SA02 - Challenges of submitting electronic study data to 2 authorities – PMDA and FDA

Torsten Petsching – 6th November 2018
Disclaimer

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Submission background

- Data of two studies were submitted to the PMDA in 2017

- The first submission of study data of the same compound to the FDA was in 2014
Submission setting for PMDA

Interim and final data for two studies were submitted in two waves

- **Wave 1:** interim data of one study AND final data of the second study
  - submitted 28-AUG-2017
  - accepted 20-SEP-2017

- **Wave 2:** final data of the first study
  - submitted 06-NOV-2017
  - accepted 09-NOV-2017
**Submission Requirements: PMDA versus FDA (1)**

<table>
<thead>
<tr>
<th>Item</th>
<th>PMDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion of study data in CDISC standard in eData Submissions</td>
<td>Transition period Mandatory for submissions with planned submission date after 31-MAR-2020 based on the PMDA Data Standards Catalog.</td>
<td>eCTD submissions required, with eData sets included for several years. Studies that start after 17-DEC-2016 must use the data standards listed in FDA Data Standards Catalog.</td>
</tr>
</tbody>
</table>
| Guidance/Notification             | • Basic Principles  
• Notification on Practical Operations  
  ▪ Specific requirements for Ph-I/CP studies  
  ▪ Analysis / ADaM creation SAS programs  
  ▪ SI unit as standard unit in SDTM | Providing Regulatory Submission In Electronic Format - Standardized Study Data                                                                 |
| Technical Guide                   | • Technical Conformance Guide  
  ▪ Specific requirements for Ph-I/CP studies  
  ▪ Analysis Results Metadata (ARM)  
  • PMDA Data Standard Catalog        | • Technical Conformance Guide  
  ▪ E.g. includes considerations on the Legacy Data Conversion  
  • FDA Data Standard Catalog        |
## Submission Requirements: PMDA versus FDA (2)

<table>
<thead>
<tr>
<th>Item</th>
<th>PMDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data File Size Limitations</td>
<td>5 GB is the current size limit</td>
<td>5 GB is the current size limit. Bigger files must be split, but the big file should also be included.</td>
</tr>
<tr>
<td>Study Data Standardization Plan</td>
<td>NA</td>
<td>For INDs, it should be created and located in the general investigational plan</td>
</tr>
<tr>
<td>Patient Data Reports (eCRFs)</td>
<td>After the application (not part of the eData package, rather as submission documentation after the application)</td>
<td>In the eCTD submission (required as part of the eData package and included in module 5)</td>
</tr>
<tr>
<td>ADaM: Analysis Results Metadata (ARM)</td>
<td>Strongly recommend to be submitted</td>
<td>Not required</td>
</tr>
<tr>
<td>Meetings</td>
<td>Consultation meeting specific to eData submission</td>
<td>pre-NDA meeting, Type C Meeting</td>
</tr>
<tr>
<td>Validation Rules</td>
<td>SDTM, ADaM, Define.xml</td>
<td>SDTM, ADaM, Define.xml, SEND</td>
</tr>
</tbody>
</table>
Meetings for discussion of eData Standards (1)

**FDA:**

- 3 different types of formal meetings (Type A, Type B, Type C)*
  - Technical questions as part of Type C meeting
  - but could also be part of Type B meetings
    (e.g. Pre-IND, End of Phase 2, Pre-NDA/Pre-BLA meeting)

Meetings for discussion of eData Standards (2)

PMDA

- eData consultation meetings
  - At least one eData consultation meeting to explain the delivery package
  - eData submission topics only
  - For this project, BI had 6 meetings (at the request of the local Japanese team in Japanese)
PMDA process - eData consultation

Application ~ Consultation: Almost 1 month

All interactions are in Japanese

Application with “Appendix form 14”
- Participants
- General info
- Question at mtg.

Submission of meeting document “Appendix form 8”
- Submission/Study info
- Question with detail
- Info about eData (cut-off, standard version)
- CDISC conformance

eData consultation (Face to face or Telephone conf.)

Question details are to be decided at application

Most information are duplicated in Reviewer’s Guide

Main purpose is to get agreement for remaining data deviation from validation rules

Most information are duplicated in Reviewer’s Guide

Main purpose is to get agreement for remaining data deviation from validation rules
# Validation Rules for SDTM (1)

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Identifier</strong> of the check</td>
<td>Pinnacle 21 Enterprise edition (PMDA ID = P21 ID)</td>
<td>Pinnacle 21 Enterprise edition (FDA ID specific, starting with FDA...)</td>
</tr>
<tr>
<td><strong>Number of rules</strong></td>
<td>326</td>
<td>314</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>• Reject: 9</td>
<td>• Reject: 4*</td>
</tr>
<tr>
<td></td>
<td>• Error: 128</td>
<td>• Error: 201</td>
</tr>
<tr>
<td></td>
<td>• Warning: 189</td>
<td>• Warning: 113</td>
</tr>
</tbody>
</table>

* No rejection in P21, but according the „Technical Rejection Criteria for Study Data“
Validation Rules for SDTM (2)

- Different handling of source data issues
  - PMDA: resolve P21 rejection
  - FDA: describe issue in Clinical Study Data Reviewers Guide (csdrg)

