



The Misery of the Miscellaneous Folder in Module 5

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Drouville, In the fish tank

Drouville is a patient, graphic designer and artist from Argentina who has survived multiple myeloma and a relapse.

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Agenda

- 1 **Regulatory Requirements**

- 2 **Organization of Files and Documents within the eCTD**

- 3 **Use Cases**

- 4 **Best Practices**

- 5 **Conclusion**

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Regulatory Requirements

Familiarize yourself with the Regulatory Requirements

FDA Documents

- [FDA Data Standards Catalog](#)
- [FDA Study Data Technical Conformance Guide](#)
- [FDA Business Rules](#) and [FDA Validator Rules](#)
- [FDA Technical Rejection Criteria](#)
- [eCTD Guidance](#)

PMDA Documents

- [Basic Principles on Electronic Submission of Study Data for New Drug Applications](#)
- [Notification on Practical Operations of Electronic Study Data Submissions](#)
- [Data Standards Catalog](#)
- [Technical Conformance Guide on Electronic Study Data Submissions \(rev Jan 2019\)](#)

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Regulatory Requirements

FDA Data Standards Catalog

- ❖ Contains specifications for the data standards and versions that the FDA supports

FDA Data Standards Catalog v6.1 (09-09-2019) - Supported and Required Standards											
For full description of column headings, see Instr.& Column Descriptions tab											
Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported 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	Statutory, Regulatory, or Guidance Authority
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015			Standardized Study Data
											Study Data Technical Conformance Guide
Clinical study datasets	SDTM	XPT	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]	Standardized Study Data
Clinical study datasets	SDTM	XPT	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]	Standardized Study Data
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		Standardized Study Data
Clinical study datasets	SDTM	XPT	CDISC	1.4	3.2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]		Standardized Study Data
Clinical study datasets	Analysis Data Model (ADaM)	XPT	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]	Standardized Study Data
Clinical study datasets	ADaM	XPT	CDISC	2.1	1.1	CDER, CBER	03/15/2018		03/15/2019 [1] 03/15/2020 [2]		Standardized Study Data
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	Standardized Study Data

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Regulatory Requirements

FDA Study Data Technical Conformance Guide

Contains technical specifications for submission of electronic study data.

Examples of the technical specifications in this document are:

- ❖ Dataset / File sizes
- ❖ eCTD directory structure
- ❖ Use of Controlled Terminology
- ❖ Reviewer's Guides
- ❖ Validation of CDISC data
- ❖ Submission of software programs
- ❖ Data Standards for integrated analyses

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

For questions regarding this technical specifications document, contact CDER at cdcr-edata@fda.hhs.gov or CBER at cber.cdsc@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019

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Regulatory Requirements

FDA Business Rules

These business requirements help ensure that study data is compliant, useful and supports meaningful review and analysis.

<i>Version 1.5 finalized June 2019</i>	
FDA Business Rule ID	FDA Business Rule
Clinical and Nonclinical	
FDAB008	All treatment exposure date/time should be between first and last study treatment date/time.
FDAB009	All paired variables should have a one-to-one relationship. Examples include short name and name of test; parameter name and parameter code or number; variable name and variable label, etc.
FDAB011	All trial design data should be submitted as specified in the FDA Study Data Technical Conformance Guide (TCG).
FDAB015	Character values should not have leading spaces or only have a period character.
FDAB016	Collection study day should be populated when date/time of collection is available.
FDAB017	Controlled terms should use the exact term (case, spelling, and punctuation) used by the terminology maintenance organizations (e.g., MedDRA, CDISC controlled terminology).
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPQUAL).
FDAB019	SUPPQUAL variable length should be no longer than the maximum length of the actual data within the dataset.
FDAB024	Large datasets should be split into smaller datasets no larger than 5 GB in size.
FDAB026	Records with a baseline flag should have a corresponding standard result with a standardized unit where available.
FDAB030	Standard units should be consistent within the same assessment (having the same --TESTCD, --CAT, --SCAT, --SPEC, --METHOD values).

