Required Electronic Submissions to CDER / CBER

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U.S. Food & Drug Administration

October 8, 2015

Disclaimer

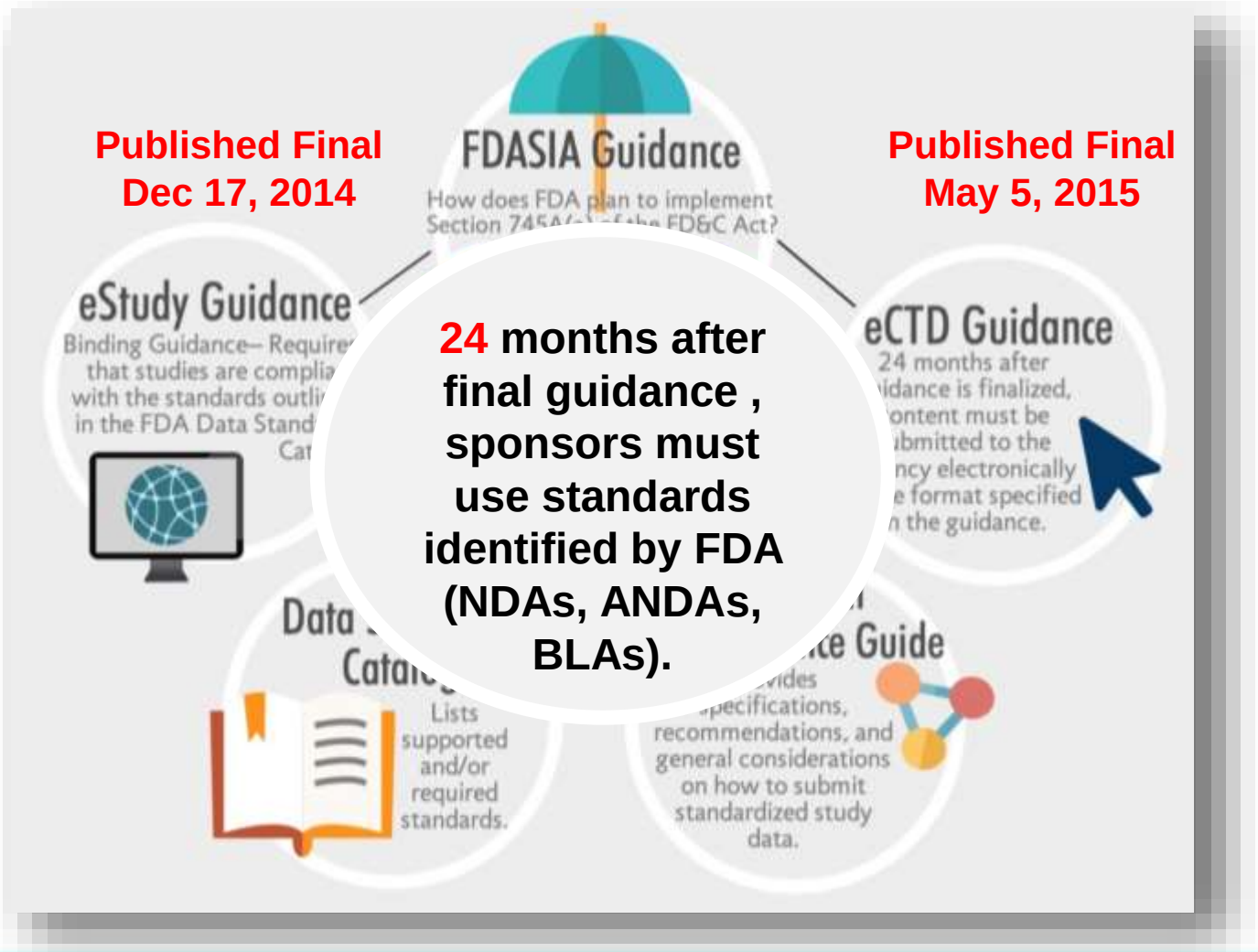
The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the Food and Drug Administration.

