



PhUSE Boston SDE April 26th 2018





A Framework for Implementing [Evolving] FDA Guidance

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Purpose

- Provide a broad overview of how the FDA mandates data standards and which guidance/best practice supersede when there are contradictions or ambiguity among guidance(s).

The Dream of A Common Language

- “... the passion to make and make again where such unmaking reigns...”
 - The Dream of A Common Language, Adrienne Rich, 1978.

Overview

- FDA
 - Laws
 - Standards
 - Guidance
 - eData
- CDISC Data/Metadata Standards
- Best Practices
 - PhUSE
 - Discussion Forums
 - FAQs
 - White Papers
- Implementing Guidance in evolving/Gray Areas

LAWS



Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 745(a)

- “... the Food and Drug Administration (FDA) has specified the electronic format for ... content ... submitted electronically ...”

— <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf>

How does this relate to Data Standards Implementation?

- FDA develops regulations based on the laws set forth in the FD&C Act.
 - The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from Sponsors.
 - FDA follows the procedures required by its "Good Guidance Practice" regulation to issue FDA guidance. FDA guidance describes the agency's current thinking on a regulatory issue. Guidance is not legally binding on the public or FDA.

Laws: PDUFA V (2013-2017)

- Information Technology/Informatics Plan
 - 2. Electronic Regulatory Submissions—providing a consistent approach to the creation and review of regulatory submissions.
 - 3. Data Standards—defining and implementing standards supporting drug efficacy, drug safety, manufacturing, product identification, and other areas.
 - 4. Metrics and Measures—tracking progress and assessing implementation of goals.

Laws: PDUFA VI (2018-2022)

- By December 31, 2017, FDA will publish and maintain up-to-date documentation for the following:
 - The rejection process for electronic submissions
 - The electronic submission validation criteria

GUIDANCES



About FDA Guidance

- *Guidance documents represent the Agency's current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.*

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>





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Notice

Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act; Availability

A Notice by the [Food and Drug Administration](#) on 12/18/2014



ACTION Notice.

SUMMARY

The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled “Providing Regulatory Submissions in Electronic Format—Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act.” The guidance announced in this notice sets forth FDA’s interpretation of the Food and Drug Administration Safety and Innovation Act (FDASIA), which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require that certain submissions under the FD&C Act and the Public Health Service Act be submitted in electronic format, beginning no earlier than 24 months after issuance of a final version of a guidance document specifying the format for such electronic submissions. This guidance describes how FDA interprets and plans to implement the electronic submission requirements and finalizes the draft guidance that was issued on February 6, 2014.

[Previous Document](#)

[Next Document](#)

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PUBLIC INSPECTION

Publication Date:

Thursday, December 18, 2014

Agencies:

[Department of Health and Human Services](#)
[Food and Drug Administration](#)

Dates:

Submit either electronic or written comments on Agency guidances at any time.



- ***Revolutionary:***

- Insofar as this guidance specifies the format for electronic submissions, or provides for exemptions pursuant to section 745A(a) of the FD&C Act, *it will have binding effect.*

FDA/CDISC Guidance's

Electronic Data in Standardized Format

Technical Conformance Guide

ADaM Model and Implementation Guide

Questionnaires, Ratings and Scales

SDTM Model Documents

SDTM and ADaM Implementation Guides

Metadata Submissions Guideline

Define-xml

Reviewers Guides for SDTM and ADaM
(PhUSE)

Technical Rejection Criteria

FDA Guidance(s) for Industry

Study Data Technical Conformance Guides

Data Standards Catalog

Study Data Standardization Plan

FDA Validation Rules

CDISC Conformance Rules

Legacy Study Data Conversion to Standardized Study

eCTD Structure (Module 5)

Standard for Exchange of Nonclinical Data (SEND)

Clinical Data Acquisition Standards Harmonization (CDASH)

ADaM-specific Guidance's (Time to Event)

Therapeutic Area Guidelines

NCI Controlled Terminology (CT)

...





