Regulatory Submissions, Information, and Document Management Forum

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North Bethesda, MD

#RSIDM22

U.S. FOOD & DRUG ADMINISTRATION

Electronic Submissions Update

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Agenda

- eCTD Validations – *What's new in 2022*
- eCTD v4.0 Update
- Benefits of eCTD
- Existing Challenges

eCTD Validations – *What's new in 2022*

Starting March 1, 2022:

- **Module 1 using DTD 2.01 no longer supported**
  - Older version of eCTD M1, utilizing DTD 2.01, will no longer be supported
  - 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

- **eCTD validations 1306 and 1323 elevated to high severity errors**
  - FDA will begin rejecting submissions which fail eCTD validations 1306 and 1323
  - 1306: “No leaf element for file”
  - 1323: “No file for leaf element”
  - For more information, please see Federal Register Notice located here: https://www.regulations.gov/document?D=FDA-2018-D-1216-0019

1306 & 1323 Error Warnings

CDER has been including a warning within the ESG 3rd Acknowledgement if 1306 or 1323 validation errors were found

Starting March 1st, 2022 these errors will result in a rejection.

ASR Successful and 3rd Acknowledgement PDF notification with
▼SPECIAL WARNING▼

Your submission has been successfully processed, however, during eCTD validation it was noted that this submission contains the following error information listed in the table below:

▼Warning: Per the 'Specifications for eCTD Validation Criteria', the severity level of the following error codes will be effective as a High error as of 03/01/2022

Error Code	Reason	Findings
1306	No leaf element for file	\0100\m1\us\FDA-3397.pdf \0100\m1\us\FDA-3938.pdf \0100\m1\FDA-3794.pdf
1323	No file for leaf element	ID=[PR105219] xlink:href=[m2/23-qos/drug-substance-sa[redacted]e.pdf] operation=[replace] Title=[quality-based-review]

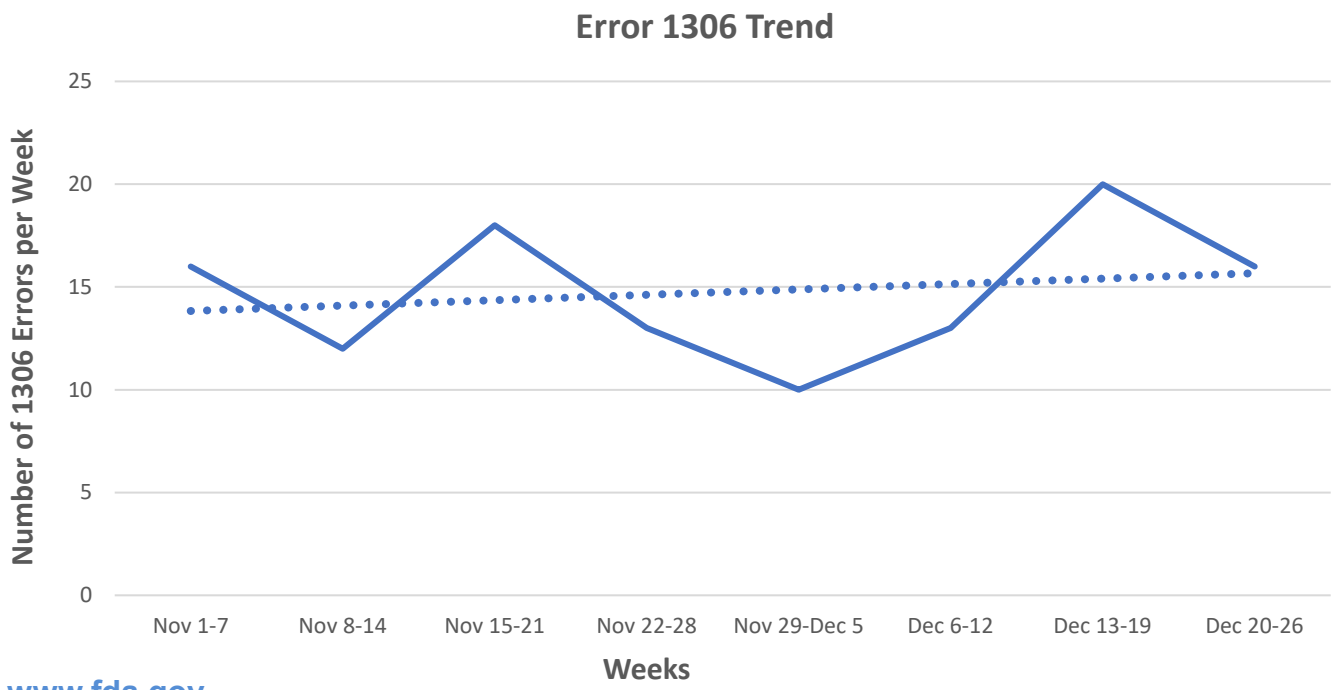
This is an informational notice that after 03/01/2022 submissions with an error code 1306 or 1323 will be rejected per the published eCTD Validation Criteria (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd), as discussed in the eCTD guidance, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