FY2013, FY2014, FY2015 (Q1-Q3)
Number (%) of NDAs with Study Data Submissions in CDISC SDTM*

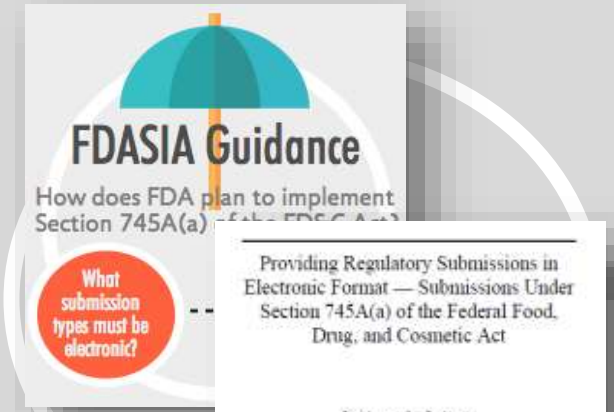
Fiscal Year	# of Submissions	% with CDISC SDTM
2013	223	55 %
2014	233	64 %
2015 (Q1-Q3)	112	71 %

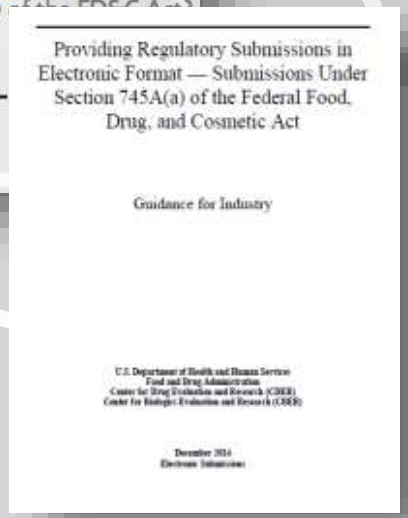
*Source: Office of Business Informatics, CDER - **One or more** explicitly stated SDTM studies (or study data structure that resembled SDTM).

Required Data and Submission Standards



How will eSubmissions be Implemented?





Final Published December, 2014

24 Months after Final Guidance

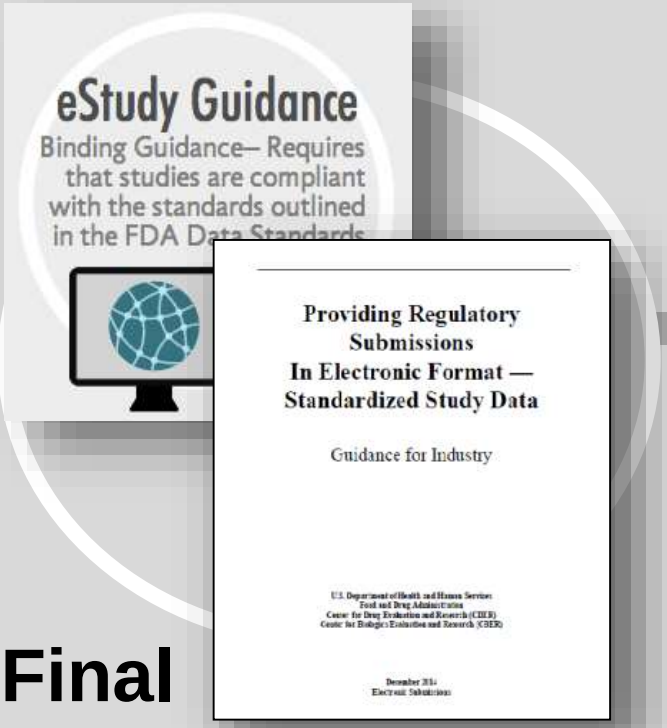
Individual Guidances

Implementation Guidance for Electronic Submissions

NDAs, ANDAs, BLAs, INDs

- **Timetable**
- **Content**
- **Format**

When will Study Data Standards be Required?



Final Published December, 2014

December 17 2014

24 Months*

December 17 2016

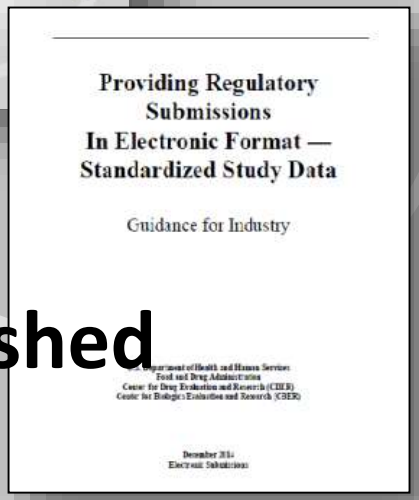
Compliance

Studies starting after MUST use the standards in the Data Catalog (NDAs, ANDAs, BLAs)**

*36 months for INDs **Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC).

