# FDA e-CTD Overview from a Programmer's Perspective

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# OUTLINE

- eCTD Overview
  - **Guidance**
  - **Module 5**
- Study Data Standardization Plan and Submission Planning
- Some Points of Considerations
- Final Remarks

# eCTD Overview - Guidance

- What is eCTD
  - **The Electronic Common Technical Document (eCTD) is CDER/CBER's standard format for electronic regulatory submissions.**
- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications (May 2015)
- eCTD TECHNICAL CONFORMANCE GUIDE (Oct 2015)
- Providing Regulatory Submissions In Electronic Format — Standardized Study Data (Dec 2014)
- STUDY DATA TECHNICAL CONFORMANCE GUIDE (Mar 2016)
- See the eCTD website www.fda.gov/ectd for further information

**Electronic Submissions to CDER**

CDER Data Standards Program

**Electronic Common Technical Document (eCTD)**

Electronic Regulatory Submissions and Review Helpful Links

Electronic Submissions Presentations

Study Data Standards for Submission to CDER

Source Data Capture from Electronic Health Records (EHRs)

Data Standards Manual (monographs)

# Electronic Common Technical Document (eCTD)



The Electronic Common Technical Document (eCTD) is CDER/CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017** submission types **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection.

As of the timeframes stated above, submissions sized 10GB and under must be submitted via the **FDA Electronic Submission Gateway**. Because most submissions fall within these limits, submitters are strongly advised to obtain Gateway accounts as soon as possible. You must submit electronic submissions using the version of eCTD currently supported by FDA. The version of eCTD currently supported is specified in the **Data Standards Catalog**.

FDA has exempted all submissions regarding noncommercial INDs from the requirements under section 745A(a). Although these submissions will be exempt, FDA also accepts their submission electronically. For additional information on the guidance, including additional exemptions, please refer to the **Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications**.

# eCTD Overview - Guidance

## Guidances

The FDA periodically publishes guidances on many matters, including eCTD. Those related to eCTD can be found below:

May 2015

*Final:*

- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications (PDF)
- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Receipt Dates (PDF)
- Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety – Location within the CTD (PDF)

