A Comprehensive Review of Data Traceability and Standardization in Regulatory Submissions: Lessons from the Study Data Standardization Plan (SDSP) and Variations Among FDA, PMDA, and NMPA

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Meet the Speaker

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Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *This presentation will focus on Clinical Data.*

Agenda

1. Importance of Data Standards
2. Study Data Standardization Plan (SDSP)
3. Overview of Data Packages
4. Data Standards Requirement
5. Technical Rejection and Validation Criteria
6. Differences between CBER and CDER
7. File Size requirements
8. Conclusion

Importance of Data Standards

Adherence to Clinical Trial data Standards

Why Data Standards is important:

- CDISC standards are **required by regulatory agencies** to be used when submitting Clinical Data
- Data is **meaningful if organized** and **standardized**
- Prior to data standards it was an **uncontrolled environment**
- **Harmonize data faster** if records are collected and submitted in the standardized format
  - Across Studies and Sponsors
- **Faster review** from agency
- **Reusability** of data for future analysis

Study Data Standardization Plan (SDSP)

Study Data Standardization Plan (SDSP)

- SDSP documents the use of data standards in **nonclinical** and **clinical** studies within a development program.
- It is a living document that cover all studies under the IND related to the product.
- Revised and updated for any subsequent Stage Gates.
- Assists the FDA in identifying potential data standardization issues early in the development program.
- Should be in the eCTD Module 1.20.
- Document SDTM and ADaM version along with the Control Terminology and dictionary used i.e., MedDRA, WHO DD etc.

SDSP CBER Appendix is created for ***CBER only***.

- Submitted no later than End of Phase II
- Living document, revised and updated for any subsequent Stage Gates.

Overview of Data Packages

Overview of Data Packages

Tabulation/ SDTM

- **SDTM data in SAS Transport file format (.xpt)** Example: ts.xpt, dm.xpt

- **define.xml version 2.0/2.1**
  - Hyperlinks navigate correctly
  - Derivation rules documented in plain English

- **Annotated CRF (acrf.pdf)**

Examples from CDISC MSG 2.0
- Annotated with SDTM domains & variables
- If two domains are used on the same page use different background color
- SUPPQUAL variables are annotated with QNAM
- Use TESTCD for --ORRES values

- **Clinical Study Data Reviewer's Guide (csdrg.pdf)**

Analysis/ ADaM

- **ADaM data in SAS Transport file format (.xpt)**

Example: adsl.xpt, adae.xpt

- **define.xml version 2.0/2.1**
  - Hyperlinks navigate correctly
  - Derivation rules are correctly document in plain English

- **analysis-results-metadata.pdf**

Supports key safety/efficacy

- **Analysis Data Reviewer's Guide (adrg.pdf)**

- **Analysis programs in ASCII text format (.txt)**

Bioresearch Monitoring (BIMO)

Pivotal studies submitted to FDA CDER only

- **Part 1:** site information, protocols, and annotated Case Report Forms

- **Part 2: BIMO listings**
  - Subject data listings organized by site for each study (PDF)
  - 10 Listings per site

- **Part 3: Clinical Site Level dataset (clinsite.xpt):** Single site level summary data for site selection tool across all pivotal studies
- define.xml 2.0/2.1
- bimo-reviewer-guide.pdf (optional)

BIMO: 10 Listings are organized by site

A: Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements (non-randomized)

B: Subject listing for treatment assignment (randomization)

C: Subject listing of drop-outs and subjects that discontinued with date and reason