What Study Data Standards will be Required?

eStudy Guidance
Binding Guidance– Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog

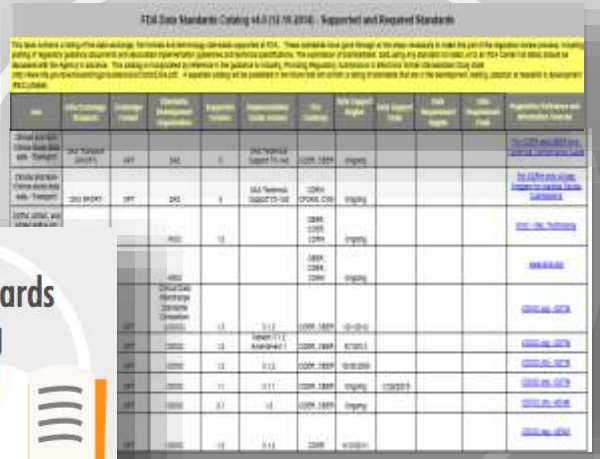


Final Published

December 2016

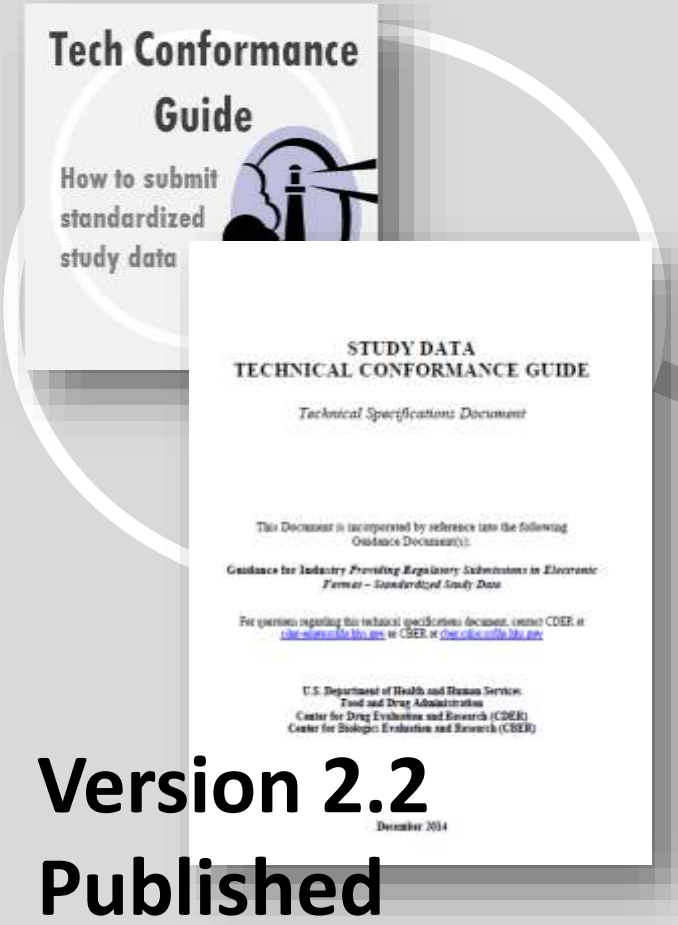
Data Standards Catalog

Study Data….SDTM, ADaM, SEND, Define.XML



Data Standards Catalog
Lists supported and/or required standards.

How Study Data Standards will Be Required?



Version 2.2 Published

Use it NOW

Technical Conformance Guide

- Study Data Standardization Plan
- Analysis Data Reviewer's Guide
- Study Data Reviewer's Guide
- SDTM Domain Specs
- Exchange Formats
- File Transport
- SDTM General Considerations
- Efficacy, Safety, Timing Variables
- SEND Domain Specs
- ADaM Domain Specs
- Controlled Terminologies
- Therapeutic Area Standards
- Data Validation & Traceability
- Elect Sub Format

eStudy Guidance
Binding Guidance– Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog

Waivers and Exemptions

Are there Waivers from the Requirement?

No.

Are there Exemptions from the Requirement?

Yes.

Where Do We Go From Here?

