specific contents
- Might be different from the contents between projects

Share information at governance level?
- Can share without variability
Consideration of timing of consultation meeting

- Timeline of FDA meeting is unclear...
- Timeline should be shared common file which can be confirmed timely and mutually
Study Data Standardization Plan (SDSP) vs Attachment 8

**SDSP**

Pick up the common term

**Attachment 8**

The content of SDSP is not same as that of Attachment 8

Creation of internal summary sheet including the following information to manage whole eData submission package in the product

- Study information
- CDISC standards Version
- Dictionary version
- Data standard (CDISC or legacy)
- Waiver
- Exemption
- Person in change
- Contents of consultation
Outline

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Summary

- Clarify the differences in regulatory Requirements between FDA and PMDA
- Communicate with related function and global closely
- Aim to create one common deliverables which meets the requirements for both FDA and PMDA as much as possible