D: Evaluable subjects/ non-evaluable subjects and reason not evaluable

E: By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

F: By subject listing, of AEs, SAEs, deaths and dates

G: By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation

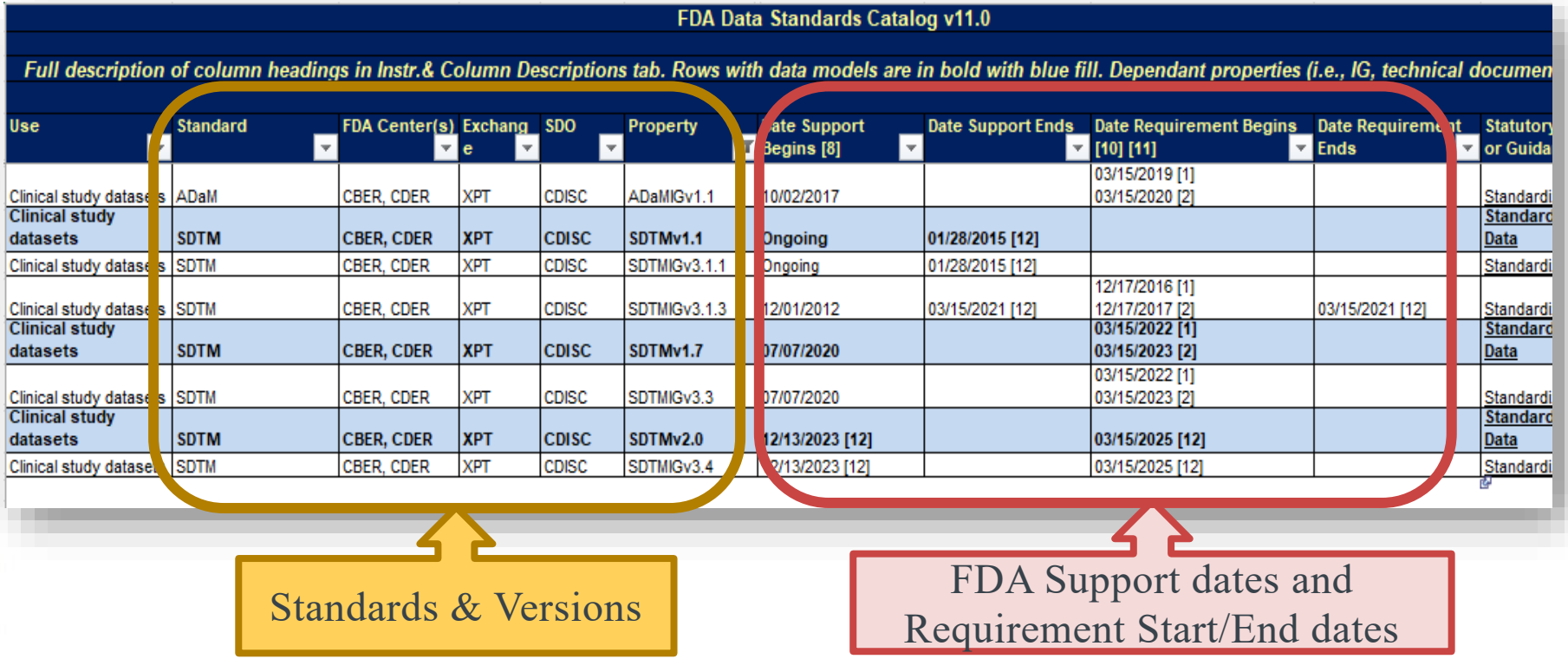
H: By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint

I: By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

J: By subject listing, of laboratory tests performed for safety monitoring

Data Standards Requirement

FDA Data Standards Catalog



FDA Data Standards Catalog v11.0

Full description of column headings in Instr.& Column Descriptions tab. Rows with data models are in bold with blue fill. Dependant properties (i.e., IG, technical documen

Use	Standard	FDA Center(s)	Exchange	SDO	Property	ate Support Begins [8]	Date Support Ends	Date Requirement Begins [10] [11]	Date Requirement Ends	Statutory or Guida
Clinical study datase	ADaM	CBER, CDER	XPT	CDISC	ADaMIGv1.1	10/02/2017		03/15/2019 [1] 03/15/2020 [2]		Standardi
Clinical study datasets	**SDTM**	**CBER, CDER**	**XPT**	**CDISC**	**SDTMv1.1**	**Ongoing**	**01/28/2015 [12]**			**Standard Data**
Clinical study datase	SDTM	CBER, CDER	XPT	CDISC	SDTMIGv3.1.1	Ongoing	01/28/2015 [12]			Standardi
Clinical study datase	SDTM	CBER, CDER	XPT	CDISC	SDTMIGv3.1.3	12/01/2012	03/15/2021 [12]	12/17/2016 [1] 12/17/2017 [2]	03/15/2021 [12]	Standardi
Clinical study datasets	**SDTM**	**CBER, CDER**	**XPT**	**CDISC**	**SDTMv1.7**	**07/07/2020**		**03/15/2022 [1] 03/15/2023 [2]**		**Standard Data**
Clinical study datase	SDTM	CBER, CDER	XPT	CDISC	SDTMIGv3.3	07/07/2020		03/15/2022 [1] 03/15/2023 [2]		Standardi
Clinical study datasets	**SDTM**	**CBER, CDER**	**XPT**	**CDISC**	**SDTMv2.0**	**12/13/2023 [12]**		**03/15/2025 [12]**		**Standard Data**
Clinical study datase	SDTM	CBER, CDER	XPT	CDISC	SDTMIGv3.4	2/13/2023 [12]		03/15/2025 [12]		Standardi

Standards & Versions

FDA Support dates and Requirement Start/End dates

Technical Rejection and Validation Criteria

Technical Rejection and Validation Criteria

- FDA developed tools to help sponsors meet updated study data standard requirements. To provide more transparency on the validation process, FDA has created Business Rules, Validation Rule and Technical Rejection Criteria.
- **FDA Business Rules and Validation Rules**: These documents outline the guidelines utilized by the FDA study data validator to verify that the data comply with standards and facilitate effective review and analysis.

