Electronic Submissions, Study Data Standardization Efforts, and the Impact on Regulatory Review in CDER, FDA

PHUSE Annual Conference 2016, Barcelona
October 11, 2016, 13:30

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Agenda

• Review the latest policy changes
  • Guidance on Electronic Submission Applications (eCTD)
  • Guidance on Electronic Standardized Data (eStudy)

• Discuss the impacts on the OCS and FDA reviewers
POLICY
FDASIA Guidance Implementation

24 Months after Final Guidance

Individual Guidances

Implementation Guidance for Electronic Submissions

Final Published December 2014

NDAs, ANDAs, BLAs, INDs

- Timetable
- Content
- Format
24 months after final guidance, sponsors must use standards identified by FDA (NDAs, ANDas, BLAs)
ELECTRONIC SUBMISSION (eCTD) REQUIREMENTS
Required Submission and Data Standards

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

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

**eCTD Guidance**
Binding Guidance – Requires that content be submitted to the Agency electronically in the format specified in the guidance.

**Data Standards Catalog**
List supported and/or required standards.

**Technical Conformance Guide**
Provides specifications, recommendations, and general considerations on how to submit standardized study data.
eCTD and Electronic Submission Requirements

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) and Center for Biologics Evaluation and Research (CBER).
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
When will eCTD Format be Required?

- **eCTD Guidance**
  - Binding Guidance – Requires that content be submitted to the Agency electronically in the format specified in the guidance.
  - Published: May 5, 2015

- **Compliance**
  - Electronic submissions using the version of eCTD currently supported by FDA, as specified in the FDA Data Standards Catalog
  - Required for NDAs, BLAs, ANDAs, and DMFs: May 5, 2017
  - Required for Commercial INDs: May 5, 2018

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What are the eCTD Specifications?

**eCTD Guidance**

Binding Guidance – Requires that content be submitted to the Agency electronically in the format specified in the guidance.

**Data Standards Catalog**

Lists supported and/or required standards.

**ICH eCTD Specs 3.2.2**

ICH eCTD Study Tagging Files

FDA eCTD - Module 1
eCTD CTOC Validation, File Format, PDF Supportive files & more
# What eCTD Formats will be Required?

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 by 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).

<table>
<thead>
<tr>
<th>Use</th>
<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Standards Development Organization (ICH)</th>
<th>Supported Version</th>
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<th>FDA Center(s)</th>
<th>Date Support Begins (MM/DD/YYYY)</th>
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<th>Date Requirement Ends (MM/DD/YYYY)</th>
<th>Regulatory Reference and Information Sources</th>
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<td>ICSR</td>
<td>XML</td>
<td>HL7</td>
<td>Release 1</td>
<td>N/A</td>
<td>CDRH</td>
<td>Ongoing</td>
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<td>Electronic Medical Device Reporting (eMDR) – Device Regulation and Guidance</td>
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<tr>
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<td>Veterinary Adverse Event Reporting for Manufacturers</td>
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</tbody>
</table>

Source: http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
How to Submit eCTD Submissions

Technical Conformance Guide

Provides specifications, recommendations, and general considerations on how to submit standardized study data.

Non-binding guidance

- Background / Purpose
- General Considerations
- Organization of eCTD
- Modules 1–5
- Issues and Solutions

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Waivers and Exemptions

Are there **Waivers** from the Requirement?

No.

Are there **Exemptions** from the Requirement?

Yes.

**INDs for**

- Non-Commercial Products
  - Investigator-sponsored INDs
  - Expanded access INDs (e.g., emergency use INDs, treatment INDs)

- **Devices Regulated by CBER**

**BLAs for Devices Regulated by CBER**
Will FDA Reject Noncompliant Submissions?

Yes.
STUDY DATA STANDARDS REQUIREMENTS
Required Submission and Data Standards

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

eStudy Guidance
- Binding Guidance – Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog.
- What types must be submission electronic?
- What is the timetable?

eCTD Guidance
- Binding Guidance – Requires that content be submitted to the Agency electronically in the format specified in the guidance.

Data Standards Catalog
- Lists supported and/or required standards.

Technical Conformance Guide
- Provides specifications, recommendations, and general considerations on how to submit standardized study data.
Study Data Standards

**Study data standards** describe a standard way to exchange clinical and nonclinical research data between computer systems.

