eCTD Guidance and Specification Updates

Jonathan Resnick
Division of Data Management Services and Solutions
Office of Business Informatics
CDER | US FDA

PRODUCTIONS
DEDICATED TO QUALITY FIRST

FDA 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 U.S. Food and Drug Administration.

AGENDA

- Electronic submission guidance and specifications – What's new?
- eCTD validations for electronic study data submissions
- Updates on FDA implementation of eCTD v4

ELECTRONIC SUBMISSION GUIDANCE

ELECTRONIC SUBMISSION GUIDANCE

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

- Updated February 2020 (Revision 7)
- Type III DMF added to exemption section
- New section on waivers to address types of submissions that may qualify for a long-term or short-term waiver from the eCTD requirement and the instructions on how to submit a request

ELECTRONIC SUBMISSION GUIDANCE

- Starting March 1, 2022
  - Older version of eCTD M1, utilizing DTD 2.01, will no longer be supported. The current version of eCTD M1, utilizing DTD 3.3, will be required to pass validation.
    - For more information, please see Federal Register Notice located here: https://www.regulations.gov/document?D=FDA-2018-D-1216-0017
  - FDA will begin rejecting submissions which fail eCTD validations 1306 (“No leaf element for file”) and 1323 (“No file for leaf element”)
    - For more information, please see Federal Register Notice located here: https://www.regulations.gov/document?D=FDA-20-D-1216-0019

ELECTRONIC SUBMISSION GUIDANCE

"**Promotional Labeling and Advertising Guidance**" - *Providing Regulatory Submissions in Electronic and Non-Electronic Format — Promotional Labeling and Advertising Materials for Human Prescription Drugs*

Starting June 24, 2021, certain submissions to CDER's Office of Prescription Drug Promotion (OPDP) will be mandatory in eCTD format.

- The following submission types **will be mandatory in eCTD** format **starting June 24, 2021** and may only be submitted through the Electronic Submissions Gateway (ESG)
  - **FDA Form 2253**
  - **Accelerated Approval Pre-submissions**
- eCTD validations will be implemented October 18, 2021 (Federal Register Notice)
- All other submission types to OPDP may be submitted in eCTD format but there is no requirement to do so

- Additional resources are available at the OPDP eCTD webpage
- Questions related to eCTD submissions to OPDP can be emailed to OPDPeCTD@fda.hhs.gov

ELECTRONIC SUBMISSION GUIDANCE

*"**Study Data Guidance**" - Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (last updated June 2021)*

- **Sponsors must conform to standards in the FDA Data Standards Catalog:**
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017
- **FDA uses eCTD validations (1734, 1735, 1736, 1789)** to confirm Sponsors are conforming to the FDA Data Standards Catalog. This subset of eCTD validations are described in detail in the Technical Rejection Criteria for Study Data (TRC)

For more information on how to submit and what will be validated, see the documents below:

- Technical Rejection Criteria for Study Data – Latest update August 2021
- Study Data Technical Conformance Guide – Latest update September 2021
- Study Data for Submission to CDER and CBER website
- SBIA Webinar, FDA Study Data Technical Rejection Criteria (TRC): What you need to know!

PURPOSE OF ECTD AND STUDY DATA REQUIREMENTS

- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)

- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions

- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of COTS reviewer's tools such as JReview, JMP Clinical, etc. to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."

Source: https://www.ich.org/products/ctd.html

TECHNICAL REJECTION CRITERIA FOR STUDY DATA

eCTD validations for electronic study data submissions

- **Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data!**
- **Submissions failing these validations will be rejected**

Error	Description (Reference to FDA Technical Rejection Criteria For Study Data Mar. 2021 version)	Severity Level
1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*	**High**
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	**High**
1736	For SEND data, a DM dataset and define.xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*	**High**
1789	Study files must be referenced in a Study Tagging File (STF). STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports	**High**

Note

1. * Refer to the latest Technical Rejection Criteria for Study Data for more details

UPDATES ON IMPLEMENTATION OF ECTD V4.0

- Status Update
- eCTD v4.0 Enhancements
- Implementation Planning

ICH STATUS UPDATE

- ICH eCTD v4.0 Implementation Package v1.4

Document	Version	Format
Package History	1.4	PDF
eCTD v4.0 Implementation Guide	1.4	PDF
eCTD v4.0 Controlled Vocabularies	4.0	Spreadsheet
eCTD v3.2.2 Transition Mapping Message Controlled Vocabularies	3.0	Spreadsheet
Genericode Files	-	Folder and files
Schema Files	-	Folder and files

- ICH eCTD v4.0 website (https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v40)
  - Implementation Package
  - Links to regional eCTD v4.0 webpages
  - Change Control – Submit questions and change requests

ICH ECTD V4.0 SUPPLEMENTAL DOCUMENTS

- Support Documentation
  - Explains the contents of the Implementation Package as an overview of the eCTD v4.0 implementation
  - Target audience is business and technical personnel
  - Updated in accordance with Implementation Guide updates
- Orientation Material
  - Provides an outline of eCTD v4.0 concept from business perspective
  - Target audience is business personnel and management
  - Updated in accordance with Implementation Guide updates