Technical Conformance Guide

March, 2018

- Purpose: Intended to complement and promote interactions between sponsors and FDA review divisions. *However, it is not intended to replace the need for sponsors to communicate directly with review divisions regarding implementation approaches or issues relating to data standards.*
 - **Takes Precedence over all previous Study Data Specification Documents**

Technical Conformance Guide

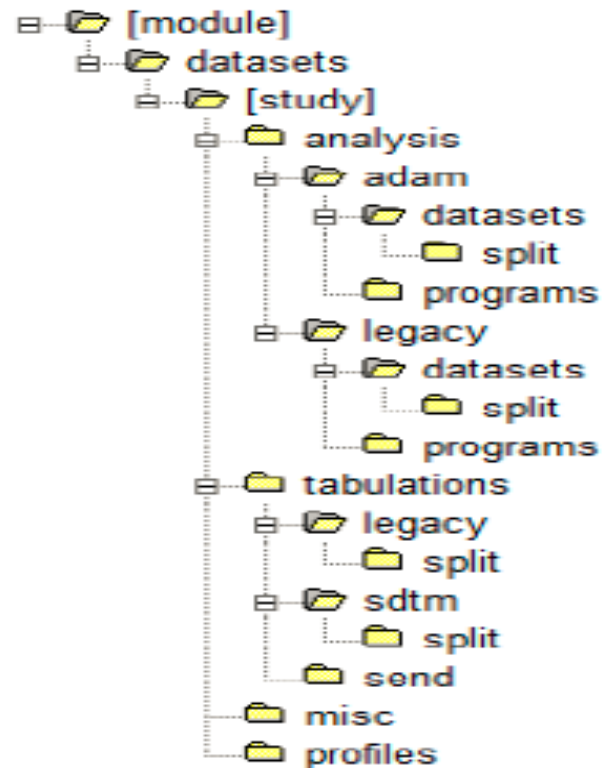
- Timing Variables
- Imputed Data
- Software Programs
- Naming Conventions in SDTM (Standard and Custom)
- Annotated Case Report Form (aCRF) for SDTM
- Supported Therapeutic Areas
- Controlled Terminologies
- Data Validation and Traceability
- Traceability Issues with Legacy Data Conversion
- File Size (and file size limitations)