*Draft:*

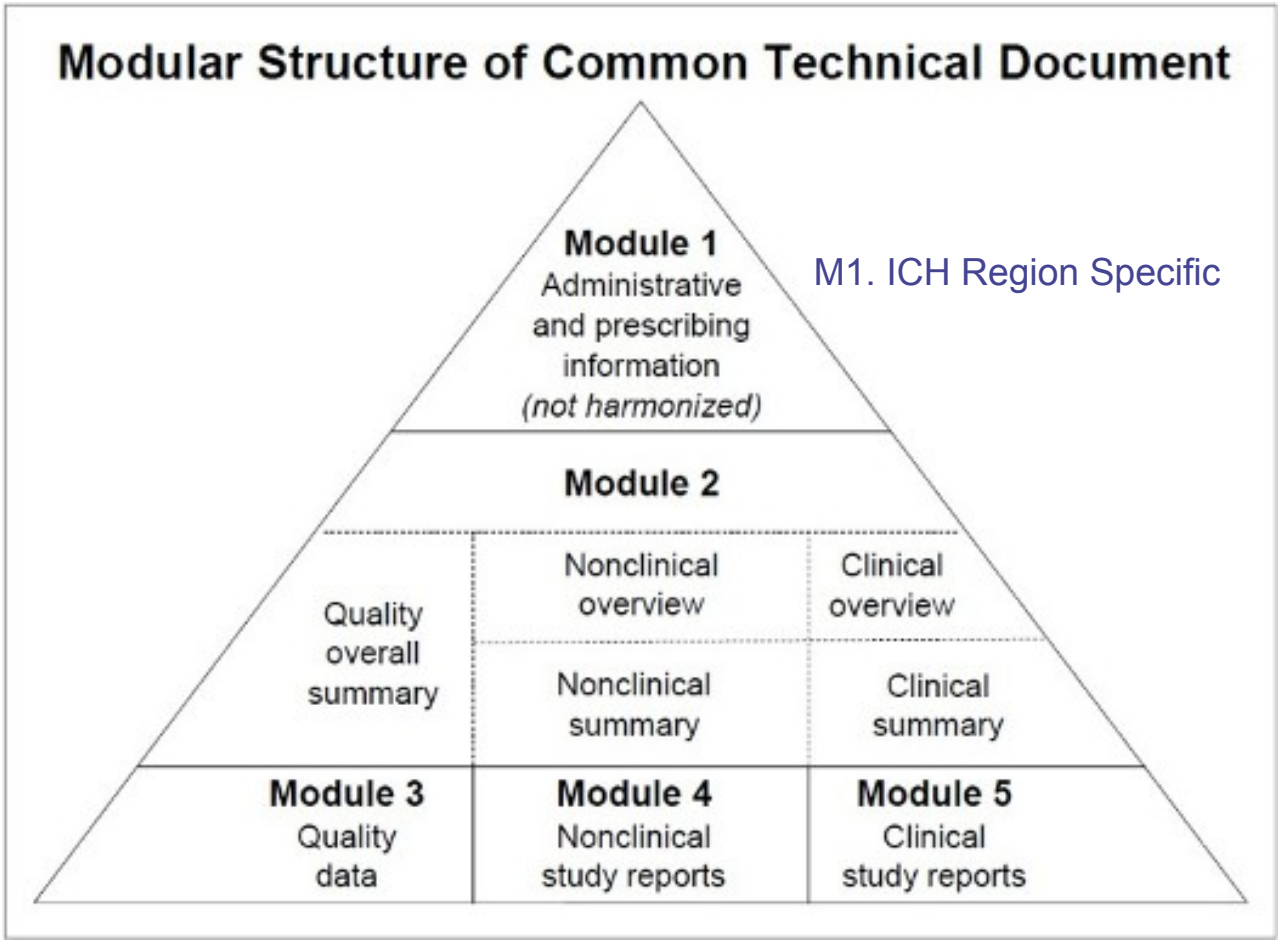
- Draft Guidance for Industry: Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertising Materials for Human Prescription Drugs (PDF)

## Presentations

For presentations, webinars, conference dates and other related information, see below:

- New Requirement for Electronic Submission of DMFs
- Recent FDA eCTD Presentations

# Organization of the eCTD – 5 Modules




https://en.wikipedia.org/wiki/Electronic_common_technical_document

# eCTD Modules
## Headings and hierarchy folder structure

Module 1 - Administrative Information

Module 2 - Summaries

- *2.7 Clinical summary*
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
- 2.7.2 Summary of Clinical Pharmacology studies
- **2.7.3 Summary of Clinical Efficacy [indication]**
- **2.7.4 Summary of Clinical Safety**
- 2.7.5 References
- 2.7.6 Synopses of individual studies

Module 3 – Quality

Module 4 - Nonclinical Study Reports

Module 5 - Clinical Study Reports

# eCTD Module 5
## Headings and hierarchy folder structure

**Module 5 Clinical Study Reports**

- ***5.2 Tabular listing of all clinical studies***
- ***5.3 Clinical study reports and related information***
  - 5.3.1 Reports of biopharmaceutic studies
  - 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
  - 5.3.3 Reports of human pharmacokinetic (PK) studies
  - 5.3.4 Reports of human pharmacodynamic (PD) studies
  - 5.3.5 Reports of efficacy and safety studies [Indication]

# eCTD Module 5
# An Example

5.3.5 Reports of efficacy and safety studies [Indication]

**5.3.5.1 Study reports and related information of controlled clinical studies pertinent to the claimed indication**

Study 1

*Protocol*

*Randomization scheme*

*Documentation of Statistical Methods and Interim Analysis Plans*

*Protocol deviation list*

*Case report forms*

*……*

*Annotated CRF*

*SDTM datasets, define.xml, SDRG*

*Analysis datasets, define.pdf, ADRG*

*Programs*

Study 2

**5.3.5.2 Study reports and related information of uncontrolled clinical studies**

# STUDY DATA SUBMISSION GUIDE

- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications (May 2015)
- eCTD TECHNICAL CONFORMANCE GUIDE (Oct 2015)
- Providing Regulatory Submissions In Electronic Format — Standardized Study Data (Dec 2014)
- STUDY DATA TECHNICAL CONFORMANCE GUIDE (Mar 2016)
- FDA Data Standards Catalog v4.4 (Aug 2015)
- Study Data Standardization Plan (May 2015)