Severity Level	Error Code	Description of Technical Rejection Criteria
HIGH	1789	Study files must be referenced in a Study Tagging File (STF). STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports
HIGH	1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSTDTC) must be present for each study in the tabulation package If legacy, a simplified ts.xpt must contain SSTDTC
HIGH	1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files
HIGH	1736	• For SDTM data, a DM dataset and define.xml must be submitted • For ADaM data, an ADSL dataset and define.xml must be submitted • For SEND data, a DM dataset and define xml must be submitted

PMDA Validation and Reject Criteria

- The PMDA categorizes severity levels as Reject, Error, and Warning
  - **Reject** Issues classified must be resolved.
  - **Error** issues should ideally be addressed; if they are not, an explanation must be provided in the reviewer's guide.
  - **Warning** do not need to be documented in the reviewer guides.

PMDA Rejection criteria can be found in the study data validation rules zip files located https://www.pmda.go.jp/english/review-services/reviews/0002.html

Differences between CBER and CDER

Differences between CBER and CDER

- The FDA Industry Guidance "Providing Regulatory Submissions in Electronic Format — Standardized Study Data" applies to both CBER and CDER, however, there are additional technical specifications published by individual offices that contain specific details for submitting data.
- The **FDA technical specifications are not binding guidance**, however, beware this guidance is documented in the **Standardized Study Data guidance which is a binding document**.
- The **reviewers' internal tools and checks are built on this requirement** and will help in review of the packages. It is **recommended that you talk to your review division** if a guidance will not be followed in which case a waiver can be submitted but is not required.

CDER	CBER
SDSP	SDSP, including the Appendix and aCRF
BIMO package required for all pivotal studies	No BIMO package
Supported Therapeutic Area guide reference in the TCG under section 5	Recommends Vaccines Technical Specification Guidance for Office of Vaccine Research and Review (OVRR)

File Size Requirements

File Size requirements

- The eSub package created for the FDA may vary for the one intended for NMPA submission due to different requirements shown in the table below.
- While the PMDA file size requirement is similar to the FDA requirement, it is best to consult PMDA on any file size issues prior to the submission.

FDA	NMPA
Split dataset larger than 5 GB	Split dataset larger than 4 GB
Submit both split and non-split datasets	Only submit split datasets
Define.xml should only include non-split datasets (e.g., LB domain)	Define.xml should only include the split datasets (e.g., LB1 and LB2 domain)
No validation error of XPT file	Validation error due to naming of XPT file name not per CDISC domain name
Create a split folder and include the split datasets in it	Not split folder, the split datasets will be included in the main folder

Conclusion: We keep calm and use correct standards by planning, then we collect data and standardize it using industry standards. Finally, we analyze the data and submit it to regulatory agencies.

- The **study start date** has a significant impact on version of SDTM and ADaM implementation.
- The study start date drives the version of study data standards that is required for FDA submission.
- Sponsors should use the Study Data Standards Catalog to ensure the correct version of study data standards is supported.
- Additional guidelines to help ensure compliance with FDA submission requirements include:
  - The FDA Technical Rejection Criteria Self-Check Worksheet
  - The latest Study Data Technical Conformance Guide
  - OVRR Guidelines etc.
- If study data is not aligned to the study data standards supported in the FDA technical specifications, then regulatory communication, such as a waiver request, is required.

References:

FDA Guidance

Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry (PDF - 136KB) (Jun. 2021)

Providing Regulatory Submissions in Electronic Format - Submissions Under Section 745A(a) of the FD&C Act: Guidance for Industry (PDF - 81KB) (Dec. 2014)

Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions

FDA Data Standards Catalog

The *FDA Data Standards Catalog* contains specifications for the data standards and versions that the FDA supports. The supported data standard versions are listed along with dates support begins and ends.

FDA Technical Conformance Guides

Study Data Technical Conformance Guide

Vaccines Technical Specification Guidance:

FDA Business Rules/FDA Validator Rules

- The *Business Rules* help ensure that the study data are compliant, useful, and will support meaningful review and analysis.
- The *Validator Rules* are used by the FDA to ensure data are standards compliant and support meaningful review and analysis.

References

The Office of *Advanced Evaluation with Electronic Data* website page provides required items for submission of study data to the PMDA.

- ***Data Standards Catalog***

  Data Standards Catalog contains a list of acceptable versions of Data Exchange Standards and Terminology Standards that PMDA supports.

- ***Technical Conformance Guide on Electronic Study Data Submissions***

  The Technical Conformance Guide provides technical details for electronic study data submission.

- ***Notification on Electronic Study Data***

  Notification on Handling of Submission of Electronic Study Data for New Drug Applications.

- ***Q&A Regarding Notification on Electronic Study Data***

  Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications

- ***Study Data Validation Rules***

  PMDA has published a set of Study Data Validation Rules for SDTM, ADaM, and define.xml. Each of these rules is assigned a severity level Reject, Error or Warning.

FAQs on Electronic Study Data Submission

References

NMPA:
https://www.cde.org.cn/main/news/viewInfoCommon/2969c293179bd697dbb64c454926dd80

Thank You!

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