Significance of Data Standards in eSubmission

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- Electronic file structure in eCTD
- Technical Deficiencies
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- eSubmission and Data Standards
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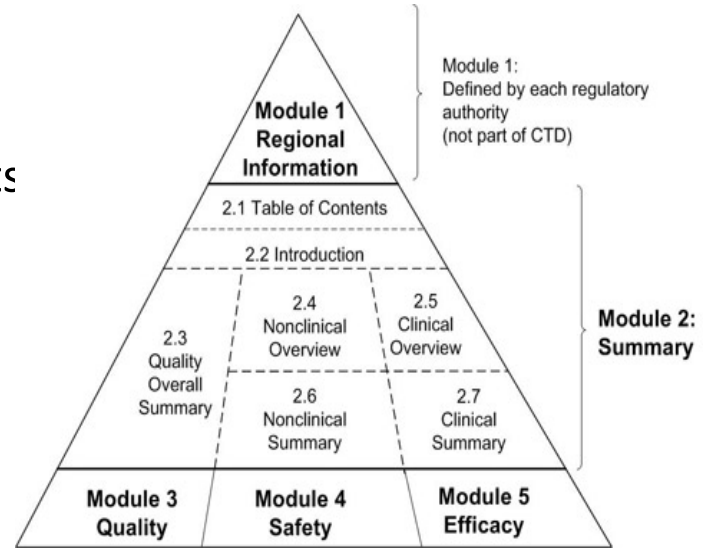
- Upcoming Standards
- Questions

Overview of eCTD submission

The **Electronic Common Technical Document (eCTD)** is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER).

- Module 1 - Administrative Information /Prescribing Information
- Module 2 - Summaries
- Module 3 - Quality
- Module 4 - Nonclinical Study Reports
- Module 5 - Clinical Study Reports



Overview of eCTD submission…

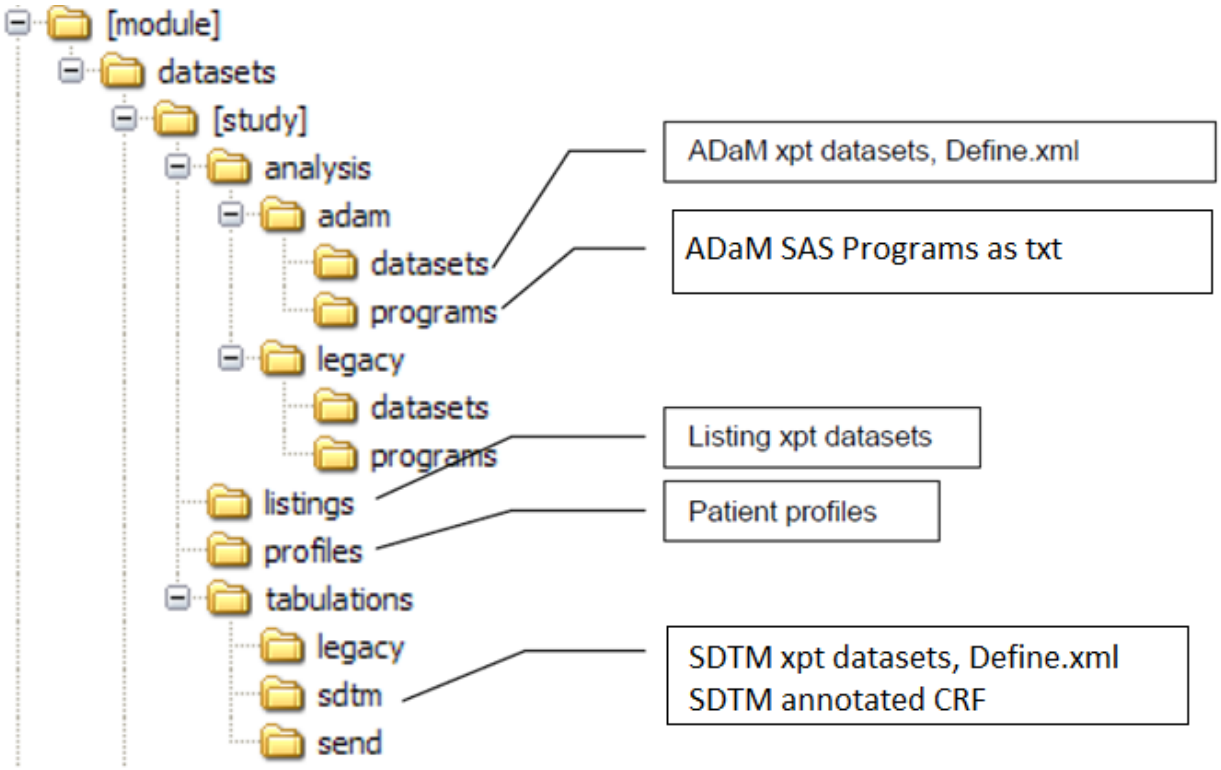
Countries accepting eCTD format currently