# STUDY DATA SUBMISSION GUIDE

- Required December 17, 2016 for NDA, ANDA, and certain BLA submissions, or December 17, 2017 for certain IND submissions

| Implementation Guide Version | FDA Center(s) | Date Support Begins (MM/DD/YYYY) | Date Requirement Begins (MM/DD/YYYY) |
|---|---|---|---|
| SDTM v3.2 | CDER, CBER | 8/17/2015 | 03/15/2018 [1]<br>03/15/2019 [2] |
| SDTM v3.1.3 | CDER, CBER | 12/01/2012 | 12/17/2016 [1]<br>12/17/2017 [2] |
| Version 3.1.2 Amendment 1 | CDER, CBER | 08/07/2013 | 12/17/2016 [1]<br>12/17/2017 [2] |
| SDTM 3.1.2 | CDER, CBER | 10/30/2009 | 12/17/2016 [1]<br>12/17/2017 [2] |
| ADaM 1.0 | CDER, CBER | Ongoing | 12/17/2016 [1]<br>12/17/2017 [2] |

| | |
|---|---|
| [1] | For NDAs, ANDAs, and certain BLAs. See section II.A of the Providing Regulatory Submissions In Electronic Format — Standardized Study Data guidance document |
| [2] | For certain INDs. See section II.A of the Providing Regulatory Submissions In Electronic Format — Standardized Study Data guidance document |

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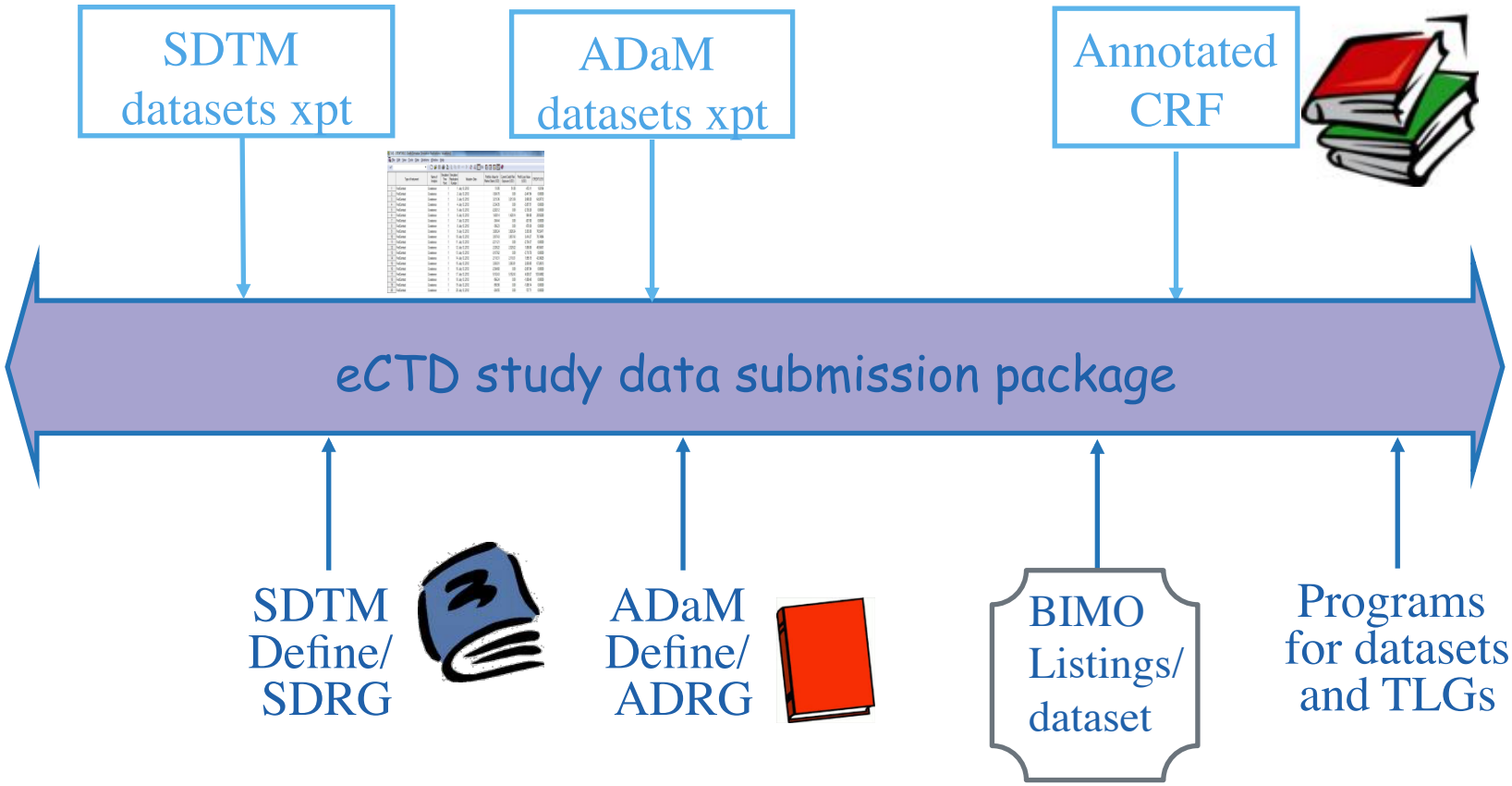
# STUDY DATA SUBMISSION PACKAGE



