Are you ready for Dec 17th, 2016 - CDISC compliant data submission?

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ABSTRACT

Are you ready for Dec 17th, 2016?

According to FDA Data Standards Catalog v4.4, all clinical trial studies starting after December 17th, 2016 with the exception of certain INDs will be required to have CDISC compliant data. Organizations who are unclear on their compliance status will have their understanding of FDA expectations elucidated in the paper. The paper will show how programmers can interpret and understand the crucial elements of the FDA Data Standards Catalog, which includes support begin date, support end date, requirement begin date and requirement end date of specific standards for both eCTD and CDISC.

First, the paper will provide the brief introduction of regulatory recommendation of electronic submission, including methods, five modules in CTD especially m5, technical deficiencies in submission and etc. The paper will also discuss what programmers need to prepare for the submission according to FDA and CDISC guidelines for CSR, Protocol, SAP, SDTM annotated eCRF, SDTM datasets, ADaM datasets, ADaM datasets SAS® programs and Define.xml.

Additionally, the paper will discuss formatting logistics that programmers should be aware of in their preparation of documents, including length, naming conventions and file formats of electronic files. For examples, SAS data sets should be submitted as SAS transport file formats and SAS programs should be submitted as text format, rather than SAS format.

Finally, based on information from FDA CSS meeting and FDA Study Data Technical Conformance guides v 3.0, the paper will discuss the latest FDA concerns and issues on electronic submission. This will include the size of SAS data sets, lack of Trial Design dataset(TS) and Define.xml, importance of Reviewer Guide and etc.

WHAT WILL HAPPEN ON DEC 17TH, 2016

Data Standards Catalog (DSC) provides the standards, formats and terminologies that FDA requires the industry to follow for the electronic data submission. It is also a single location for all the stakeholders to identify all data and their standards formats that FDA support. It contains data exchange standards, use, exchange format, standards development organization, supported version, implementation guide version, FDA centers that support, support start date, support end date, requirement start date, requirement end date and reference.

INTRODUCTION OF DATA STANDARDS CATALOG

Data Standards Catalog (DSC) provides the standards, formats and terminologies that FDA requires the industry to follow for the electronic data submission. It is also a single location for all the stakeholders to identify all data and their standards formats that FDA support. It contains data exchange standards mainly CDISC and eCTD, their use, exchange format, standards development organization, supported version, implementation guide version, FDA centers that support, support start date, support end date, requirement start date, requirement end date and reference. The most current version is version 4.4.

INTRODUCTION OF eCTD

The eCTD (electronic common technical document) is CDER/CBER's standard format for electronic regulatory submission. The eCTD can be sent two different methods: thru the submission on a CD-ROM or into the electronic submission gateway (ESG).

Five modules in eCTD according to comprehensive table of contents headings and hierarchy are

1. Module 1 – Administrative information
2. Module 2 – eCTD summary document
3. Module 3 – Quality
4. Module 4 – Non-clinical Study Reports
5. Module 5 – Clinical Study Reports.

Usually, the programmers will deal with module 5.

TECHNICAL DIFICIENCIES IN SUBMISSION

The followings could be the technical deficiencies in the submission

- Defect in the media
- An electronically non-readable from thru ESG
- A previously-submitted sequence number
- No index.xml
- A presence of a virus
- An incompatible file format

The technical deficiencies in the submission can lead to

- "Not Received" –Until the technical deficiencies are resolved, the submission is considered as not received. It will delay the review process.
- "Refuse to File" – If the technical deficiency is not resolved by 60 days after the submission, FDA will refuse to file

Refuse to file can also happen for the absence of electronic datasets, inadequate analysis and illegible, uninterpretable and inadequate submission.

SUBMISSIN DATA AND DOCUMENTS

The followings are usual CDISC data and submission document preparation in electronic submission.

- Protocol
- SAP
- eCRF
- SDTM
- ADaM
- SEND
- CSR
- Define.xml
- ADaM SAS programs
- Efficacy SAS programs (sometimes)
- SPDP (Study Data Standardization Plan)
- SDRG (Study Data Reviewer's Guide)
- ADRG (Analysis Data Reviewer's Guide)

File formats

"Specification for File Format Types using eCTD specification" document provides the file format types that FDA accept in electronic submission. There are a couple of recommendations by FDA.