- US-FDA
- European Medicines Agency (EMA)
- Japan
- Health Canada
- Swiss medic

Types of US-FDA eCTD submissions

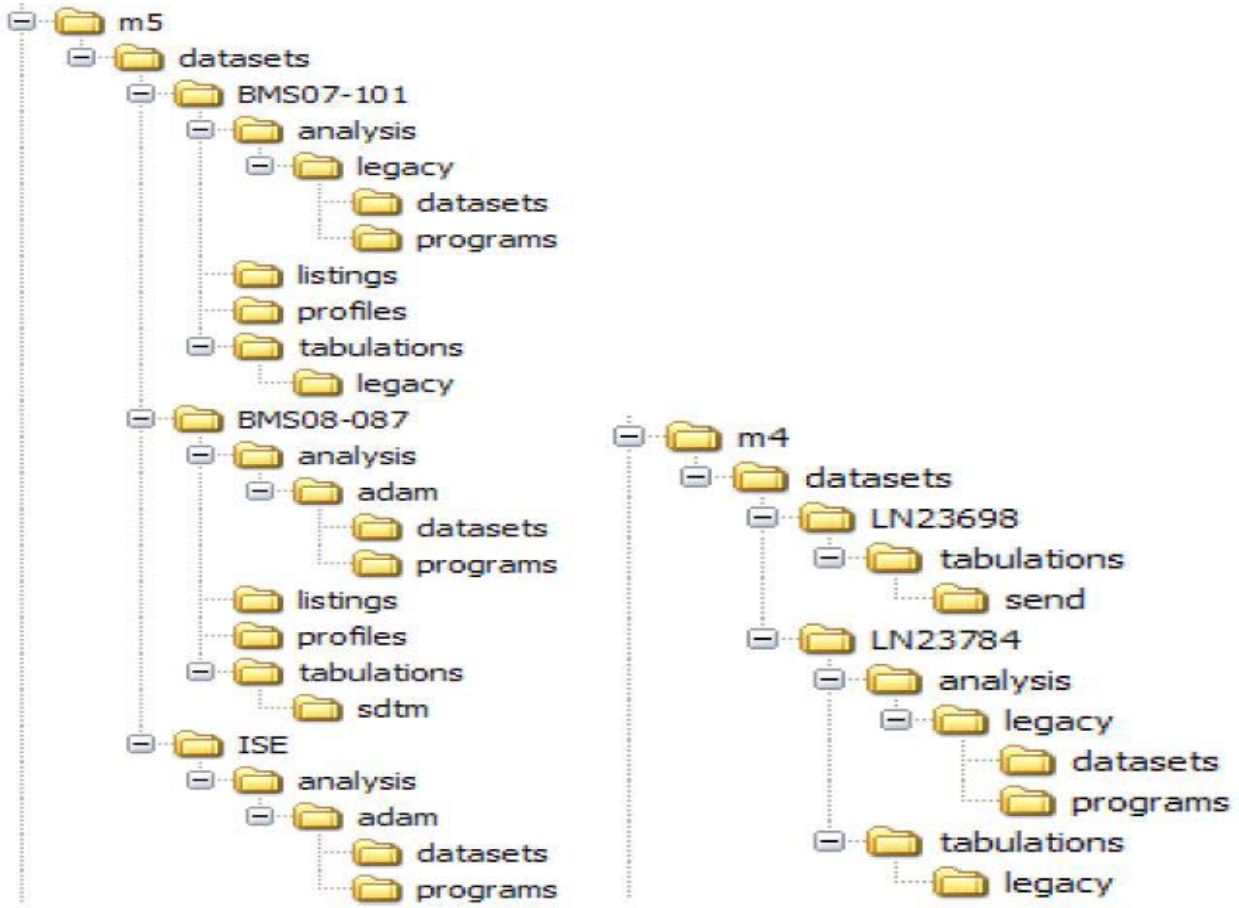
- New Drug Applications (NDAs) - 5th May 2017
- Abbreviated New Drug Applications (ANDAs) - 5th May 2017
- Biologics License Application (BLAs) - 5th May 2017
- Investigational New Drug Applications (INDs) - 5th May 2018