Conformance to Data Standards

Data Validation

- Process that attempts to ensure that submitted data are both compliant and useful.
  - **Compliant** (conformance) - Data conform to the applicable and required data standards.
  - **Useful** (Quality) - Data support the intended use (i.e.,regulatory review and analysis).

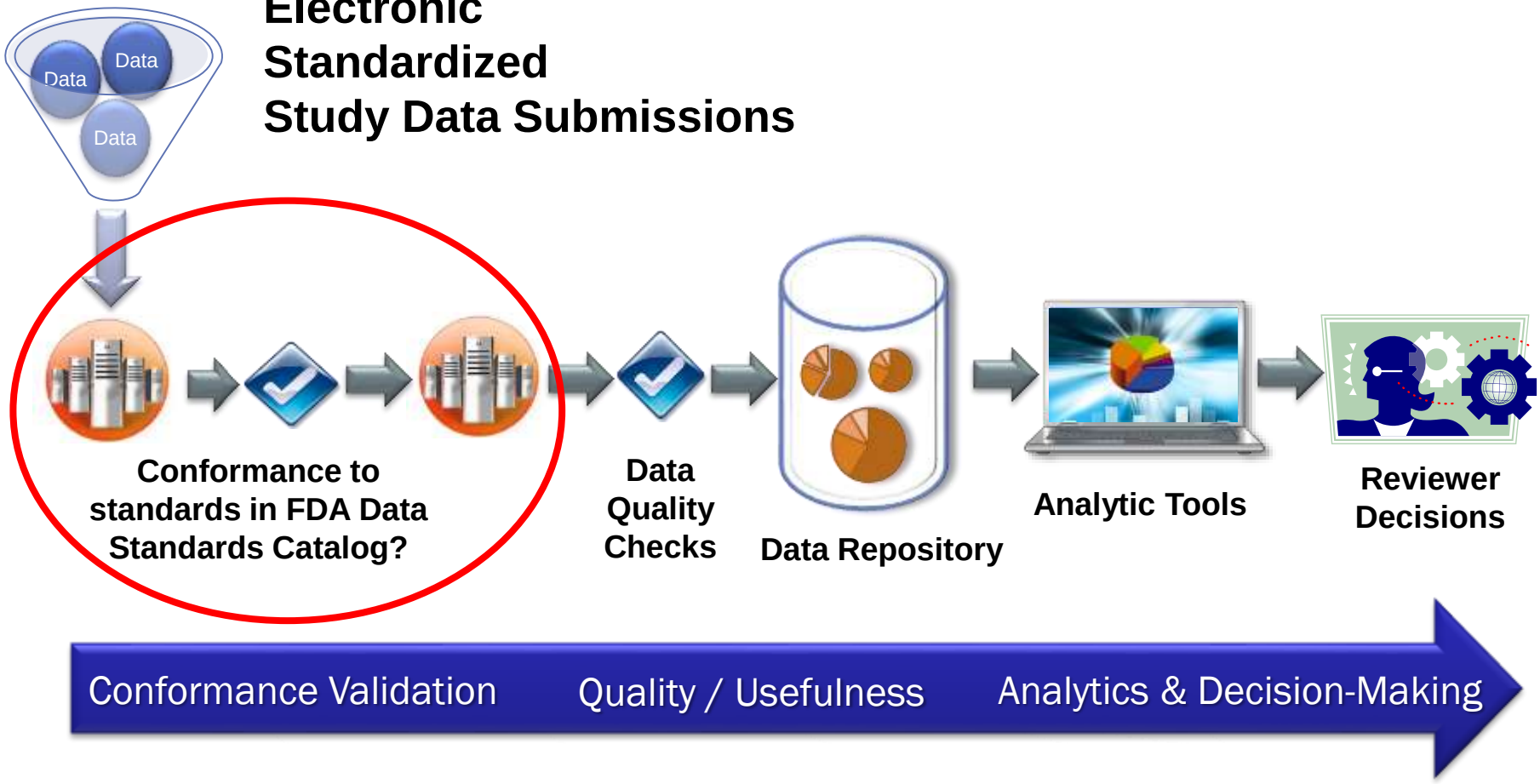
Data Validation

"Sponsors should validate their study data before submission using the published validation rules and either correct any validation errors or explain in the SDRG why certain validation errors could not be corrected."