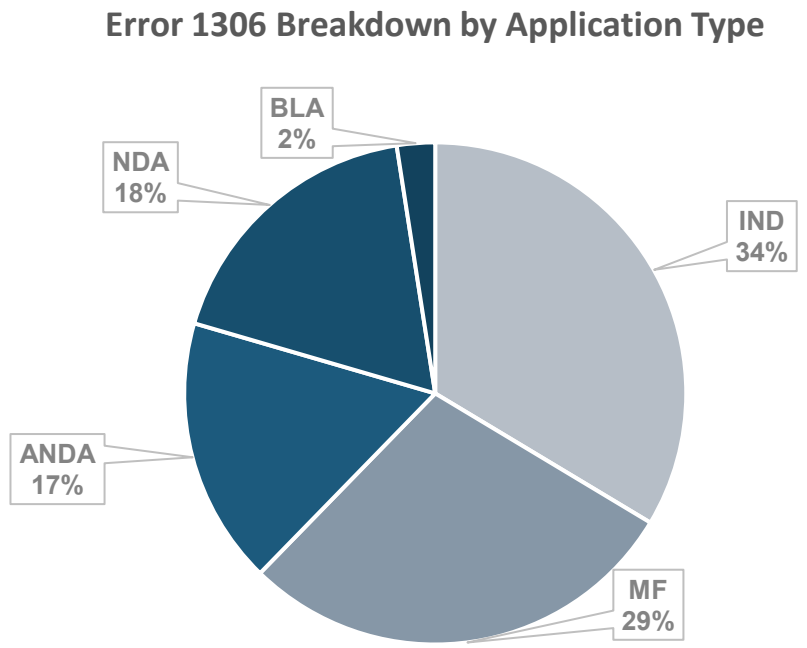
eCTD Validation 1306 Metrics

Time Period: 11/1/2021 – 12/31/2021

- 122 submissions (0.25% of total submissions processed)
- Average of 2 submissions per day

Error	Description	Severity Level	Effective Date
1306	You have submitted the file(s) listed in the validation report without corresponding reference in the backbone.	High	3/1/2022





Impacts from 1306 Errors

Submitted Files

m5 › datasets

Name

Study XYZ-123

m5 › datasets › Study XYZ-123 › tabulations › sdtm

Name

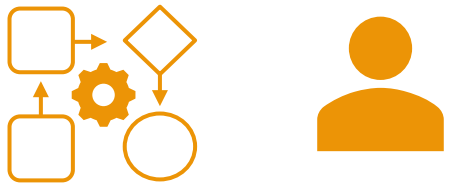
split
adae.xpt
adcm.xpt
adsl.xpt
ae.xpt
ce.xpt
cm.xpt
da.xpt