# Study Data Standardization Plan

- Sponsor to initiate discussions at the pre-NDA stage
- The *Standardization Plan* should include, but is not limited to the following:
  1. **List of the planned studies**
  2. **Type of studies (e.g., phase I, II or III)**
  3. **Study designs (e.g., parallel, cross-over, open-label extension)**
  4. **Planned data standards, formats, and terminologies and their versions or a justification of studies that may not conform to the currently supported standards**


Study DataStandar dizationPlar

# STUDY DATA SUBMISSION PANNING

| Study ABC123 | | | | | | |
|---|---|---|---|---|---|---|
| Task | Creation | Complete by | Prog Review | Stat Review | 1st round Review complete | Review final doc ready |
| SDTM specs | A. Smith | 1/1/2015 | F. Wilson | H. Sun | 2/1/2015 | 4/30/2015 |
| SDTM datasets | A. Smith | 2/1/2015 | F. Wilson | H. Sun | 2/15/2015 | 4/30/2015 |
| SDTM transport | A. Smith | 2/1/2015 | F. Wilson | H. Sun | 2/15/2015 | 4/30/2015 |
| SDTM define xml & pdf | A. Smith | 3/1/2015 | F. Wilson | H. Sun | 3/15/2015 | 5/31/2015 |
| SDTM annotated CRF | B. Miller | 3/1/2015 | F. Wilson | H. Sun | 3/15/2015 | 5/31/2015 |
| SDRG | B. Miller | 4/1/2015 | F. Wilson | H. Sun | 4/15/2015 | 5/31/2015 |
| ADS specs | C. Johnson | 2/1/2015 | F. Wilson | H. Sun | 2/15/2015 | 5/31/2015 |
| ADS datasets | C. Johnson | 3/1/2015 | F. Wilson | H. Sun | 3/15/2015 | 5/31/2015 |
| ADS transport | C. Johnson | 3/1/2015 | F. Wilson | H. Sun | 3/15/2015 | 5/31/2015 |
| ADS define | C. Johnson | 4/1/2015 | F. Wilson | H. Sun | 4/15/2015 | 5/31/2015 |
| ADRG | C. Johnson | 4/1/2015 | F. Wilson | H. Sun | 4/15/2015 | 5/31/2015 |
| Efficacy programs/ descriptions | D. Williams | 4/1/2015 | G. Li | J. Taylor | 4/15/2015 | 5/31/2015 |
| Safety Programs/ descriptions | D. Williams | 4/1/2015 | G. Li | J. Taylor | 4/16/2015 | 5/31/2015 |
| BIMO site listing | E. Zhao | 3/1/2015 | G. Li | J. Taylor | 4/1/2015 | 4/30/2015 |
| BIMO (clinsite dataset) | E. Zhao | 4/1/2015 | G. Li | J. Taylor | 4/18/2015 | 5/31/2015 |