-- Study Data Tech Conformance Guide v.2.2

Data Validation

Electronic
Standardized
Study Data Submissions



eCTD Submissions: Part 1

Ginny Hussong, Director
Division of Data Management Services & Solutions
Office of Business Informatics, CDER
U.S. Food and Drug Administration

End of Paper

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

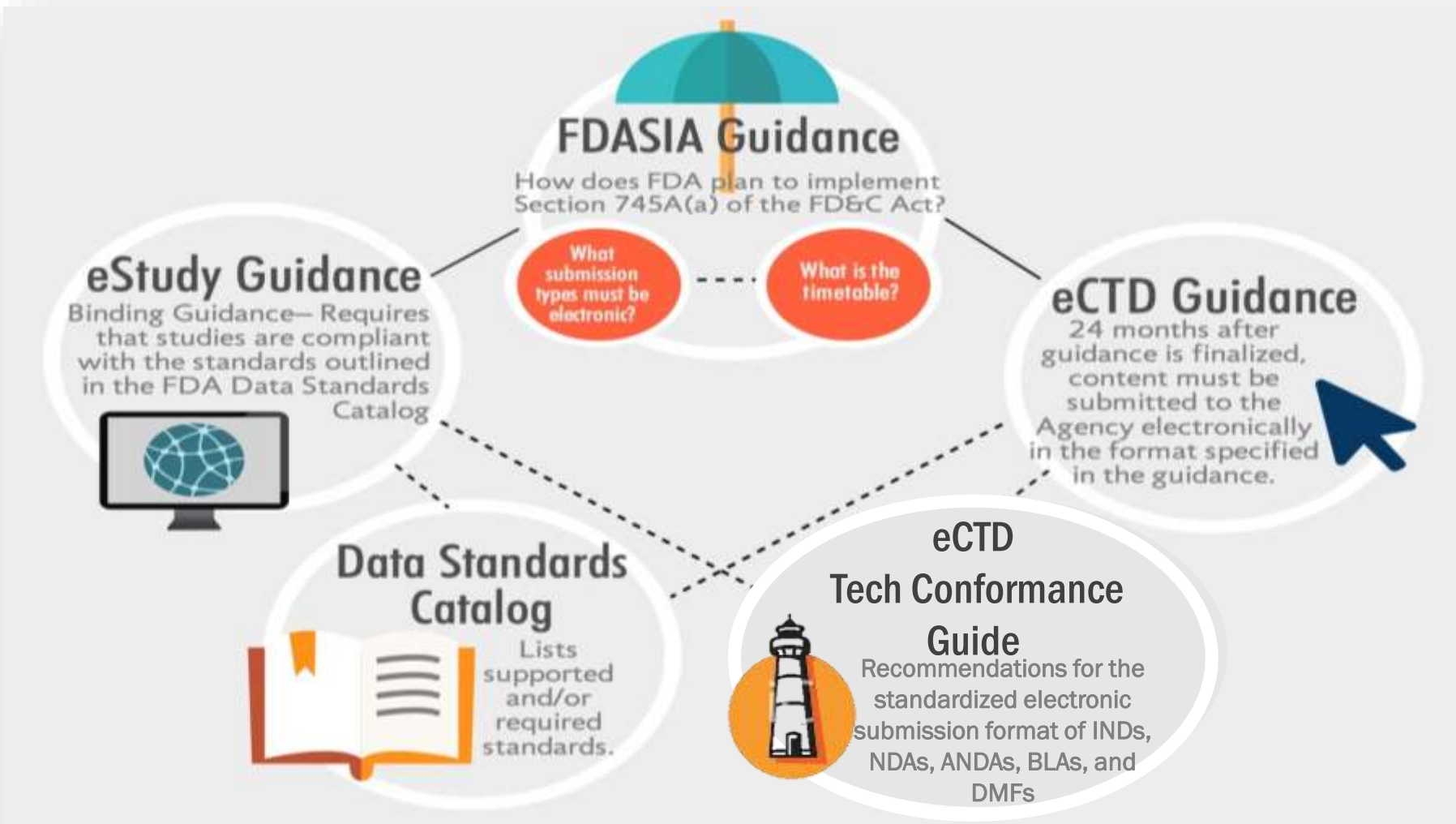
NATIONAL ARCHIVES AND RECORDS ADMINISTRATION
WASHINGTON, D.C. 20408

August 24, 2012

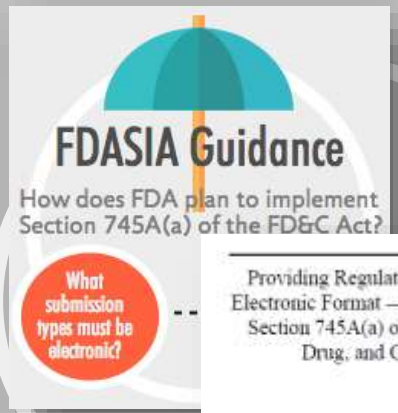
1.1 ***By 2019, Federal agencies will manage all permanent electronic records in an electronic format***

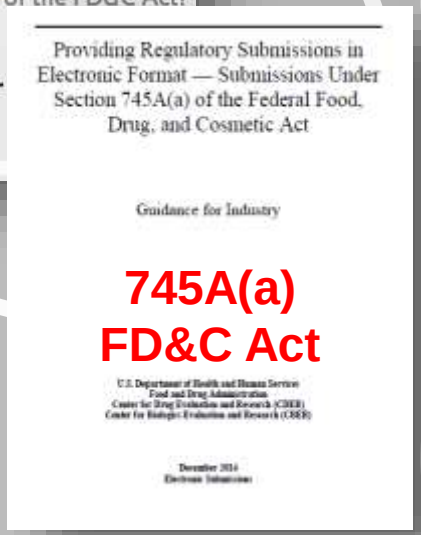
By December 31, 2019, all permanent electronic records in Federal agencies will be managed electronically to the fullest extent possible for eventual transfer and accessioning by NARA in an electronic format. By December 31, 2013, each agency will develop and begin to implement plans to achieve this