- PDF for reports and forms like CSR reports.
    1. FDA accepts PDF versions 1.4 to 1.7, and PDF files should be readable by Adobe Acrobat X.
    2. The font size is recommended from 9 to 12 pints.
    3. There is no restriction of font type, but Arial, Courier New and Times New Roman are recommended.
    4. For naming files, one should use lower case characters and avoid a special characters such as hyphen, underscore, punctuation, spaces and non-alphanumeric variables (e.g., ? #$% < > +) .
    5. The print area of pages should be 11 by 8.5 inches and at least ¾ margins should be applied to all sides of pages. The titles and footnotes should be outside of margin
- ASCII Text file for SAS program files like c-dm.txt or c-dm.sas.txt
- XML for documents, data, and document information files like Define.xml
- XSL (Style sheets) and DTD (document type definition) for XML document

Name of Electronic file

The name of electronic files such as SAS programs and TFL names should follow the followings.

- The file name should be less than or equal to 64 characters including extension.
- It should contain only letters (lower case), numbers or hyphens.
- It should not contain blank.
- Its path cannot be longer than 230 characters.

FORMATS OF ELECTRONIC FILES IN ELECTRONIC SUBMISSION

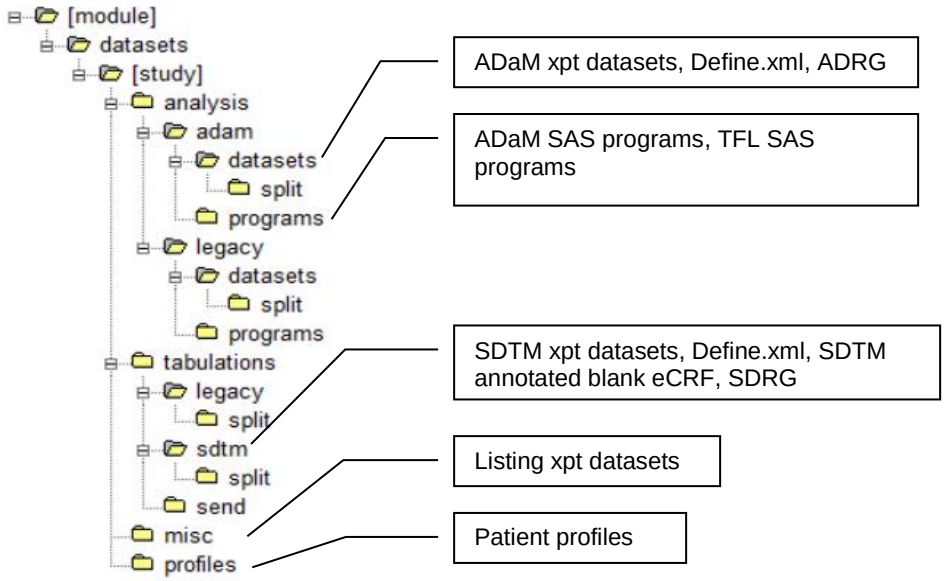
The followings components are usual CDISC submission.

- Protocol – pdf (e.g., study001-protocol.pdf)
- SAP – pdf (e.g., sutdy001-sap.pdf)
- eCRF – pdf (e.g., sutdy001-blankecrf.pdf)
- SDTM – xpt (e.g., dm.xpt, ae.xpt and ds.xpt)
- ADaM – xpt (e.g., adsl.xpt, adae.xpt and adtteos.xpt)
- SEND – xpt (e.g., dm.xpt, se.xpt, and bw.xpt)
- CSR – pdf (e.g., sutdy001-csr.pdf)
- Define file – xml or pdf (e.g., define.xml/define.pdf)
- ADaM SAS programs – txt (e.g., c-adsl.sas.txt)
- Efficacy SAS programs – txt (e.g., t-14-01-001-ds.sas.txt)
- Study Data Reviewer Guide, Analysis Data Reviewer Guide, Study Data Standardization Plan – pdf (e.g., study001-SDRG.pdf)

