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Legacy Study Submission Components Review - Step by Step

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CDISC Implementation Key Milestone

- FDA
  - Start after Dec 17, 2016
- PMDA
  - Mandatory effective on Apr 1, 2020.
  - Initiation date is Oct 1, 2016.
  - Transitional period from Oct 1, 2016 to Mar 31, 2020.

Legacy Study

NON-CDISC Compliance

Legacy Package:

- Study Tabulation Data (SDS), Semi-SDTM
- Analysis Datasets (ADS)
- Define.pdf
- Data Reviewer's Guide
- SAS Programs

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Gap Analysis

Actual vs. Expected

Study Number	CSR to be submitted for BA NDA/MAA	CSR available	Protocol available	SAP available	CRF available	aCRF available	Number of SDTM datasets (including SUPPs and RELREC)	Number of ADaM datasets	Number of raw datasets	Number of Legacy Analysis datasets	PK data available?	SAS programs for ADAM, TLF (including macros)	SDRG available	ADRG available	SDTM define.xml avaiable	ADaM define.xml available	Conformant with current CDISC standard?
1002-001	Y	N	Y	N	Y	t status: Y)	0	0	31	21(Current status: 22)	Yes (raw, and analysis data)	Y	N (no SDTM)	N (only have DDT)	NA	NA	Legacy data -- only raw data and analysis sets
1002-002	Y	N	N	N	N	N	0	0	41	17	Yes (raw, and analysis data)	Y	N (no SDTM)	N (only have DDT)	NA	NA	Legacy data -- only raw data and analysis sets
1002-004	Y	N	N	Y	N	N	0	0	38	16	Yes (raw, and analysis data)	Y	N (no SDTM)	N (only have DDT)	NA	NA	Legacy data -- only raw data and analysis sets
~~011~~	~~N~~					~~Unknown~~	~~Unknown~~	~~Unknown~~	~~Unknown~~	~~Unknown~~	~~Unknown~~		~~Unknown~~	~~Unknown~~			~~Unknown~~
1002-012	Y	N	Y	Y	Y	N	0	0	46	15	Yes (raw, and analysis data)	Y	N (no SDTM)	N (only have DDT)	NA	NA	Legacy data -- no define or CDISC conformant check for SDTM or ADaM, version unknown
1002-013	Y	N	N	N	Y	Y(Current status: N)	37(Current status: 32)	9(Current status: 0)	17	0	Yes (Current status: no SDTM PC Data)	N	Y(Current status: N)	Y(Current status: N)	N	N	CDISC standard (SDTMIG 3.1.3, ADaM IG 1.0 define.xml 1.0, CDISC CT 2013-06-28), define.xml might need upgrade to 2.0, no relrec
1002-016	Y	Y	N	Y	Y	Y	26	7	17 (plus external)	0	Yes	Y	Y	Y	Y(define.xml 1.0)	Y(define.xml 1.0)	CDISC standard (SDTMIG 3.2, ADaM IG 1.0 define.xml 1.0, CDISC CT 2014-09-26), define.xml might need upgrade to 2.0
1002-017	Y	Y	N	Y	Y	Y	26	7	17 (plus external)	0	Yes	Y	Y	Y	Y(define.xml 1.0)	Y(define.xml 1.0)	CDISC standard (SDTMIG 3.2, ADaM IG 1.0 define.xml 1.0, CDISC CT 2014-09-26), define.xml might need upgrade to 2.0
1002-022	Y?	Y	N	Y	Y	Y	32	9	22	0	Yes	N	N	N	Y(define.xml 2.0)	Y(define.xml 2.0)	have SDTM and ADaM datasets, define.xml 2.0, but not sure about version
1002-023	Y?	Y	N	Y	Y	Y	21	7	only external files (Current status: 20 raw datasets plus external data files)	0	Yes	Y	Y	Y	Y(define.xml 1.0)	Y(define.xml 1.0)	CDISC standard (SDTMIG 3.2, ADaM IG 1.0 define.xml 1.0, CDISC CT 2014-09-26), define.xml might need upgrade to 2.0