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# Points of Considerations
# SAS DATA SETS

- Perform data set checks
  - **Proc Content to check the datasets: eg. dataset label, variable, label, format/informat etc.**
- Make sure that SAS data sets have the following properties:
  - **Variable length >=3 bytes**
  - **Variable names <= 8 characters**
  - **Variable labels <= 40 characters**
  - **No user defined format / informat in datasets**
- Resize data (should save as a permanent SAS dataset, because we need to read the variable attributes, eg. variable length)
- Split data sets if need
- Pinnacle 21 validation
- Address the validation findings
  - **May need to update the dataset / specifications**
- Create XPT files

# Points of Considerations
# SAS Transport Files

- SAS XPORT Transport Format selected by FDA
- Processed by the XPORT engine in Version 6 of SAS software and later, and by PROC XCOPY in Version 5
- An open, published file format developed by SAS Institute
  - **By US law, the FDA must remain "vendor neutral." The FDA cannot endorse or require use of any specific vendor's product**
  - **Specifications for the XPORT transport format are in the public domain. Data can be translated to and from the XPORT transport format to other commonly used formats without the use of programs from SAS Institute or any specific vendor**
- Compare to CPORT transport file format

# Points of Considerations
# Define.xml and Define.pdf

- Both define.xml and define.pdf are required for SDTM
- Define.pdf required for ADaM/ADS (define.xml may be required very soon)

- Dataset in XML format (xx.xml) may be required soon
- XML improves navigation for regulatory review

- To create define file -
  - **Final datasets metadata**
    - Ensure all information is complete and updated
    - If additional programming notes are prepared, ensure the programming notes comply to CDISC standards
  - **Final datasets XPT files**

# Points of Considerations Submission Ready Programs

- A trend from regulatory agency
  - **More and more submissions are requested with programs**
- Black-box company-tools not recommended
- Straight code is very much encouraged
- Less macros, Macro names should be consistent with their contents
- Clean up programs and documents
- Follow Good Programming Practices
  - **Header with clear documentation**
  - **Adequate commenting**
  - **Proper indentation**
  - **No hardcoding**
  - **Check for clean logs**
    - no error, warning, uninitialized, merge with multiple values, invalid, out of range etc.
- QC according to company SOPs