- SDTM (including Therapeutic Areas)
- SEND
- ADaM
- Define-XML
  
  ...and more

For the full list of study data standards, see the Data Standards Catalog at [www.fda.gov/ForIndustry/DataStandards/StudyDataStandards](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards)
When Will Study Data Standards be Required?

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

Published December 17, 2014

Required for NDAs, BLAs, ANDAs, and DMFs
December 17, 2016

Required for Commercial INDs
December 17, 2017

Compliance
Studies starting after required date MUST use the standards in the Data Standards Catalog (NDAs, ANDAs, BLAs)

www.fda.gov
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.

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

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

Technical Conformance Guide

Provides specifications, recommendations, and general considerations on how to submit standardized study data.

USE IT NOW

Study Data Standardization Plan
Analysis Data Reviewer’s Guide
Study Data Reviewer’s Guide
Exchange Formats
SDTM General Considerations
File Transport
SEND Domain Specs
SDTM General Considerations
ADaM Domain Specs
Controlled Terminologies Therapeutic Area Standards
Data Validation and Traceability
Elect Subformat

Source:
IMPACTS
Electronic Submission and Data Standards: What Do They Mean To CDER?

- More efficient review process
- Predictability
- Traceability
- Data Quality

= More efficient review process
Impact on Regulatory Review

Does the application conform to the applicable eCTD standards?

eCTD Submission → eCTD Format Validation → Study Data Validation → Data Warehouse → Analytical Tools → Review Decisions
Standardized Study Data

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

Technical Conformance Guide

www.fda.gov
Title??

Does the data conform to the applicable eStudy 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).
eCTD Study Data Validation Rules and Severity

High
Demographic dataset (DM) and the define.xml must be submitted in Module 4 and the DM dataset Subject level analysis dataset (ADSL) and define.xml must be submitted in Module 5

High
Trial Summary (TS) dataset must be presented for each study in Module 4 or 5

Medium
Correct STF file-tags must be used for all standardized datasets
- Data-tabulations-dataset-sdtm
- Data-tabulations-dataset-send

Medium
For each study, no more than one dataset of the same type should be submitted as new

* Hold until posting comment??
Study Data Validation Rules

FDA Specific SEND Validation Rules
The following document outlines FDA’s validation rules for SEND formatted non-clinical studies. Nonclinical Validator Specifications (XLS)

FDA Specific SDTM Validation Rules
The following document outlines FDA’s validation rules for SDTM formatted clinical studies. SDTM Validator Specification (XLS)

Source: http://www.fda.gov/forindustry/datastandards/studydatastandards/
Electronic Submission and Data Standards: What Do They Mean To CDER?

Predictability + Traceability + Data Quality

= More efficient review process
Analytical Tools

- Tool Guide for Reviewers
- MAED
- JReview
- JMP / JMP Clinical
- Inspection Tools
- FDALabel
The JumpStart service provides CDER’s drug review teams with data quality assessments and exploratory data analyses early in the review process.

This gives reviewers a better understanding of their data and provides important information for conducting an effective evaluation of the drug submission.

The JumpStart service is transforming the way that reviewers approach their review by helping them be prepared and proactive early in the 21st century drug review process.
Delivering Clinical Data to Reviewers

Standard Safety Analysis Reports

Standard AE Analyses

CTR Reporting for JumpStart Service

Regulatory Review

Analysis-Ready Views

Views Supporting Regulatory Review & Data Integration

JMP/JMP Clinical JReview MAED CTR Tools SAS R Inspection Tools
KickStart
Fit for Use Pilot
Delivering Non-Clinical Data to Reviewers
How we are Doing

• eStudy stats
Conclusion

• Review the latest policy changes
  • Guidance on Electronic Submission Applications (eCTD) – May 5, 2017
  • Guidance on Electronic Standardized Data (eStudy) – Dec 17, 2016

• Electronic submissions and standardized study data allows CDER to fully leverage data with tools, technology and services to support regulatory review
eCTD Resources

Final Binding eCTD Guidance:

eCTD Website:
www.fda.gov/ectd

FDA Data Standards Catalog:

General eSUB Questions:
eSUB@fda.hhs.gov

Clinical and Nonclinical Data Questions:
edATA@fda.hhs.gov
eStudy Resources

Final Binding eStudy Guidance:

Data Standards Website:
http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

FDA Data Standards Catalog:

Study Data Technical Conformance Guide:

Questions:
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