Electronic file structure in eCTD



Electronic file structure in eCTD

Electronic file structure in eCTD (Module 4 & Module 5)



Technical Deficiencies

Following are some of the possible technical deficiencies that may occur in eSubmission:

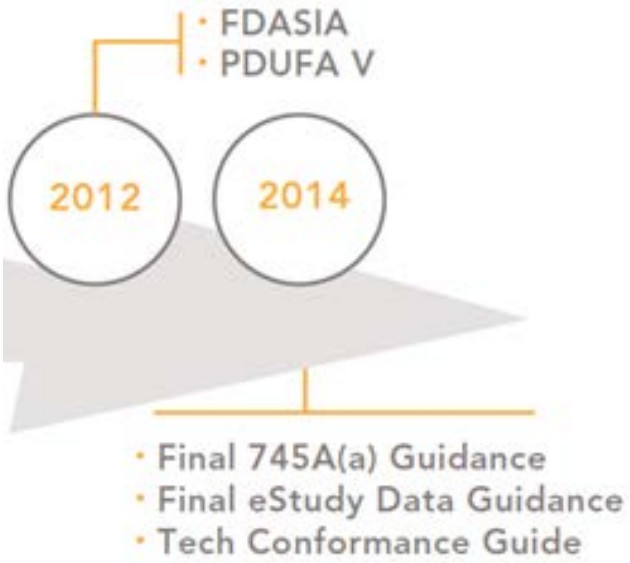
- Defect in the media package
- Electronically non readable through ESG
- No index.xml
- Presence of a virus
- Incompatible file format
- Incorrect or inaccurate metadata, such as application type or number

"Not Received" - Until the technical deficiencies are resolved.

"Refuse to File" - If the technical deficiency is not resolved by 60 days after the submission

Significant Regulatory Changes

- FDA signed FDA Safety and Innovation Act (FDASIA) into law on July 9th 2012, and announced Prescription Drug User Fee Act (PDUFA) V – December 31st 2012



- In Section 745A(a) of FD&C Act, Congress granted explicit authorization to FDA to implement Electronic submission requirements in guidance

Significant Regulatory Changes…

- **Deadlines for Standardized study data (for studies that start after)**
  - *December 17, 2016 - NDA, BLA and ANDA submissions*
  - *December 17, 2017 - IND submissions*
- **Deadlines for required eSubmission**
  - *May 5, 2017 - NDA, ANDA, BLA, and DMFs must be in eCTD format*
  - *May 5, 2018 - Commercial INDs must be in eCTD format*

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be **not be filed or received**

CDISC - Data Standards

Study Data Standards

Study data standards describe a standard way of exchanging study data between computer systems

- The Study Data Tabulation Model (**SDTM**) – "Clinical Trial Data"
- The Standard for Exchange of Non-clinical Data (**SEND**) – "Pre-Clinical or Animal Studies"
- The Analysis Data Model (**ADaM**) – "Clinical Trial Analysis Data"

CDISC - Data Standards…

Exchange Format Standards

An exchange format standard specifies a particular way that information is encoded in a computer file.

Format standards currently supported by FDA are :

- Adobe Portable Document Format (pdf)
- SAS XPORT File format (xpt)
- Extensible Mark-up Language (xml)
- Stylesheets (XSLT) and document type definition (DTD) for the XML document information files.
- Microsoft Word for draft labelling (Track Changes)

CDISC - Data Standards…

Terminology Standards

It is an adopted standard expressions (values) used with data items within CDISC-defined datasets.