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FDA Data Standards Catalog

FDA Data Standards Catalog v4.10 (10-24-2017) - Supported and Required Standards									
Use	Data Exchange Standard	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends
Clinical study datasets	Study Data Tabulation Model (SDTM)	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015		01/28/2015
Clinical study datasets	SDTM	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
Clinical study datasets	SDTM	CDISC	1.2	3.1.2	CDER, CBER	10/30/2009	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
Clinical study datasets	SDTM	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]	
Clinical study datasets	(SDTM)	CDISC	1.4	3.2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]	
Clinical study datasets	Analysis Data Model (ADaM)	CDISC	2.1	1.0	CDER, CBER	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
Clinical study datasets	Analysis Data Model (ADaM)	CDISC	2.1	1.1	CDER, CBER	03/15/2018		03/15/2019 [1] 03/15/2020 [2]	
Study data definition	Define	CDISC	1.0	N/A	CDER, CBER, CDRH	Ongoing	03/15/2018 [1] 03/15/2019 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2018 [1] 03/15/2019 [2]
Study data definition	Define	CDISC	2.0	N/A	CDER, CBER, CDRH	08/07/2013		12/17/2016 [1] 12/17/2017 [2]	
Notes:									
[1]	guidance document								
[2]	For certain INDs. See section II.A of the Providing Regulatory Submissions In Electronic Format — Standardized Study Data guidance document								

V4.10 Oct 24, 2017

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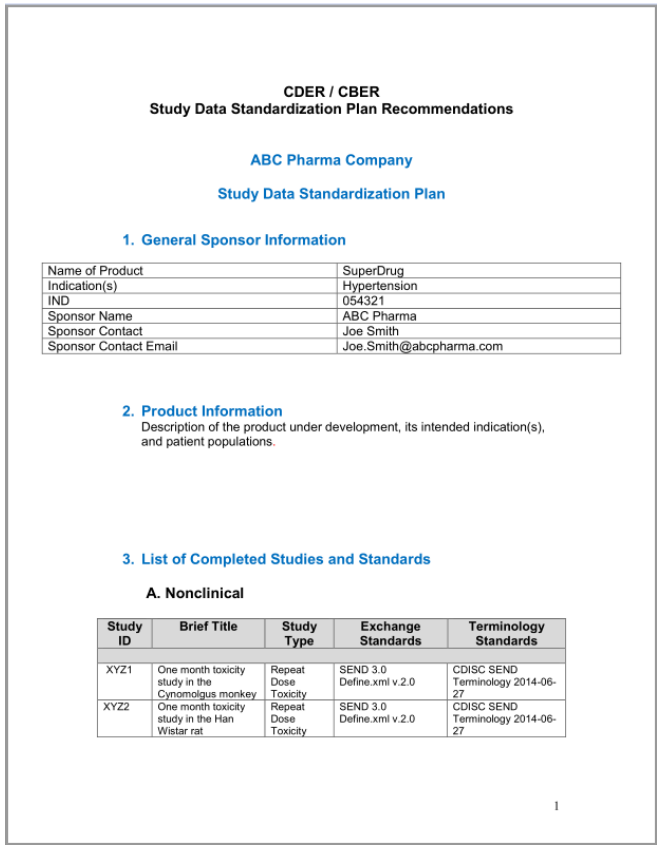
Study Data Standardization Plan

- Assists FDA in identifying potential data standardization issues early in the development program.
- Should include, but is not limited to the following:
  - List of the planned studies
  - Type of studies
  - Study designs4.
  - Planned data standards, formats, and terminologies and their versions
  - A justification of studies that may not conform to the currently supported standard



CDER / CBER
Study Data Standardization Plan Recommendations

ABC Pharma Company

Study Data Standardization Plan

1. General Sponsor Information

Name of Product	SuperDrug
Indication(s)	Hypertension
IND	054321
Sponsor Name	ABC Pharma
Sponsor Contact	Joe Smith
Sponsor Contact Email	Joe.Smith@abcpharma.com

2. Product Information
Description of the product under development, its intended indication(s), and patient populations.