transition. Agencies should also consider the benefits of digitizing permanent records created in hard-copy format or other analog formats (e.g., microfiche, microfilm, analog video, analog audio).

Framework for Required Electronic Submissions



How will eSubmissions be Implemented?





Final Published December, 2014

24 Months after Final Guidance

Individual Guidances

"745A(a) Umbrella" Implementation Guidance

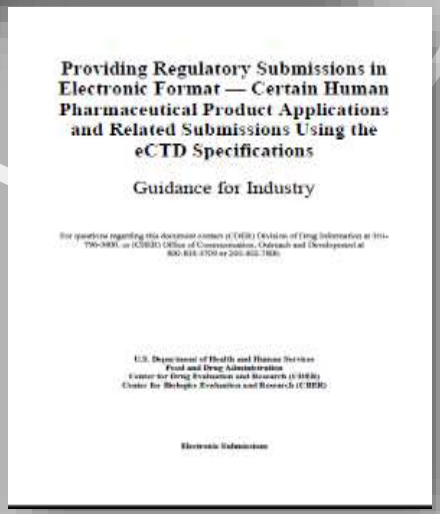
NDAs, ANDAs, BLAs, INDs

- **Timetable**
- **Content**
- **Format**

When will eCTD Format be Required?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

Published May 5, 2015

24 Months*

Required May 5, 2017

Compliance

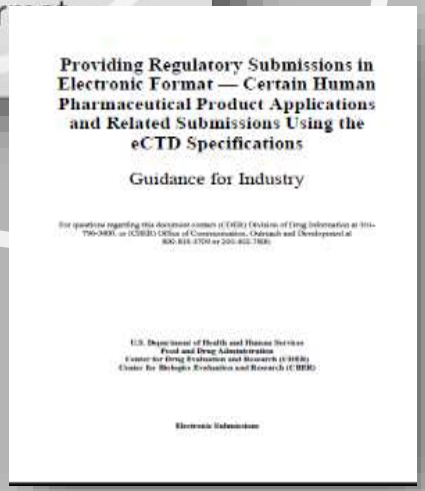
Electronic submissions using the version of eCTD currently supported by FDA. As specified in the FDA Data Standards Catalog

*36 months for Commercial INDs

What Submission Types are Applicable?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD For