- Example
  - For the interim data, hard-coding in SDTM was done to omit a Pinnacle 21 rejection error
  - Hard-coding does not fit to the CDISC philosophy
Validation Rules for SDTM (3)

Options to run the validation rules

- SDTM – ADaM cross-check:
  AE, DM and EX should be included for traceability checks between ADaM and SDTM

Version

- PMDA:  Pinnacle 21 Enterprise edition (v3.0.5)
- BI/BDLS:  Free version of Pinnacle 21 Community tool
  (started with version 2.2.0, but then changed to version 2.1.3)
Findings domain (Laboratory / Vital signs) concept (1)

- **BI Standard units <> SI units <> US conventional units**

  - **PMDA:** SI units
  - **FDA:** SI units and/or US conventional units
  - **Examples:**
    - **SYSBP:**
      - BI unit = FDA US conventional unit: mmHg
      - PMDA SI unit: Pa
    - **Haemoglobin:**
      - BI unit: g/L
      - PMDA SI unit: kg/L
      - US conventional unit: g/dL
Findings domain (Laboratory / Vital signs) concept (2)

Solution for the FDA → 2 different LB datasets created:

- **LB dataset submitted:**
  - The values in the unit used for the clinical trial report included in the Result/Finding in standard format (LBSTRESC)

- **Second LB dataset:**
  - The values in US conventional unit included in the Result/Finding in standard format (LBSTRESC)
  - Prepared, but submitted only on request
Findings domain (Laboratory / Vital signs) concept (3)

Solution for the PMDA \(\rightarrow\) One LB / SUPPLB dataset created:

- **LB dataset:**
  - The values in SI units included in the Result/Finding in standard format (LBSTRESC)

- **SUPPLB dataset:**
  - The values in the units used for the clinical trial report as separate QNAMs (Units, results, lower range, higher range)
Conclusions (1/2)

- If the same package is to be submitted to both authorities → **plan for it** (Many similarities, but also some differences which need considerations and resource planning upfront)

- As better you have the **data under control**, the better for the submission → as for all Data Management processes 😊

- Consider to develop a submission subject matter expert for PMDA/FDA
Conclusions (2/2)

- Industry need to see how the authorities drive the eData within the eCTD submissions in the future (i.e. development in the same direction of rather more differences)

- Open the **dialog with the authorities** as early as possible!!
Questions...
Back-up Slides
## PMDA rejection rules (SDTM)

<table>
<thead>
<tr>
<th>RULE ID</th>
<th>MESSAGE</th>
<th>DESCRIPTION</th>
<th>DOMAINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT2001</td>
<td><code>&lt;Variable Name&gt;</code> value not found in <code>&lt;Codelist Name&gt;</code> non-extendible codelist</td>
<td>Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extendible codelists.</td>
<td>ALL</td>
</tr>
<tr>
<td>CT2004</td>
<td><code>&lt;Variable Name&gt;</code> value not found in <code>&lt;Codelist Name&gt;</code> non-extendible codelist</td>
<td>Variable must be populated with terms from its CDISC controlled terminology codelist. When its value level condition is met. New terms cannot be added into non-extendible codelists.</td>
<td>QS, TS</td>
</tr>
<tr>
<td>SD0002</td>
<td>NULL value in variable marked as Required</td>
<td>Required variables (where Core attribute is ‘Req’) cannot be NULL for any records.</td>
<td>ALL</td>
</tr>
<tr>
<td>SD0056</td>
<td>SDTM Required variable not found</td>
<td>Variables described in SDTM IG as Required must be included in the dataset.</td>
<td>ALL</td>
</tr>
<tr>
<td>SD0062</td>
<td>Incompatible data source</td>
<td>Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited).</td>
<td>ALL</td>
</tr>
<tr>
<td>SD0064</td>
<td>Subject is not present in DM domain</td>
<td>All Subjects (USUBJID) must be present in Demographics (DM) domain.</td>
<td>ALL</td>
</tr>
<tr>
<td>SD1020</td>
<td>Missing DM dataset</td>
<td>Demographics (DM) dataset must be included in every submission.</td>
<td>DM</td>
</tr>
<tr>
<td>SD1073</td>
<td>Variable prohibited for use in SDTM</td>
<td>Variables described in IG as inappropriate for usage must be not included in the dataset.</td>
<td>ALL</td>
</tr>
<tr>
<td>SD1074</td>
<td>Variable which can be used only in SEND</td>
<td>Variables designed only for SEND pre-clinical studies must be not included in the SDTM dataset.</td>
<td>ALL</td>
</tr>
</tbody>
</table>
A “Trial Summary (TS)” dataset must be present for each study in module 4/5

The correct STF file-tags must be used for all standardized datasets in module 4/5

DM dataset and define.xml must be submitted in module 4/5

For each study in module 4 and in module 5 no more than one dataset of the same name should be submitted as new
**PMDA process-eData consultation (Appendix form 14)**

<table>
<thead>
<tr>
<th>Code of active ingredient</th>
<th>Name of active ingredient</th>
<th>Section in PMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Title of consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

1. Planned question at consultation - 1
2. Planned question at consultation - 2...

Consultation history in this project

Consultation document in previous
PMDA process - eData consultation (Appendix form 8)