3. List of Completed Studies and Standards

A. Nonclinical

Study ID	Brief Title	Study Type	Exchange Standards	Terminology Standards
XYZ1	One month toxicity study in the Cynomolgus monkey	Repeat Dose Toxicity	SEND 3.0 Define.xml v.2.0	CDISC SEND Terminology 2014-06-27
XYZ2	One month toxicity study in the Han Wistar rat	Repeat Dose Toxicity	SEND 3.0 Define.xml v.2.0	CDISC SEND Terminology 2014-06-27

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STUDY DATA TECHNICAL CONFORMANCE GUIDE
https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf

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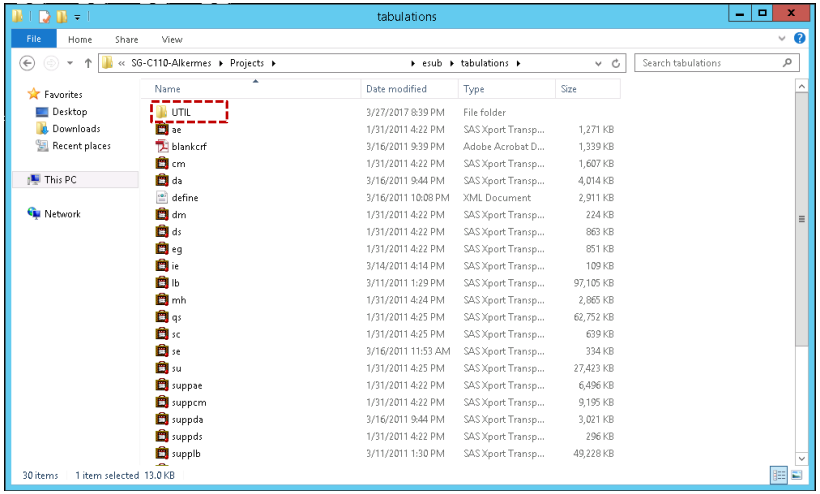
M5 Folder Structure

- [module]
  - datasets
    - [study]
      - analysis
        - adam
          - datasets
            - split
            - programs
        - legacy
          - datasets
            - split
            - programs
      - tabulations
        - legacy
          - split
        - sdtm
          - split
        - send
      - misc
      - profiles

- The define.xml and supportive style sheet should reside in the same folder as the datasets they pertain to.
- No empty file folders.
- No additional subfolders



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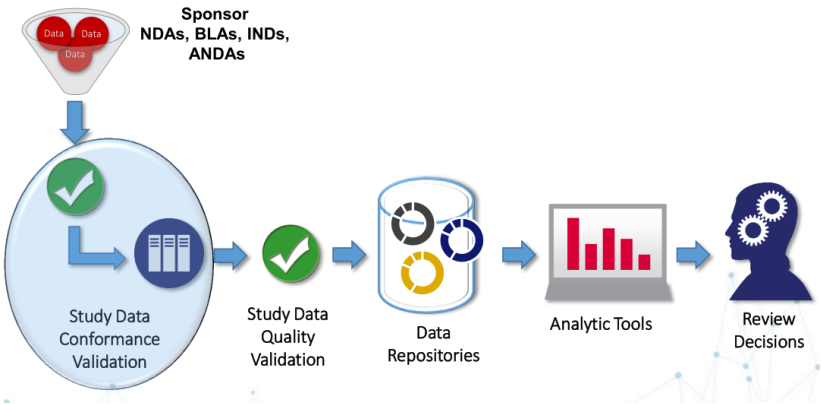
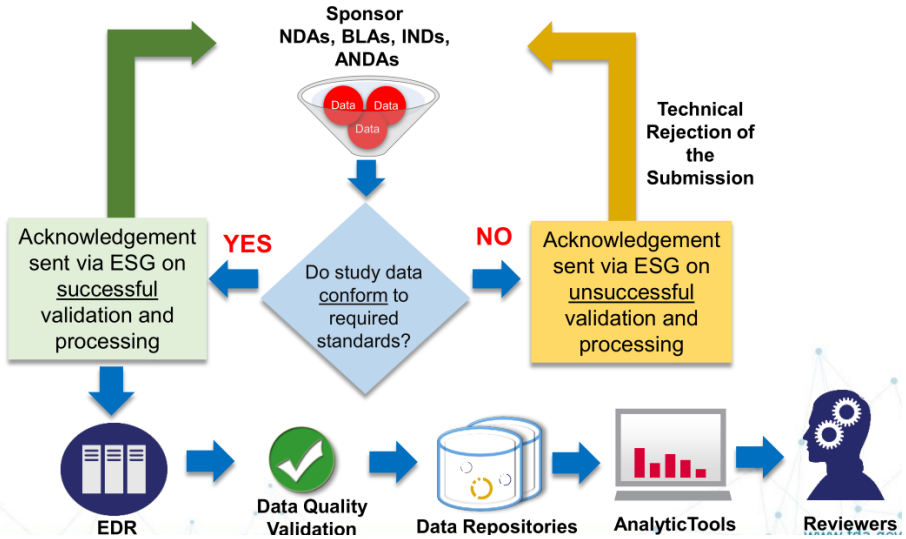
Study Data Standards in eCTD