# Points of Considerations SDRG and ADRG

- SDRG – Study Data Reviewer's Guide
- ADRG – Analysis Data Reviewer's Guide

- **Why do we prepare SDRG and ADRG?**

  FDA Study Data Technical Conformance Guide

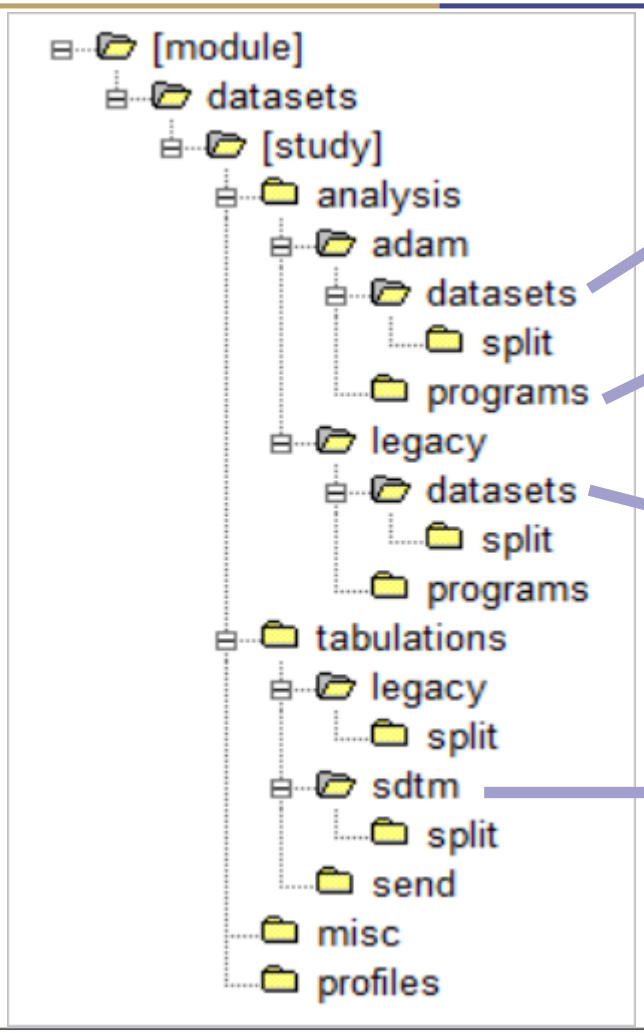
- PhUSE CSS (Computational Science Symposium) templates and guidance available

  SDRG guide  SDRG template

  ADRG guide  ADRG template

# Study Data Folders

(Study Data Technical Conformance Guide v3.0, March 2016)




ADaM data sets in transport fmt
Define.pdf (& Define.xml)
ADRG.pdf

ADaM creation programs
TL&F creation programs

ADS data sets in transport format
Define.pdf (& Define.xml)
ADRG.pdf

aCRF
SDTM data sets in transport format
Define.xml & Define.pdf
SDRG.pdf

# Final Remarks

- eCTD Module 5 for Clinical Studies
- Study Data Plan and Preparation
- Considerations for SAS Datasets and Programs
- Programming Package can include
  - **SAS Xport Transport Files and splits**
  - **Define.xml and Define.PDF**
  - **SDTM Annotated CRF**
  - **Programs**
  - **SDRG & ADRG**
- Follow Study Data Folder for Easy Automation of Review Package

# Contact Information

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# Backup Slides

# DMF

- **Drug Master File** or **DMF** is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Typically, a drug master file is filed when two or more firms work in partnership on developing or manufacturing a drug product. The DMF filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details.

- SEND - Standard for Exchange of Nonclinical Data

| Folder Name | Folder Level | Description/Contents |
|---|---|---|
|  [module] | 1 | Refers to the eCTD module in which study data is being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level. |
|  datasets | 2 | Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level. |
|  [study] | 3 | Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level. |
|  analysis | 4 | Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level. |
|  adam | 5 | Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level. |
|  datasets | 6 | Place ADaM datasets in this subfolder. |
|  split | 7 | Place any split ADaM datasets in this subfolder. |
|  programs | 6 | Place software programs for ADaM datasets, tables and figures in this subfolder. |

| | | |
|---|---|---|
| legacy | 5 | Contains legacy formatted analysis datasets and corresponding software programs. Do not place files at this level. |
| datasets | 6 | Place legacy analysis datasets in this subfolder. |
| split | 7 | Place split legacy analysis datasets in this subfolder. |
| programs | 6 | Place software programs for legacy analysis datasets, tables and figures in this subfolder. |
| misc | 4 | Place miscellaneous datasets that don't qualify as analysis, profile, or tabulation datasets in this subfolder. This subfolder was formerly named "listings". |
| profiles | 4 | Place patient profiles in this subfolder. |
| tabulations | 4 | Contains subfolders for tabulation datasets. Do not place files at this level. |
| legacy | 5 | Place legacy (non-standardized) tabulation datasets in this folder. |
| split | 6 | Place any split legacy tabulations datasets in this subfolder. |
| sdtm | 5 | Place SDTM tabulation datasets in this subfolder. Should only be used in m5 for clinical data. |
| split | 6 | Place any split SDTM files in this subfolder. |