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

FDASIA Section 745A(a) applies to

Submissions under section 505(b), (i), or (j) of the FD&C Act

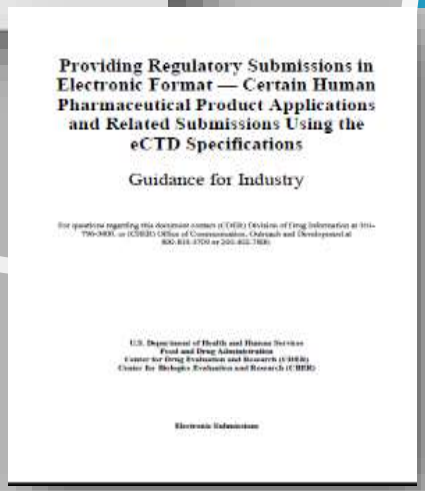
NDAs
ANDAs
BLAs
INDs
DMFs or BPFs
Combo products

Final Published May 5, 2015

What are the eCTD Specifications?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format


Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

Published May 5, 2015

ICH eCTD Specs 3.2.2
ICH eCTD Study Tagging Files
FDA eCTD - Module 1
eCTD CTOC
Validation, File Format, PDF
Supportive files & more

Data Standards Catalog

Lists supported and/or required standards.

What eCTD Formats will be Required?

FDA Data Standards Catalog v4.1 (04-09-2015) - 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)*. A separate catalog will be published in the future that will contain a listing of standards that are in the development, testing, adoption or research & development (R&D) phases.

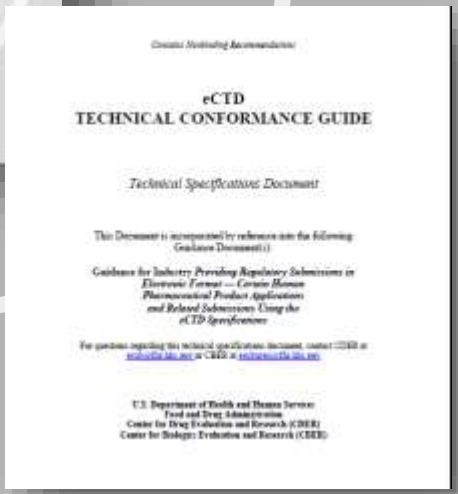
Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Regulatory Applications (IND, NDA, ANDA, BLA, master files)	Electronic Common Technical Document (eCTD)	Extensible Markup Language (XML)	International Conference on Harmonisation (ICH)	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	CDER, CBER	06/01/2008				Electronic Submissions-Electronic Common Technical Document (eCTD)
Product Labeling Submissions	Structured Product		Health Level 7			CDER,			04/01/2005 [3]		StructuredProductLabeling (SPL) Implementation Guide with Validation Procedures

How to Submit eCTD Submissions ?

Non-binding guidance

eCTD
Tech Conformance Guide

Recommendations for the standardized electronic submission format of INDs, NDAs, ANDAs, BLAs, and DMFs


eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

- **General Considerations**
- **Organization of eCTD**
  - **Modules 1 -5**
- **Issues and Solutions**

Published October 5, 2015

Advertising & Promotional Labeling

- These submissions have their own guidance and timetable
- This guidance is not final yet; timetable not started yet
- Must use DTD 3.3 or higher, known as “new Module 1” of eCTD
- Test submissions are welcome; see eCTD website for instructions
- See guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf

Drug Master Files

- No need to resubmit anything that has already been submitted in paper
- If you choose to resubmit your entire DMF upon conversion to eCTD, that is acceptable but it is not required

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format

Will FDA Reject non-compliant submissions?

Yes.

*See the Guidance for a *complete* list of the "musts"*

- **Must** submit electronic submissions using the eCTD version currently supported by FDA.
  - The version of eCTD currently supported is specified in the Data Standards Catalog
- **Must** obtain a pre-assigned application number by contacting the appropriate Center.
- **Must** follow the FDA eCTD technical specification *Table of Contents Headings and Hierarchy.*

- **Must** adhere to the formats and versions specified in the FDA *Specifications for File Format Types Using eCTD Specifications*.
- **Must** adhere to the FDA *Portable Document Format (PDF) Specifications.*
- **Must** use the eCTD *replace* operation rather than submitting the file as *new* if a document replaces a document previously submitted …

- **Must** include only FDA fillable forms (e.g., 1571 or 356h) and electronic signatures to enable automated processing of the submission … *Scanned images of FDA forms will not be accepted.*

- **Must** not submit paper copies of the application, including review & desk copies when *submitting in eCTD format.*

- **Must** use the FDA Electronic Submission Gateway for submissions 10 GB or smaller.