Study Data Standards Validation



Study Data Conformance Validation



Reference: Study Data Standards in eCTD: What You Need to Know About the New Technical Rejection Criteria by Ron Fitzmartin (FDA Senior Advisor)

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New Technical Rejection Criteria

- A Trial Summary dataset (ts.xpt) must be presented for each study in sections identified below even if the study started prior to December 17, 2016.
- DM dataset, ADSL dataset, define.xml must be submitted in module 5
- There must be only one dataset of the same name submitted as new.

Reference:
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

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Tabulation Data

- To avoid Technical Rejection Criteria for Study Data: must contain a ts.xpt with a record for SSTDTC (first informed consent date of an enrolled subject) and dm.xpt.
- Run Pinnacle21 and Correct/Explain the related issues
- Check that no datasets are greater than 5 gigabyte in size. If they are then they must be split.
- Check TI/AE/TDM

Analysis Data

- To avoid Technical Rejection Criteria for Study Data: must contain adsl.xpt
- Run Pinnacle21 and Correct/Explain the related issues
- Check that no datasets are greater than 5 gigabyte in size. If they are then they must be split

Define XML

- The Origin Type attribute must have a value of 'CRF', 'Derived', 'Assigned', 'Protocol', 'eDT', or 'Predecessor'. There cannot be multiple origins; rather these should be broken out in Value Level Metadata.
- A sampling (of all types) of internal and external links opens to the correct file and file location.
- Datasets with no observations should not be included in define or in the submission.
- Make sure define.pdf exists for any studies that use define.xml v1.0

Define PDF

- Initial View
  - Navigation Tab: Bookmarks Panel and Page
  - Page Layout and Magnification: Default
- Fast Web View: Optimized
- List of Standard Fonts
- Ensure that all links in future submissions are set to 'Inherit Zoom'

Annotation CRF

- Ensure that all fields are annotated with SDTM variables or marked as “Not Submitted”
- Review for correctness of annotations. All annotations are documented in define.xml origin column.
- Duplicate CRF pages are not re-annotated, but rather are marked as “For annotations see CRF Page X”
- SUPPQUAL variables are annotated as “SUPPXX.QVAL where QNAM=XXX”
- A footnote with Page X of Y exists and the page numbers match the page of the PDF file.

Data Reviewers Guide

- Should use the PhUSE template

  http://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer's_Guide

  http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

- Well written with appropriate spacing. All tables that break across a page should have a repeating header.

- Make sure standards references are correct and consistent across cSDRG, SDTM define.xml, ADRG, and ADAM define.xml (CT, MedDRA, WHO Drug, and etc.)

Discussion

- Up-Version: SDTM
- Revised Previously Submitted Studies
- Note to File
- eCTD STF File Tags

Thanks for your time!