- The National Drug File (NDF)— Reference Terminology for drug classifications
- Medical Dictionary for Regulatory Activities (MedDRA)
- WHO Drug
- SNOMED CT

FDA Recommendation

SAS DATASET

- FDA accepts SAS xport (V5) transport file
- The length of variables should be less than or equal to 8
- The length of variable and dataset label should be less than or equal to 40
- The size of the dataset is recommended to be
  - *Less than 5 GB (CDER)*
  - *Check with respective divisions in various agencies*
- The length of character variables to be reduced to maximum length used
- No Special characters

FDA Recommendation…

REVIEWER'S GUIDE (SDTM, SEND & ADAM)

- Study protocol title, number and version
- Study design
- Standards, formats, and terminologies and their versions
- Description of study datasets
- Data standards validation rules, versions and issues

FDA Recommendation…

SDTM

- SDTM Implementation Guide (SDTMIG)
- SDTM datasets should be submitted along with define.xml and SDRG.
- No data should be imputed
- USUBJID is consistent through entire application
- Custom domains should follow SDTMIG and should be explained in SDRG
- Trial design domains should be included in SDTM submission

FDA Recommendation…

ADaM

- ADaM Implementation Guide (ADaMIG)
- ADaM datasets should be submitted along with define.xml and ADRG
- ADaM programming codes must be submitted in txt formats
- ADSL is required for each study
- ADaM datasets should be derivable from SDTM (not from other internal raw data)
- Imputed data must be documented in ADRG

FDA Recommendation…

SEND

- SEND follows SEND implementation guide
- SUPPQUAL and custom domain could be used as well

DEFINE

- Define.xml describes SDTM, SEND and ADaM datasets structure
- Clear and accessible to Code list, origin and derivation for each variables
- Data definition specification for submitted datasets
  - Ver-1: Define.xml or Define.pdf
  - Ver-2 and later: Only Define.xml

FDA Recommendation…

aCRF

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

TERMINOLOGY

- NCI, MedDRA, WHO drug
- Terms and versions for each study should be documented in Reviewers guide.

FDA Recommendation…

eSUBMISSION – SUBMITTING MODE

- eSubmission with 10GB and smaller - no more CD/DVDs

eSubmission Standards & Requirements

FDA Data Standards Catalog v4.5.1 (08-31-2016) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*.

Use	Data Exchange Standard	Exchange Format	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	Regulatory Reference and Information Sources
Regulatory Applications (IND, NDA, ANDA, BLA, master files)	Electronic Common Technical Document (eCTD)	Extensible Markup Language (XML)	International Council for Harmonisation (ICH)	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	CDER, CBER	06/01/2008		05/05/2017 [5] 05/05/2018 [6]		Electronic Submissions-Electronic Common Technical Document (eCTD)
Product Labeling Submissions	Structured Product Labeling (SPL)	XML	Health Level 7 (HL7)	Release 5		CDER, CBER	Ongoing		04/01/2005 [3] 12/11/2003 [4]		StructuredProductLabeling (SPL) Implementation Guide with Validation Procedures
Postmarketing Safety Reporting - Adverse Events for Medical Devices	Individual Case Safety Report (ICSR)	XML	HL7	Release 1	N/A	CDRH	Ongoing				Electronic Medical Device Reporting (eMDR) - Device Regulation and Guidance
Postmarketing Safety Reporting- Adverse Events for Animal Drugs (ICSR)	ICSR	XML	ISO/HL7	Release 2	N/A	CVM	Ongoing				Veterinary Adverse Event Reporting for Manufacturers

Source: http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

eSubmission Standards & Requirements…

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Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.4	3.2	CDER, CBER	08-17-2015		03/15/2018 [1] 03/15/2019 [2]		CDISC.org - SDTM See Technical Conformance Guide
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12-01-2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08-07-2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	30-10-2009		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.1	3.1.1	CDER, CBER	Ongoing	01-28-2015			CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06-13-2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND
Study data definition	Define	XML	CDISC	1.0	N/A	CDER, CBER, CDRH	Ongoing	03-15-2018	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML
Study data definition	Define	XML	CDISC	2.0	N/A	CDER, CBER, CDRH	08-07-2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML

CDISC components and file formats

Following are the CDISC eSubmissions components:

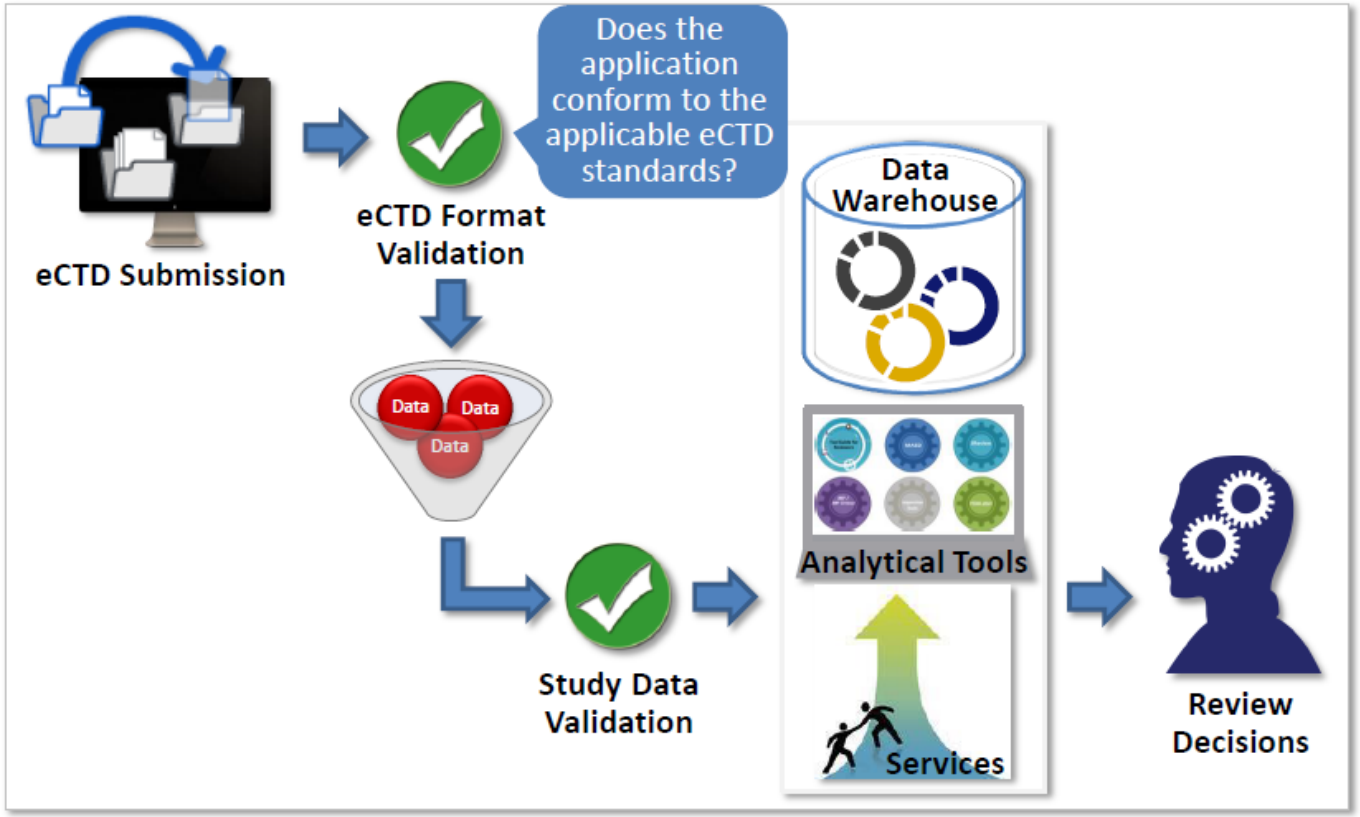
- Protocol - .pdf
- SAP - .pdf
- eCRF - .pdf
- SDTM - .xpt
- ADaM - .xpt
- SEND - .xpt
- CSR - .pdf
- Define.xml - .xml
- ADaM SAS programs - .txt
- Efficacy SAS programs (if Required) - .txt
- Study Data Standardization Plan , Study Data Reviewer's Guide , Analysis Data Reviewer's Guide - .pdf

eSubmission and Data Standards

Electronic Submission and Data Standards - What do they mean to agencies?

= More efficient review process

Validation - Impact on Regulatory review



eSubmission benefits

- Reduced time and cost involved in clinical trials
- Improve the efficiency and effectiveness of regulatory reviews
- High effective communication and quicker response
- Streamlining the workflows in development, regulatory and marketing departments
- Global standardized format, enables eCTD for cost effective eSubmissions to various agencies

Upcoming Standards

What's New and upcoming Standards:

- Define XML v2.1 Draft Standard has been released for Public Review and it closes on **May 5th 2017**
- Starting from **May 5th 2017 the** NDAs, ANDAs, BLAs, and MFs must be submitted using eCTD v3.2.2 format for submissions to CDER and CBER

Thank you!

Questions?

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