A Framework for Implementing [Evolving] FDA Guidance

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Background/Abstract

On July 21, 2004 the US Food and Drug Administration announced a format, called the Study Data Tabulation Model (SDTM), that sponsors can use to submit data to the agency. Now, fourteen years on and with the FDA now (as of December 17, 2016) only accepting SDTM/ADaM data formats, there are multiple sources (and versions) of data Standards many of which are mandated by the Prescription Drug User Fee Act (PDUFA V/VI), such as:

- Electronic Data in Standardized Format
- Technical Conformance Guide
- ADaM and SDTM Model Documents
- SDTM and ADaM Implementation Guides
- Metadata Submissions Guideline
- Define-xml Version 2
- Reviewers Guides for SDTM and ADaM
- FDA Guidance for Industry (December, 2014)
- Study Data Technical Conformance Guide (March, 2016)
- Data Standards Catalog
- FDA Business Rules
- CDISC Conformance Rules
- Legacy Study Data Conversion to Standardized Study Data
- eCTD Structure (Module 5)
- Standard for Exchange of Nonclinical Data (SEND)
- Clinical Data Acquisition Standards Harmonization (CDASH)
- ...
Purpose

The purpose of this paper is to provide a broad overview of FDA/CDISC data standards, what laws mandate those standards, what versions of the standards are acceptable, and which standards and guidance/best practices 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 definition of genius is taking the complex and making it simple.”
  - Albert Einstein
Overview

A Brief History of Electronic Standardized Data

• FDA Sponsored
  ◦ Laws
  ◦ Standards
  ◦ Guidance
    ◦ Other Guidance
    ◦ Best Practices (e.g., PhUSE White Papers/Working Groups)

• How to Apply Standards, Guidance and Laws Apply to a New Drug Program
  ◦ Address Gray Areas in Implementing Standards
    ◦ How to Determine which Document/Guidance to use in Gray Areas
    ◦ Which guidance supersedes when there is conflicting information
    ◦ Examples and Considerations
A Brief History of Electronic Standardized Data

Path to Electronic Standardized Study Data

- 1980s
  - FDA Clinical / Statistical Sections Guideline
  - SAS Datasets or ASCII

- 1999
  - FDA Support for SAS XPT
  - CDISC-FDA Collaboration

- 2004
  - Final 745A(a) Guidance
  - Final eStudy Data Guidance

- 2012
  - PDUFA V
  - Tech Conformance Guide

- 2014
  - FDASIA

Mary Ann Slack: FDA Webinar, February 9, 2015
Clinical Data Laws, Standards and Guidelines

- Guidance's
  - Guidance for Industry
    - Providing Regulatory Submissions in Electronic Format
    - Integrated Summaries of Effectiveness and Safety – Location within the CTD
  - Technical Conformance Guide
  - Metadata Submissions Guideline
- Clinical Data Standards
  - FDA Data Standards Catalog
  - SDTM (Version 1.5)
    - IG Version 3.2
  - ADaM (Version 2.1)
    - IG Version 1.1
  - CDISC SDTM Therapeutic Area Guidelines
  - Define-XML (Version 2.0)
- eCTD (Electronic Common Technical Document)
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 …”
How does this relate to Standards Implementation?

- FDA develops regulations based on the laws set forth in the FD&C Act.
- 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. The Good Guidance Practice regulation can be found at [21 CFR 10.115](#).
The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products.

PDUFA must be reauthorized every five years, and was renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V) and 2017 (PDUFA VI). On August 18, 2017, the President signed into law the Food and Drug Administration Reauthorization Act (FDARA), which includes the reauthorization of PDUFA through September 2022. PDUFA VI will provide for the continued timely review of new drug and biologic license applications.

- Prescription Drug User Fee Act Reauthorization (V)
  - 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.
    - ...

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Information Technology/Informatics Plan (really took off in PDUFA V): IMPROVE THE PREDICTABILITY AND CONSISTENCY OF PDUFA ELECTRONIC SUBMISSION PROCESSES

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
“About FDA Guidances

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.
EXCEPT: Guidance for Industry – December 18, 2014

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.

‘Guidance for Industry’

Revolutionary.

- FDA guidance's ordinarily contain standard language explaining that guidance's should be viewed only as recommendations ...
- 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.
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 other FDA–sponsored Guidances
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)
Technical Conformance Guide:
January 2014–March 2018 (Highlighted Changes)

- January 2014, 1.0
- December 2014 2.0 (Revisions based on public comment period)
- March 2015 2.1
  - Analysis Data Reviewer’s Guide (ADRG)
  - Data Definition File
- March 2016 3.0
  - Study Data Reviewer’s Guide (SDRG) – the following sections were updated to reflect define-xml and the SDRG
    - Therapeutic Area Standards – General
    - Supported Therapeutic Area Standards
    - Use of the specific controlled term “OTHER”
    - Study Data Traceability Overview
- July 2016 3.1
  - Updated Trial Design Model (TDM)
  - Added Trial Design (TD), QT Guidance
  - Expanded Conformance Validation, Quality Check and Data Validation Rules
- October 2016 3.2
  - Added ECTD File Directory Structure and FDA Business Rules
- November 2016 3.2.1
  - Updated naming convention for clinical Study Data Reviewer’s Guide (“csdrg.pdf”) and the non-clinical Study Data Reviewer’s Guide (“nsdrg.pdf”) to reflect lower case instead of upper case. eCTD requires lower case file names
- March 2017 3.3
  - Clarification on (1) Study Validation and Traceability and (2) Legacy Study Data Conversion to Standardized Study Data
- October 2017 4.0
  - Software Programs - Updated and clarified text
  - Annotated Case Report Form (aCRF) for SDTM - Updated and clarified text. The recommendation to use the SDTM Metadata Submission Guidelines was removed pending further FDA review.
- March 2018 4.1
  - Software Programs - Updated and clarified text
  - Annotated Case Report Form (aCRF) for SDTM - Updated and clarified text. The recommendation to use the SDTM Metadata Submission Guidelines was removed pending further FDA review.
CDER New Molecular Entity (NME) NDA/BLA Median Time to Approval*