Metadata Submission Guidelines

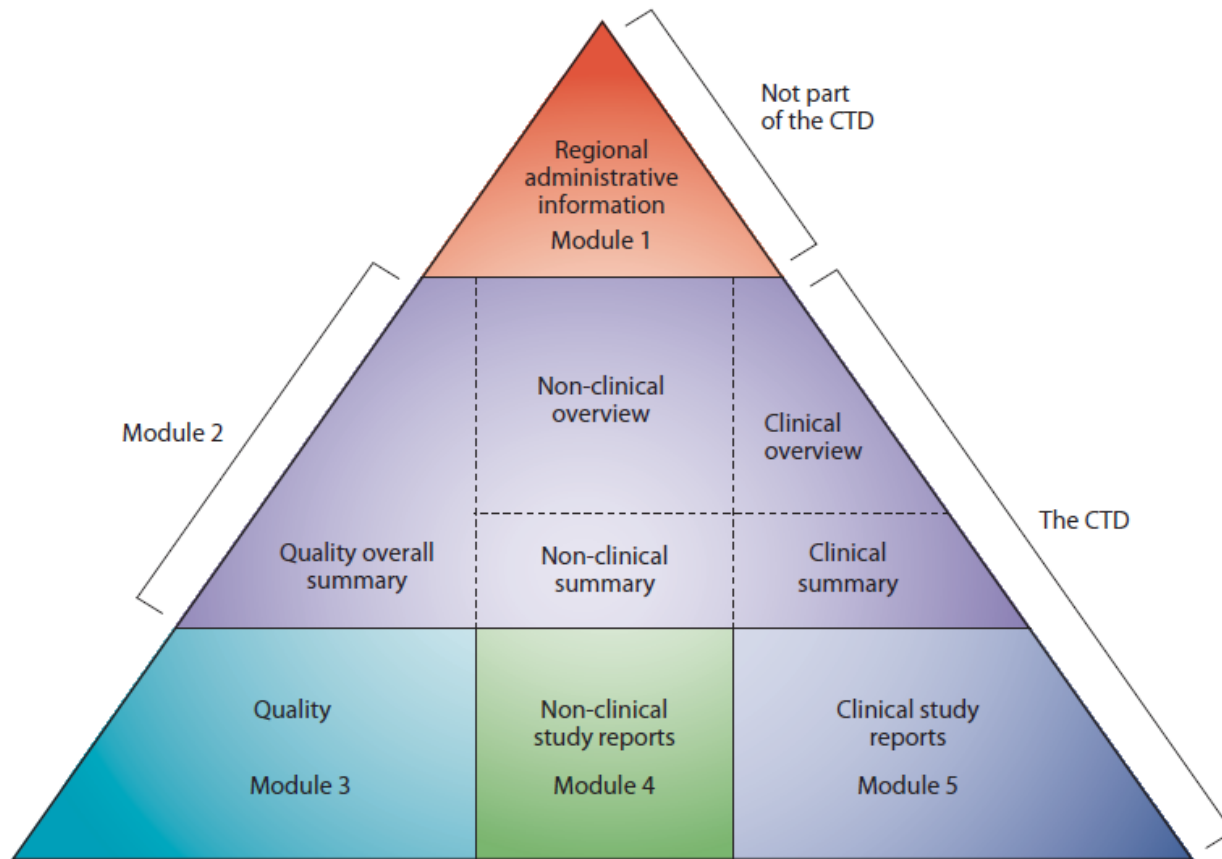
- Provide guidance for compiling the eCTD Module 5 folder
 - Submission Structure
 - Define.XML
 - Annotated CRF
 - Tabulation Datasets (SDTM)
 - Reviewer's Guides
 - ...

Overview of Module 5

Figure 1: Folder Structure for Study Datasets



eCTD Required: May 5, 2017



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Technical Rejection Criteria (Independent of Conformance Criteria)

1. “A Trial Summary (TS) dataset must be present for each study....”
2. “The correct STF file-tags must be used for all standardized datasets....”
 - XPT files must be submitted with the following correct file tags:
 - data-tabulation-dataset-sdtm
 - data-tabulation-dataset-send
 - analysis-dataset-adam
3. “DM dataset and define.xml must be submitted...”
 - Demographic dataset (DM) and define.xml must be submitted for each study
 - Subject level analysis dataset, and define.xml must be submitted for each study
4. “No more than one dataset of the same name can exist...”

