Required Electronic Submissions to CDER / CBER

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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*

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th># of Submissions</th>
<th>% with CDISC SDTM</th>
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</thead>
<tbody>
<tr>
<td>2013</td>
<td>223</td>
<td>55 %</td>
</tr>
<tr>
<td>2014</td>
<td>233</td>
<td>64 %</td>
</tr>
<tr>
<td>2015 (Q1-Q3)</td>
<td>112</td>
<td>71 %</td>
</tr>
</tbody>
</table>

*Source: Office of Business Informatics, CDER - **One or more** explicitly stated SDTM studies (or study data structure that resembled SDTM).
24 months after final guidance, sponsors must use standards identified by FDA (NDAs, ANDAs, BLAs).
How will eSubmissions be Implemented?

Final Published December, 2014

Implementation Guidance for Electronic Submissions

24 Months after Final Guidance

Individual Guidances

NDAs, ANDAs, BLAs, INDs

- Timetable
- Content
- Format
When will Study Data Standards be Required?

- 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?

Data Standards Catalog
Study Data....SDTM, ADaM, SEND, Define.XML

Final Published December 2016

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
How will Study Data Standards be Required?

Technical Conformance Guide

Use it NOW

Version 2.2
Published

http://www.fda.gov/forindustry/databstandards/studydatastandards/default.htm
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

Conformance to standards in FDA Data Standards Catalog?

Data Quality Checks

Data Repository

Analytic Tools

Reviewer Decisions

Conformance Validation Quality / Usefulness Analytics & Decision-Making
eCTD Submissions:  Part 1

Ginny Hussong, Director
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Office of Business Informatics, CDER
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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

FDASIA Guidance
How does FDA plan to implement Section 745A(a) of the FD&C Act?

eCTD Guidance
24 months after guidance is finalized, content must be submitted to the Agency electronically in the format specified in the guidance.

eCTD Tech Conformance Guide
Recommendations for the standardized electronic submission format of INDs, NDAs, ANDAs, BLAs, and DMFs

Data Standards Catalog
Lists supported and/or required standards.

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

What is the timetable?

What submission types must be electronic?
How will eSubmissions be Implemented?

“745A(a) Umbrella” Implementation Guidance

NDAs, ANDAs, BLAs, INDs
- Timetable
- Content
- Format

Final Published December, 2014

24 Months after Final Guidance

Individual Guidances

FDASIA Guidance
How does FDA plan to implement Section 745A(a) of the FD&C Act?

745A(a) FD&C Act
Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act
Guidance for Industry

24 Months after Final Guidance

December 2014 Electronic submissions
When will eCTD Format be Required?

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

**Published**
May 5, 2015

**Required**
May 5, 2017

**24 Months***

**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?

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

eCTD Guidance

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

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

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

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

Guidance for Industry

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.

<table>
<thead>
<tr>
<th>Use</th>
<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Standards Development Organization (SDO)</th>
<th>Supported Version</th>
<th>Implementation Guide Version</th>
<th>FDA Center(s)</th>
<th>Date Support Begins (MM/DD/YYYY)</th>
<th>Date Support Ends (MM/DD/YYYY)</th>
<th>Date Requirement Begins (MM/DD/YYYY)</th>
<th>Date Requirement Ends</th>
<th>Regulatory Reference and Information Sources</th>
</tr>
</thead>
</table>

[http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm](http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm)
How to Submit eCTD Submissions?

Non-binding guidance

- 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
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
Will FDA Reject non-compliant submissions?

Yes.
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?
Waivers and Exemptions

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

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

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