* See References Section at End for Source
Drug Approval Times, cont’d**

**DRUG APPROVAL TIMES**

*Estimated review time to approval for NME/NBE submission cohorts, FY 2000-2015*

- Red: More than 2 years
- Yellow: 1-2 years
- Green: Less than 1 year

*Estimated review time (incl. in-process)

Review time (approved Rx only)

*Lighter shades indicate projections for drugs in-process*

*Includes estimates of approval times for drugs still in process*

**SOURCES:** BCG analysis based on FDA data, EvaluatePharma, literature reviews and press releases

**See References Section at End for Source**
Technical Rejection Criteria (Independent of Conformance Criteria)

1. Paraphrased
2. A Trial Summary (TS) dataset must be present for each study in Modules 4 & 5
3. Each Dataset must be in .XPT Format
4. DM and ADSL datasets and define.xml’s must be submitted for each study in modules 4 & modules 5
5. No more than one dataset of the same name can exist in module 4 & module 5
CDISC

https://www.cdisc.org/
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
## FDA Data Standards Catalog

→ Also, Study Data Standardization Plan

<table>
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<tr>
<th>Use</th>
<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Standards Development Organization (SDO)</th>
<th>Supported Version</th>
<th>Implementation Guide Version</th>
<th>FDA Center(s)</th>
<th>Date Support Begins (MM/DD/YYYY)</th>
<th>Date Support Ends (MM/DD/YYYY)</th>
<th>Date Requirement Begins (MM/DD/YYYY)</th>
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<th>Regulatory Reference and Information Sources</th>
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<td><a href="http://www.ansi.org">www.ansi.org</a></td>
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Metadata Submission Guidelines (SDTM–MSG – Version 1.0)

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

  A Reviewers’ Guide provides additional information for the reviewers about the submitted data. The inclusion of a Reviewers’ Guide and its content are at the discretion of the sponsor. When the SDTM data are validated, errors and/or warnings may occur. All structural errors, those that are related to dataset and variable attributes, are generally within the sponsor’s control and should be corrected. Any errors or content that cannot be resolved may be explained in a Reviewers’ Guide.
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.
BEST PRACTICES
‘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 IG?
- 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. Start with the FDA Data Standards Catalog
2. Determine which Model it impacts: SDTM/ADaM – understand what is ‘gray’
3. Review the IG(s) to determine if more detail is included
4. Review in detail company conventions and try to be consistent when possible
5. Refer to the Technical Conformance Guide for issues related to format (e.g., file size)
6. Contact regulatory to try and discuss with FDA*

* See Next Page
Best Practices

- PhUSE Working Groups
  - [https://www.phuse.eu/working-groups](https://www.phuse.eu/working-groups)

- PhUSE White Papers
  - [https://www.phuse.eu/white-papers](https://www.phuse.eu/white-papers)

- eData

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at [cder.edata@fda.hhs.gov](mailto:cder.edata@fda.hhs.gov).

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact [CBER.edata@fda.hhs.gov](mailto:CBER.edata@fda.hhs.gov).

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

[https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm](https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm)
Example: Epoch – Assumptions

1. The SDTM SE dataset exists and contains the following variables: SESTDTC, SEENDTC.
2. The macro expects SESTDTC, SEENDTC, and target date to be in ISO 8601 format.
3. The SEENDTC should not overlap with the following EPOCH’s SESTDTC. In other words, EPOCHs cannot have overlapping dates. Likewise, the SEENDTC cannot come before the SESTDTC for an EPOCH.
4. If SESTDTC is missing and SEENDTC is not missing, the macro will only assign EPOCH to target date if target date = SEENDTC
5. If SEENDTC is missing and SESTDTC is not missing and it is not the last EPOCH, the macro will only assign EPOCH to target date if target date = SEENDTC
Example Epoch – Assignment

In this example, the EPOCH assigned is WASHOUT
Example Epoch – Assignment

In this example, the EPOCH assigned is WASHOUT
Example Epoch – Assignment

In this example, the EPOCH can be determined by logic and will be set to WASHOUT.
Example Epoch – Assignment

The EPOCH assigned is NULL as partial date may have occurred before study.
Example Epoch – Assignment

In this example, the EPOCH cannot be assigned, even with the use of the PRIORITY parameter. The EPOCH will be assigned as NULL.
Example Epoch – Assignment

14. If a date falls outside of the first or last EPOCH, the EPOCH assigned will be NULL:

The EPOCH assigned is NULL
References

- Slide 10: [https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194909.htm](https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194909.htm)
- Slide 11: [https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm](https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm)
- Slide 23: [https://califesciences.org/2016fdadreport/](https://califesciences.org/2016fdadreport/)
- PhUSE White Paper: Best Practices – Assigning VISITNUM to Unscheduled Visits and Assigning EPOCH to Observations
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