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Regulatory Requirements

FDA Validator Rules

Provide detail regarding FDA's assessment of study data for purposes of review and analysis.

version 1.3, finalized October 2018											
FDA Validator Rule ID	FDA Validator Message	Publisher	Publisher ID	Business or Conformance Rule Validated	FDA Validator Rule	Domains	SDTM 3.1.2	SDTM 3.1.3	SDTM 3.2	SEND 3.0	SEND 3.1
SD1097	No Treatment Emergent info for Adverse Event	FDA	FDAB001	A treatment-emergent flag must be submitted.	A treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3.	SUPPAE	X	X	X		
SD1321	No Treatment Emergent info for Adverse Event (missing SUPPAE)	FDA	FDAB001	A treatment-emergent flag must be submitted.	A treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3.	AE	X	X	X		
SD1037	Missing value for --TOX, when --TOXGR is populated	FDA	FDAB002	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is greater than 0.	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is populated and greater than 0.	AE, MH, CE, EG, LB, PC, PP	X	X	X		
SD0008	Value for --DECOD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for the Dictionary-Derived Term (--DECOD) variable must be populated using a Preferred Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE	X	X	X		
SD1114	Value for --BODSYS not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Body System or Organ Class (--BODSYS) variable must be populated using a System Organ Class of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE	X	X	X		
SD2007	Value for --PTCD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Preferred Term Code (--PTCD) variable must be populated using a Preferred Term Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X		
SD2008	Value for --LLT not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Lowest Level Term (--LLT) variable must be populated using a Lowest Level Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X		

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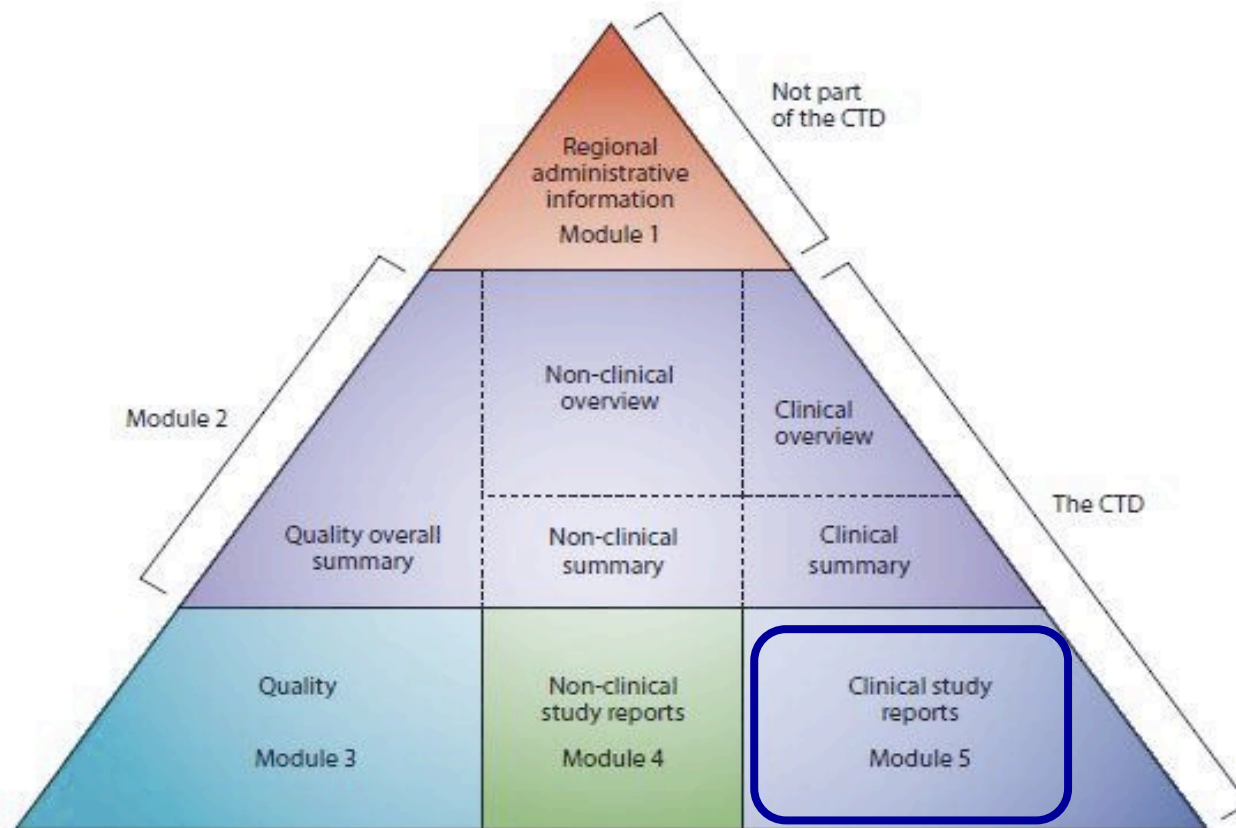
Regulatory Requirements

