CDISC data Submission FDA vs PMDA

CDISC German User Group Meeting

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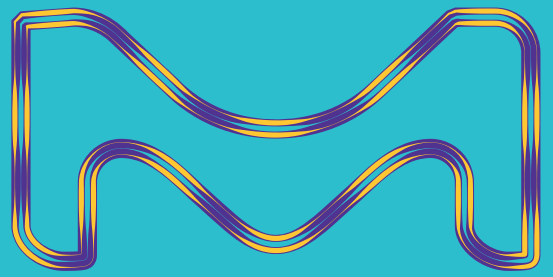

MERCK

Key areas of different SDTM requirements FDA - PMDA

- Information and advice in pre-submission phase
- Datasets and define.xml
- Data validation requirements
- eSubmission/eCTD
- Further data submissions after the initial data submission

Ways of adressing general questions on CDISC standards
Before submission

FDA

- **Technical Questions on Data Standardization**
- eData Group for questions on CDISC standards via email
- Questions/answers independent of any submission
- **Mock (Test) Submission**
- Submission of (live) sample CDISC data in eCTD structure
- Assessment by FDA eSub/eData groups: Validation Report, Additional Feedback

PMDA

- **CDISC Consultation Meetings**
- Description of studies
- Planned CDISC versions
- List of planned data standards used
- Free-form questions on standards requirements
- Discretion of sponsor which supporting documents to include:
- e.g. Annotated CRF, Study Data Reviewers Guides (if available)

Pre-submission CDISC advice comparison

FDA

- Helpful consultation and advice
- **No** information passed on to review division
- Actual datasets and files provided for consultation

Feedback from Mock Submission: approx 2mths

Feedback from eData: few days

PMDA

- Thorough check of all documents (incl. aCRF, reviewers guides) provided for the consultation meeting
- **Information discussed at the consultation meeting was considered binding for the actual submission**:
  - No changes to the submitted documents (aCRF, reviewers guid) at the time of actual submission expected
  - Any instructions received at the consultation meeting are considered binding
- No datasets submitted (paper only)

Instant feedback at meeting

Key differences on submitted SDTM packages

Laboratory Units:

FDA: recognizes SI units but prefers some US conventional units

PMDA: strict requirement for SI units only

Issue: CDISC Unit terms vs official SI unit terms

- Internal Standard Units used in Lab & Vital Signs datasets
- PMDA accepted workaround for traceability to existing (FDA) ADaM package:
  - SI units placed in SUPPLB, SUPPVS; original datasets in separate eCTD folder
- Terms for unit codelist based on CDISC, not on SI (explanation to PMDA)
- Additional appendix in reviewers guide for units and conversion factors required for PMDA

File Naming Conventions Reviewers Guides (see Technical Conformance Guides)

FDA: reviewersguide.pdf/csdrg.pdf - for SDTM

PMDA: study-data-reviewers-guide.pdf, analysis-data-reviewers-guide.pdf

- Separate define.xml backbones to hyperlink to reviewers guides with different file names

Different Pinnacle 21 (P21) Validation Rules

Additional validation rules for PMDA, e.g.:

- Inconsistent value of Reference Time Points
- Date is after the Study Reference Period End Date

Different view on severity of some issues

- Some FDA errors are PMDA warnings and vice versa
- PMDA reject rules (reject issue => data package not accepted by PMDA)

- Validation with PMDA P21 configuration to identify potential reject criteria before database lock
  - Key reject criterion: “NULL value in variable marked as Required”
    - AEDECOD (not all adverse events coded)
    - IETEST (incorrect Inclusion/Exclusion criterion in IETESTCD)

Different requirements for Pinnacle 21 (P21) Validator Version

FDA:

- **Latest** P21 validatator version prior to submission

PMDA:

- **Specific** P21 validator version as published on PMDA website (no other version accepted)

- Separate reviewers guides to explain P21 validation issues targeted to each authority
  - Taking care to name the retrospective validator versions correctly in the reviewers guides

- For FDA, in case of P21 version change with modified validation rules prior to submission => update of reviewers guide potentially necessary
- For PMDA, more stability (yearly updates)

Submission of electronic study data

FDA

- CDISC data packages are part of the regular eSubmission
- Data packages are directly included in eCTD module 5

PMDA

- CDISC data packages need to be submitted prior to the actual submission for PMDA validation (1-3 weeks prior)
- Outside of the general submission process
  - manual upload of files to PMDA gateway or via DVD
  - folder structure set-up as tsv file (manual entries in Excel sheet):

A	B	C	D	E	F	
data type	file path	study data ID	operation	previous stud	Anaylsis type	de
F	m5\datasets\study\misc\lb.xpt	0900babe80b40cbd	new		Non-CP	
F	m5\datasets\study\misc\supplb.xpt	0900babe80b40cd0	new		Non-CP	
F	m5\datasets\study\misc\suppvs.xpt	0900babe80b40cdb	new		Non-CP	
F	m5\datasets\study\misc\vs.xpt	0900babe80b40ce7	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\acrf.pdf	0900babe80c3dc30	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\define.pdf	0900babe80c3dc35	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\study-data-reviewers-guide.pdf	0900babe80c3dc62	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\define.xml	0900babe80c3dc36	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\ae.xpt	0900babe80c3dc31	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\cm.xpt	0900babe80c3dc32	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\co.xpt	0900babe80c3dc33	new		Non-CP	
F	m5\datasets\study\tabulation\sdtm\dm.xpt	0900babe80c3dc4f	new		Non-CP	

Submission of Follow-up Data

FDA

- Initial submission
- 90d/120d after initial submission: Safety follow-up submission

PMDA

- Only initial submission
- Additionally: information request => reports and data submitted to other authorities
  - E.g. FDA safety follow-up report + datasets
  - E.g. EMA report + datasets

➢ For PMDA, additional data submission potentially required in short period of time

- P21 validation isssues when datasets were not intented previously for submission (e.g. in case of EMA)

Summary

- Data packages need to be targeted for each authority

- No convenient solution found for handling different units for each authority
  - Accpetance with SI units in Supplemental datasets is accepted currently by PMDA
  - Permanent solution?

- Different P21 validation rules and requirements with two sets of reviewers guides

- PMDA strict rules: correction needed before datasets are accepted (update of reviewers guide or datasets, depending on issue)

- Be prepared to submit more data to PMDA than planned (follow-up safety data) - early preparation and validation

Questions ?