FDA STATUS UPDATE

- USFDA Module 1 Implementation Package v1.4
  - USFDA Module 1 Electronic Common Technical Document (eCTD) v4.0 Implementation Guide v1.4
  - USFDA Module 1 Regional XML Samples

- FDA eCTD v4.0 website (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40)
  - Implementation Package (June 2021)
  - Technical Conformance Guide (January 2021)
  - Validation Specifications (June 2021)
  - Comprehensive Table of Contents Headings and Hierarchy (June 2021)
  - Link to ICH eCTD v4.0 webpage

ECTD V4.0 ENHANCEMENTS

- **Complete standard**
  - Regional model/xml
    - Currently handled separately by each region
    - eCTD v4.0/RPS model incorporates regional requirements to enable harmonization
  - Simplified submission management
    - Currently requires sending numerous messages per submission
    - eCTD v4.0 combines all submission information into a single message

- **Message is managed through the use of controlled vocabularies**
  - Currently requires modification of the eCTD DTD
  - eCTD v4.0:
    - Headings are a controlled vocabulary and will not require modification of the RPS standard
    - No substantial update of software tools should be necessary
    - Capability to tailor requirements based on application type (e.g., NDA, MF)

ECTD V4.0 ENHANCEMENTS

- **Enhanced control of dossier**
  - Document reuse
    - Currently possible but it's not well understood and CBER does not allow
    - eCTD v4.0 greatly simplifies reuse using a unique id
  - Document Ordering
    - Currently defined by each review tool; may not be the same between tools
    - eCTD v4.0 allows the submitter to explicitly define the display order for files in a specific section
  - Keyword/attribute modifications
    - Currently a slight misspelling in eCTD attributes (e.g., manufacturer) creates separate eCTD sections
    - eCTD v4.0 user-defined keywords/attributes are managed by the submitter and mistakes are easier to correct

ECTD V4.0 ENHANCEMENTS

- **Enhanced control of dossier**
  - Enhanced Life-cycle control
    - Currently life-cycle only allows for one-to-one
    - eCTD v4.0 life-cycle allows one-to-one, one-to-many, many-to-one
  - New eCTD v4.0 Keyword “Group Title”
    - Sponsors can use group titles based on M4 Granularity Document where “One or multiple documents can be submitted”
    - Can be applied to a Context of Use or Context of Use and Keyword combination to further organize content under a CTD heading
    - The sender assigns the group title and priority number to specify how the content should appear together in a particular order
    - Replaces regional implementation of Node Extensions

ECTD V4.0 ENHANCEMENTS

- **Enhanced identification of information contained within a submission**
  - Identify certain content (e.g., datasets) for additional processing
  - Currently by folder or leaf title
  - eCTD v4.0 applies this to the document metadata

ECTD V4.0 – FDA IMPLEMENTATION STRATEGY

- Initial release/acceptance of new applications in eCTD v4.0
  - Allows for development of eCTD v4.0 applications across regions
  - FDA is working with Lorenz to incorporate eCTD v4.0 functionality
    - Receive/install software update - Q42021
  - Perform testing with industry in 2022
  - Begin accepting new applications in eCTD v4.0 in 2023
- Future phases
  - Transition of current applications (existing 3.2.2 transitioning to 4.0)
  - Two-way communication

FDA ECTD WEBSITES

- FDA eCTD Webpage (https://www.fda.gov/ectd)
  - eCTD Guidance and Specifications
  - Important Notices
  - Getting Started
  - Presentations
- FDA eCTD v4.0 Webpage (when we start accepting this info will be moved to the main eCTD page)
  (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40)
  - FDA Regional Implementation Package
    - Implementation Guide
    - Code List (Spreadsheet and Genericode Files)
    - XML Samples
  - Technical Conformance Guide
  - Validation Specifications
  - Comprehensive Table of Contents Headings and Hierarchy

SUPPORT FOR YOUR ELECTRONIC SUBMISSION

- eCTD and General Electronic Submission Questions – esub@fda.hhs.gov
- Study Data Submissions – edata@fda.hhs.gov
- CDER OPDP Submissions – OPDPeCTD@fda.hhs.gov

SUMMARY

- FDA Electronic Submission Guidance
  - eCTD Guidance Feb 2020 Update
  - Promotional Guidance is active as of June 24, 2021 making certain submission types required in eCTD
  - FDA ending support for old version of M1 (DTD v2.01) on March 1, 2022
- eCTD Validations for Study Data Submissions
  - Submitting Study Data? It's critical to read the TRC even if your study is not required to follow standardized format
- eCTD v4 Implementation
  - FDA eCTD v4.0 web page for latest information
  - Timeline for FDA accepting submissions is no earlier than 2023

Thank you for attending!

PRODUCTIONS
DEDICATED TO QUALITY FIRST