Standards



CDISC



CDISC

Secure | <https://www.cdisc.org/standards>



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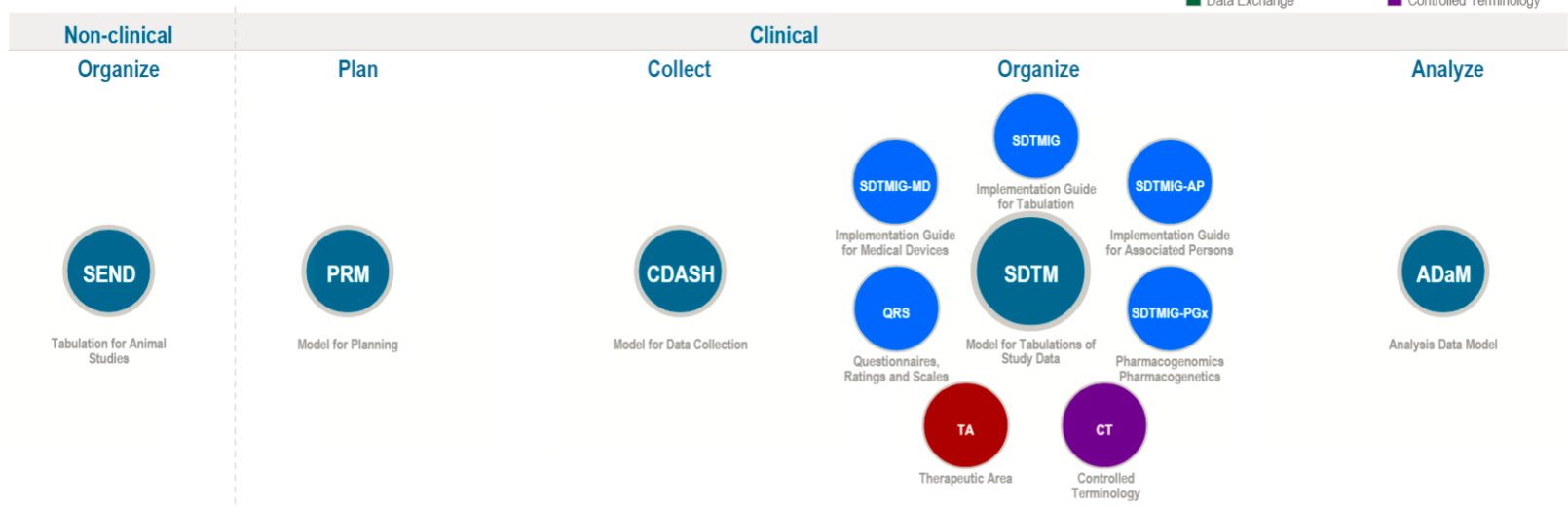
CDISC Standards in the Clinical Research Process

Foundational Standard

Therapeutic Area

Data Exchange

Controlled Terminology





FDA Data Standards Catalog

August 17, 2016

This catalog is a single location for stakeholders to identify all data and data exchange standards FDA supports. It outlines the date the support begins, date support ends, date requirement begins and the date the requirement ends. *The submission of standardized data using any standard not listed, or to an FDA component not listed, should be discussed with the Agency in advance.* It includes:

- SDTM
- ADaM
- Define
- ASCII (for SAS programs)
- eCTD
- SAS XPT Files



BEST PRACTICES



Best Practices

- PhUSE Working Groups
 - <https://www.phuse.eu/working-groups>
- PhUSE White Papers
 - <https://www.phuse.eu/white-papers>
- eData
 - <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>
 - cder-edata@fda.hhs.gov
 - esub@fda.hhs.gov
 - cber.cdisc@fda.hhs.gov
 - esubprep@fda.hhs.gov

'Gray Areas'

- **Creating a Custom Domain**
 - Prefix with X, Y, Z
 - Depends on the SDTM IG Version
 - Does a similar domain exist in a CDISC TA?
- **Populating unscheduled visits**
 - Sequential vs. Static Values
- **Populating EPOCH**
 - Use partial dates?
 - If so, are dates imputed?
- **Mapping Screen Failures**
 - Do we or don't we?
 - What is the source?
 - CRF or IVRS
- **Populating actual treatment**
- **Mapping 'Not Done' records**
 - CRF or Database Build Variables?
- **Adding VISIT Structure (VISIT, VISITNUM, VISITDY) to SDTM domains (e.g., EX) where Visit is Scheduled**
 - Example: home-based exposure was collected

Steps to Address Gray Areas

1. Determine which Model it impacts: SDTM/ADaM – what and why is it ‘gray’
2. Review the IG(s) to determine if more detail is included
3. Refer to the Technical Conformance Guide for issues related to format (e.g., file size)
4. Review in detail company conventions and try to be consistent when possible
5. Contact regulatory to try and discuss with FDA
 - Questions regarding submission of datasets to CDER may be sent to edata@fda.hhs.gov.*
 - * <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm>

Key Takeaways

- Don't meet the Technical Rejection Criteria
- Adhere to the SDTM/ADaM/Define/eCTD Standards
- Follow the FDA Technical Conformance Guide
- Look to PhUSE for Best Practices
- If still in search of an answer use Company Standards/Conventions

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