ELECTRONIC FILE STRUCTURE in eCTD

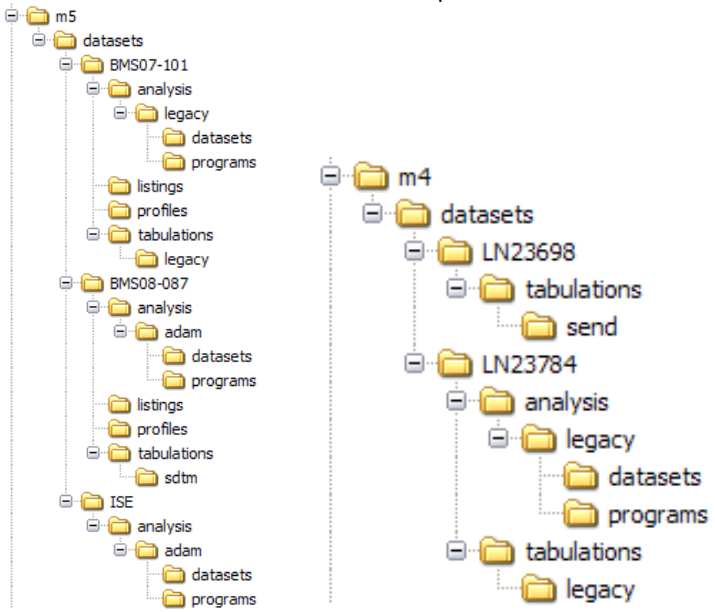
Folder Structures for Study Datasets

Datasets and submission documents are placed in datasets folder as shown below.



eCTD m4 and m5 Folder Structure

Datasets and submission documents are placed in m4 and m5 folder as shown below.



STUDY DATA TECHNICAL CONFORMANCE GUIDE

The study data technical conformance guide (SDTCG) provides sponsors with specifications, recommendations, and general consideration on how to prepare standards data that FDA supports. FDA communicates to sponsors with this documents on standards data preparation and continues to update the documents. The latest version is 3.0 and is published on March 2016.

Electronic Submission Data

There are a couple of recommendations by FDA.

1. FDA accepts SAS xport (Version 5) transport file. Since we need to prepare SAS transport file, there are a couple of things to consider
    a. The length of variables should be less than or equal to 8.
    b. The length of variable labels should be less than or equal to 40.
    c. The length of dataset label should be less than or equal to 40.

2. The size of dataset is recommended to less than 5 GB. Especially, SDTM LB dataset can be too huge, so FDA recommended splitting LB into such as LB1, LB2 and LB3 with the same variable length. They should be placed in "split" folder.
3. The lengths of character variables are recommended to be reduced to the maximum length used. For example, we should reduce the length of ADSL.SUBJID to 20 if the maximum length used is 20, rather than keeping it to 200 long.
4. No special characters on datasets and variables.

Electronic Submission Documents

Study Data Standardization Plan

The sponsor needs to discuss about Study Data Standardization Plan with FDA at pre-IND stage. For INDs, the Study Data Standardization Plan should be located in general investigational plan.

1. List of the planned studies
2. Type of studies
3. Study Design
4. Planned data standards, formats and terminologies and their revisions
5. List of and justification for studies that may not conform to the standards

Study Data Reviewer's Guide (SDTM, SEND and ADaM)

The Study Data Reviewer's Guide needs to be placed in each study of eCTD in Module 5. It should provide study data standards and their conformance validation of each study.

1. Study Protocol title, number, and version
2. Study Design
3. Standards, formats, and terminologies and their versions
4. Description of study datasets
5. Data Standards conformance validation rules, versions and issues.

With a meeting with FDA, FDA strongly recommended reviewer's guides along with CDISC data sets. FDA praised some sponsors to provide data flow diagram to show traceability and strongly appreciated sponsor's efforts on reviewer's guide.

SDTM

Below are FDA recommendations on Study Data Tabulation Model.

- SDTM Implementation Guide (SDTMIG) is main document. SDTM datasets should be prepared with define.xml and SDRG. No data should be imputed in SDTM datasets.
- USUBJID is consistent thru entire application (studies and datasets)
- DM
    - One single record for each subject
    - For screen failures, ARM is blank
    - If a subject is randomized, but not treated, ARM is "Planned Treatment" and ACTARM is blank.
- DS: EPOCH for more than one disposition event
- SE should be included
- AE
    - Include all AE records
    - If AESER ='Y', serious AE criteria (i.e., death and hospitalization) should be included.
- Custom domain should follow SDTMIG and should be explained in SDRG.
- LB: submit both split data (LB1, LB2,, in../SPLIT) and original data(LB) according to LBCAT and LBSCAT.
- Trial design SDTM domains should be included in SDTM submission

ADaM

- ADaM Implementation Guide (ADaMIG) is the main document. ADaM datasets should be prepared with define.xml and ADRG.
- General consideration
    - Traceability: ADaM should be from SDTM.
    - ADaM programming codes should be submitted in txt or pdf (e.g., adsl.sas.txt).
    - Key Efficacy and Safety ADaM datasets should be submitted.
- Core Variables should be included in all ADaM datasets - study/protocol, center/site, region, country, treatment assignment, sex, age, race, analysis population flag and other important baseline variables.
- For same domain, ADaM dataset label should be different from SDTM domain label.
- ADSL is required for each study.
- Imputed data should be documented in ADRG or define.xml

SEND

SEND follows SEND Implementation Guide and SDTM. SUPPQUAL and custom domain could be used as well.