Looking Forward to a Smooth Transition

Standardized electronic format = more efficient review process

eCTD Submissions: Part 2

Mark Gray, Senior Project Manager
Bioinformatics Support Staff
Office of the Director, CBER
U.S. Food and Drug Administration

eCTD Topics

- eCTD Guidance Waivers and Exemptions

- eCTD v4.0
  - Update
  - How does this relate to the eCTD Binding Guidance?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format

Waivers and Exemptions

Are there Waivers from the Requirement?

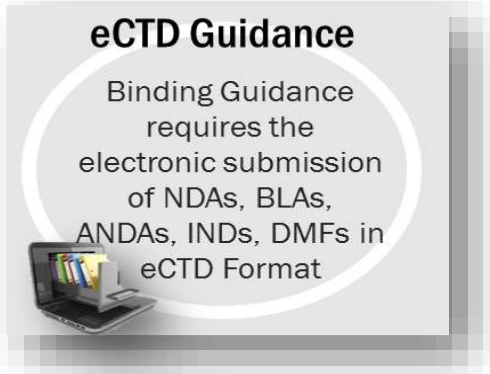
No.

Are there Exemptions from the Requirement?

Yes.

Types of Submissions Exempted

- **INDs for**
  - **Non Commercial Products**
    - Investigator-sponsored INDs
    - Expanded access INDs (e.g., emergency use INDs, treatment INDs)
- **Blood and blood components, including Source Plasma**
- **Devices Regulated by CBER**



eCTD v4.0 Project

- Implementation of the Health Level Seven (HL7) Regulated Product Submission (RPS) standard
  - HL7 exchange standard that can be used for the submission of any regulated product
  - HL7 Normative Standard
- eCTD v4.0 Enhancements include
  - Enhanced control of dossier
    - Document Reuse & Ordering
    - Keyword/attribute functionality
    - Life-cycle functionality (one to one, one to many, many to one)
  - Two-way communication (regional)
    - Regulatory authority can use RPS to send correspondence to the submitter
  - Message is managed through the use of controlled vocabularies
    - Headings changes or new keywords will not require modification of the standard or review tool

eCTD v4.0 Accomplishments

- Successful RPS Normative Ballot (September 2014)
- ICH Step 2 signoff (January 2015)
  - ICH eCTD v4.0 Implementation Guide (Draft)
  - Controlled Vocabulary
  - Submission Format Specification
- Posting of ICH & Regional Specifications for Public Comment (February 2015 – May 2015)
- Posting of the HL7 RPS Normative Standard (September 2015)

eCTD v4.0 Schedule

- ICH Step 4 Signoff (December 2015)
- Finalize FDA eCTD v4.0 M1 Implementation Guide (December 2015)
- 2015 - 2017
  - Training of technical staff on HL7 RPS standard and eCTD implementation guides
  - Update automated submission processes and systems
  - Conduct pilot with industry
  - FDA Guidance
  - FDA acceptance of eCTD v4.0 submissions
- ICH M8 eCTD v4.0 Information
  - http://estri.ich.org/new-eCTD/index.htm
  - Links to Regional eCTD v4.0 web pages

eCTD Binding Guidance

- When FDA implements eCTD v4.0 will eCTD v4.0 submissions be mandatory?
  - NO, but submitting eCTD v4.0 submissions will meet the eCTD requirement
    - There is a risk of waiting for eCTD v4.0 implementation before transitioning to the eCTD
    - Mandatory eCTD submission requirement may be in place before FDA acceptance of eCTD v4.0
- When will eCTD v4.0 become mandatory?
  - FDA has not set a timeline for requiring eCTD v4.0 submissions
  - FDA will issue a Federal Register notice before mandating eCTD v4.0

Thank You

Mark Gray, CBER
EsubPrep@fda.hhs.gov

Esub Resources for YOU

Click for:

- The Final Binding eCTD Guidance
- The eCTD Website
- The FDA Data Standards Catalog
- eSUB@fda.hhs.gov – General eSUB questions
- eDATA@fda.hhs.gov – Clinical / non-clinical data questions

Questions about material presented during this webinar?
CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click for Evaluation and Certificate