The Common Technical Document (eCTD)

- ❖ An internationally agreed format for the preparation of applications regarding new drugs intended for submission to regional regulatory authorities in participating countries.
- ❖ Created by International Conference on Harmonisation (ICH)
- ❖ Specifies:
 - ❖ What documents should be included in regulatory filings (e.g. Protocols, Clinical Study Reports, Risk Management Plans, etc.)
 - ❖ Specifications on the content and format of many documents
 - ❖ Associated document type-definitions (DTDs) and stylesheets
 - ❖ The folder structure for storing files and the naming conventions for folders and files
 - ❖ Technical specifications for an XML backbone file providing metadata about content files

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Organization of Files and Documents within the eCTD



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.

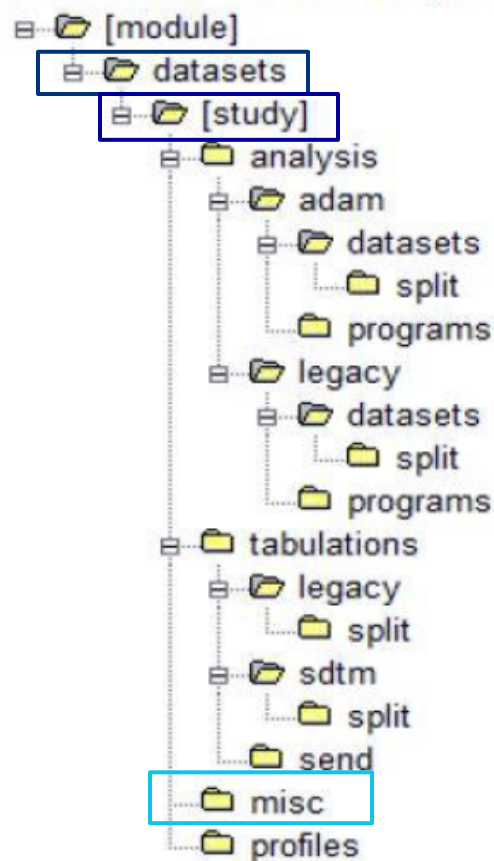
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eCTD Module 5

Structure

- ❖ Study datasets and their supportive files should be organized into a specific file directory structure
- ❖ eCTD Module 5 Folder Structure for Study Data
- ❖ Allows automated systems to detect and prepare datasets for review
- ❖ Minimizes the need for manual processing by the reviewer

Figure 1: Folder Structure for Study Datasets



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eCDT Module 5

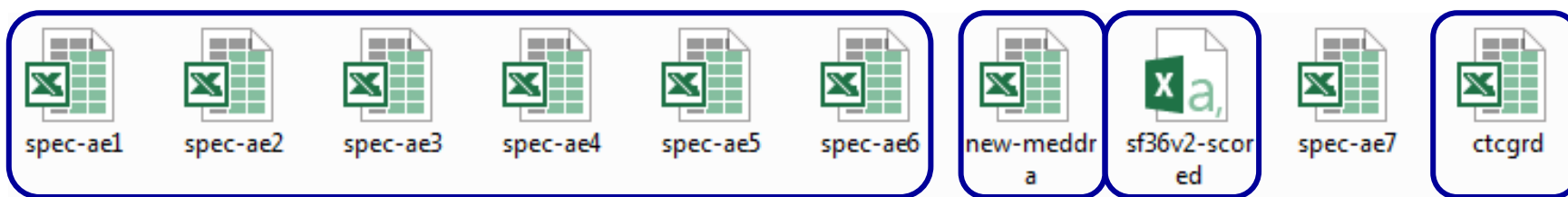
Miscellaneous Folder

- ❖ FDA Study Data Technical Conformance Guide (SDTCG)
- ❖ Miscellaneous datasets are those that do not qualify as analysis, profile, or tabulation datasets
- ❖ Place in misc folder (formally the listings folder)
- ❖ Any data not captured in SDTM but used in the creation of ADaM datasets or Tables/Listings/Graphs (TLGs) within the submission
 - ❖ Look-up tables, such as a list of prohibited concomitant medications
 - ❖ AEs of special interest
 - ❖ CTC Toxicity grades
 - ❖ Deviations collected somewhere other than on the CRF
- ❖ Traceability