Define

- Define.xml describes SDTM, SEND and ADaM data sets.
- Clear and accessible to Code list, origin and derivation for each variables
- Data definition specification for submitted datasets
- Version 1: Define.xml and Define.pdf
- Version 2 and later: only Define.xml

aCRF

Annotated Case Report Form (aCRF) should be submitted along with data submission, and it includes treatment assignment forms and map all variables that are in submitted datasets.

Terminology

- Supported in Standard Catalog
- Sponsor-defined terminology in Define.xml or Data Reviewer Guide
- Verbatim in eCRF and coded term in submitted datasets
- Discourage the custom term, but if present, it should be documented in SDRG.
- Most current versions for each study, but for pooling coded data, a single version is recommended. If not, the justification should be documented in Standardization Plan.
- Terms and Versions for each study should be documented in SDRG.

CDISC Terminology

- CT: from NCI
- AE: MedDRA
- Medication: FDA UNII (Unique Ingredient Identifier)
- Pharmacologic Class: Veterans Administration's NDF-RT (National Drug File – Reference Terminology)
- Indication: SNOMED CT (Systematized Nomenclature of Medicine – Clinical Terms)

Study Data Validation

FDA check two types of validation rule

1. Conformance validation rule: submitted data conform to standards.
2. Quality checks: submitted data support meaningful analysis.

Study Data Traceability

FDA strongly recommends study data traceability such as a data flow diagram from CDASH to data submission.

- Relationship between analysis results, analysis datasets, SDTM datasets and source data.
- Maybe legacy data in submission
- Common Issues involving traceability
    - Legacy data conversion to SDTM only
        - No traceable path from legacy analysis data to SDTM.
        - No ability to confirm analysis variable imputation or derived variables.
        - Unable to replicate tables, listings and figures (TLFs) and legacy analysis datasets using SDTM datasets.
        - No ability to confirm derivation of intermediate datasets or custom domains.
        - No ability to determine location of collected CRF variables in the converted SDTM data.
        - Difficulty in understanding the source or derivation methods for imputed or derived variables in integrated/pooled data, supplemental qualifiers, and related records.
    - Independent legacy data conversion to SDTM and ADaM
        - No traceable path from legacy to SDTM to ADaM and to Study Report.

        - No explanation or source for analysis imputed or derived variables.
        - No traceable path to ISS and ISE / pooled data.
        - TLFs do not match datasets (analysis datasets or SDTM datasets (when used)).
        - No traceable path to intermediate datasets or custom domains.
        - No explanation or source for imputed or derived variables in datasets.
    - Legacy data conversion to SDTM and ADaM in sequence
        - May not be able to replicate the results in the TLFs and CSR using the ADaM or the SDTM datasets.
- FDA recommendation
    - Submit a Legacy Data Conversion Plan and Report
    - aCRF for legacy data
    - Documentation in SDRG
    - Submission of Legacy data

CONCLUSION

Ones can wonder why it is so important for sponsors? At PhUSE Computational Science Symposium, FDA clearly indicated that non-compliant submission data can lead to "Refuse to File". Any sponsors do not want their submission to "Refuse to File".

So, standards such as CDISC and eCTD were recommended by FDA beforehand, but after Dec 17th, 2016, standards such as CDISC will be mandated by FDA in electronic submission. Since FDA Data Standard Catalog (DSC) provides the support start date, support end date, and requirement date of each standard, sponsors can save resources and time by planning their submission according to DSC timeline. Programmers and statisticians can also save huge amount of time and resources by preparing study data and documents with appropriate standards while doing study rather than converting them to standards for submission purpose.

REFERENCES

Study Data Technical Conformance Guide v3.0
FDA Data Standards Catalog v.4.4
Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A (a) of the Federal Food Drug, and Cosmetic Act (Draft)
Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data (Draft)
Electronic Common Technical Document Technical Conformance Guide Version 1
Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Revision 3
Portable Document Format (PDF) Specifications Version 4
Specifications for File Format Types using eCTD Specification Version 1
The ADaM Implementation Guide, Version V 1.0 (ADaMIG v1.0)
The Analysis Data Model, Version 2.1 (ADaM 2.1)
The ADaM Basic Data Structure for Time-to-Event Analyses
Providing Regulatory Submission in Electronic Format – Receipt Date

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