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Use Cases

Example 1

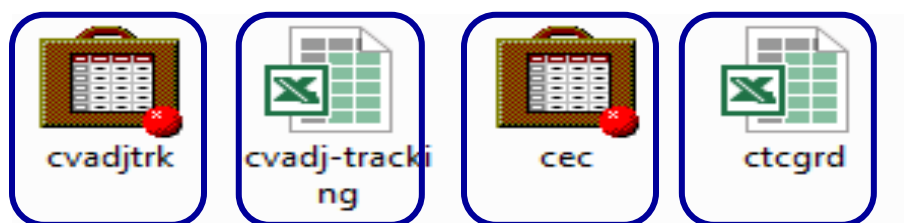


- ❖ `../m5/datasets/CNTO####/misc`
- ❖ files for the CTC Toxicity Grade (ctcgrd), several files for AEs of special interest, a file of new MedDRA terms and the Short Form 36 Health Survey (SF-36) question score information
- ❖ toxicity grade spreadsheet is used in deriving the toxicity grades for laboratory data in the analysis datasets
- ❖ files for the AEs of Special Interest were used in the creation of several of the AE related tables and listings

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Use Cases

Example 2

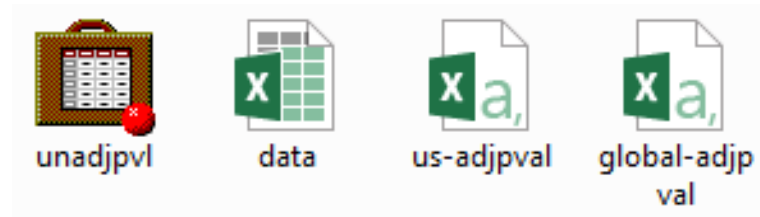


- ❖ ../m5/datasets/CNTO####/misc
- ❖ files for the CTC Toxicity Grade (ctcgrd)
- ❖ files for the Cardiovascular Adjudication
 - ❖ cec.xpt file contains data transferred from the adjudication committee
 - ❖ cvadjtrk.xpt is the tracking file containing records from the locked database
 - ❖ cvadj-tracking.xls is the tracking file used by clinical and contains the dossier number for each case to be adjudicated
 - ❖ used in the creation of the analysis dataset for Cardiac Adjudication.

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Use Cases

Example 3



- ❖ ../m5/datasets/SCE####/misc
- ❖ combining the efficacy data from several studies
- ❖ files containing the adjusted and unadjusted p-values for the specific multiplicity adjusted testing procedure
- ❖ used in the creation of tables in the submission

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Best Practices

- ❖ Review and understand the relevant regulatory requirements
- ❖ Discuss and plan well in advance the strategy that you will use for items such as the handling of non-CRF data within the submission
- ❖ Included all data sources in the CRT package
 - ❖ non-CRF data, such as Excel spreadsheets that are used as look-up tables
 - ❖ Decide as early as possible whether you will convert these data sources to SDTM, provide them in ADaM datasets, or deliver them in the misc folder of Module 5
- ❖ Work closely with your companies Regulatory Affairs and/or Regulatory Operations department throughout the submission planning and preparation process
- ❖ During the Pre-NDA/Pre-BLA meetings and communications seek agreement with the regulatory agencies to confirm the specific requirements and preferences for a submission
- ❖ Ensure that your documentation is clear and consistent across the submission

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Additional Resources

- ❖ FDA CDER eData Team

- ❖ Send questions to cder-edata@fda.hhs.gov

- ❖ PHUSE SDTM ADaM Implementation FAQ Work Group

- ❖ Home page

https://www.phusewiki.org/wiki/index.php?title=SDTM_ADaM_Implementation_FAQ

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Conclusion

- ❖ Preparing regulatory submissions packages in the pharmaceutical industry can be very challenging
 - ❖ large amount of work
 - ❖ research and understand regulatory and CDISC submission requirements
 - ❖ large amount of documentation that goes into a submission
- ❖ Understanding the data, the analysis that is required and the documents needed to support the analysis early in the study will assist you in determining how and where you will place this documentation in the Module 5 folders and whether you will need to utilize the misc folder.



Q & A

Group of human B cells



Thank You

Group of human B cells



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