Files not referenced in eCTD backbone and can't be easily identified or located by reviewers or FDA systems

eCTD Viewing Tool

5 Clinical Study Reports
5.2 Tabular Listing of all Clinical Studies
5.2 Tabular List of Clinical Studies
5.3 Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies
5.3.5.1 Study Reports of Controlled Clinical Studi
8-Year Efficacy Study XYZ-123
16.2.9 Other Safety
Study Report Body Chapter
16. APPENDICES
Datasets
Analysis Datasets
Tabulation Datasets
Tabulation Datasets (SDTM)
define1-0-0
Define - XML
Define - PDF
Datasets
ADAE
ADCM
ADSL
AE
CE
?

Data Analytics Tools

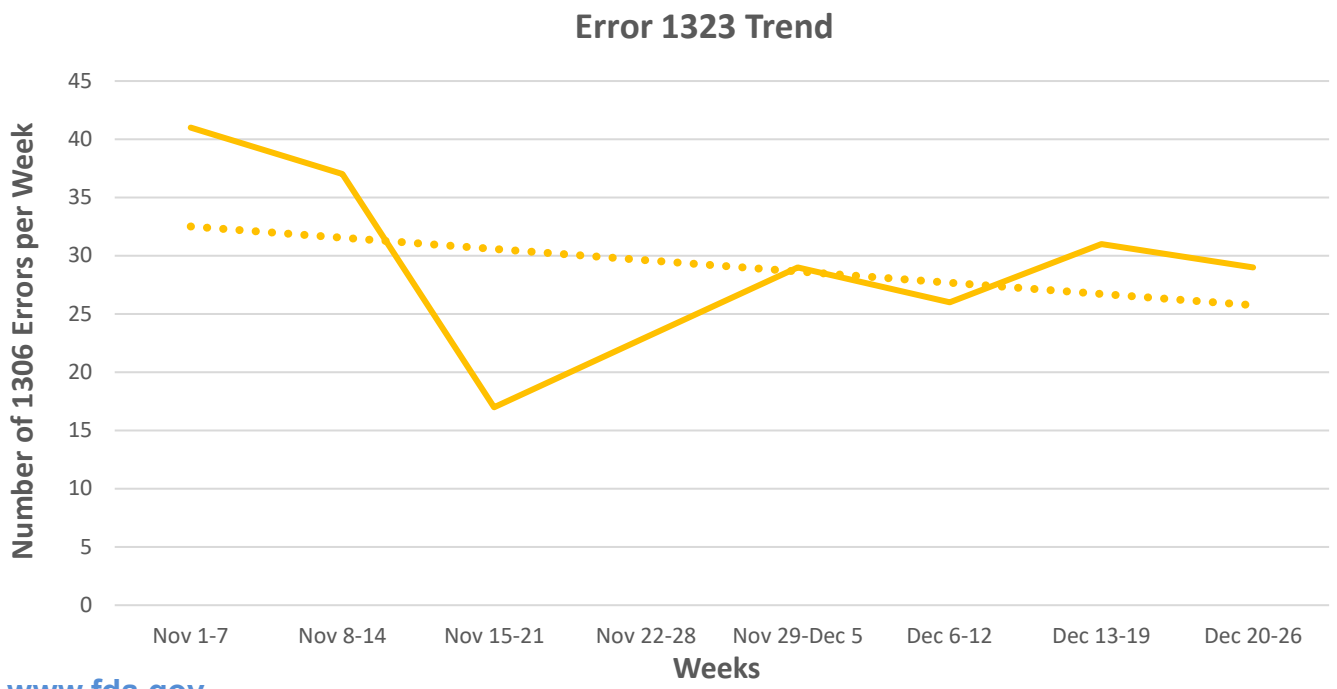


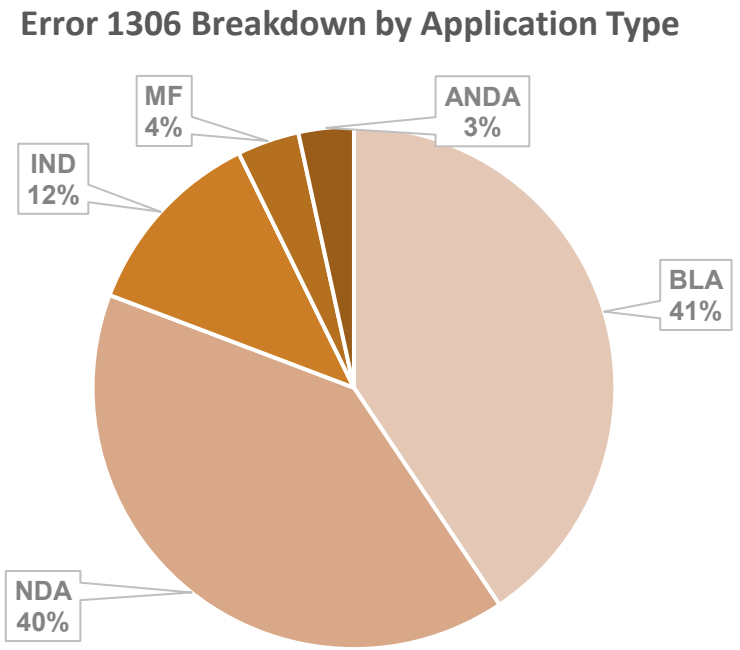
eCTD Validation 1323

Time Period: 11/1/2021 – 12/31/2021

- 235 submissions (0.49% of total submissions processed)
- Average of 3-4 submissions per day

Error	Description	Severity Level	Effective Date
1323	You have referenced the file(s) listed in the validation report from the us-regional.xml or index.xml files without providing the actual file(s).	High	3/1/2022



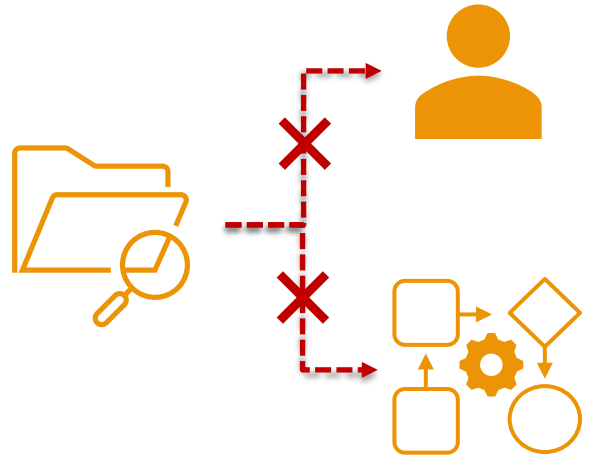


Impacts from 1323 Errors

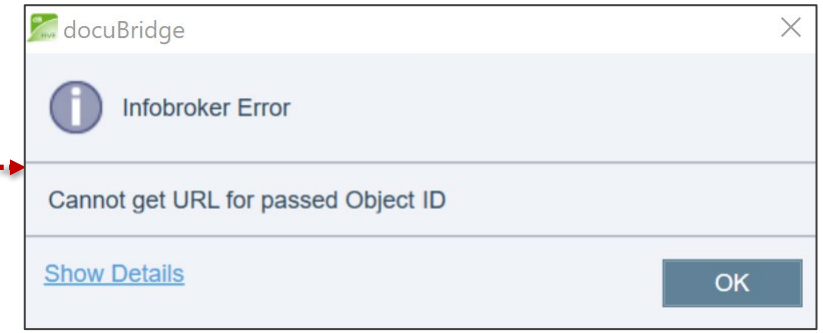
Files appear to be in the submission but can't be located by reviewers or FDA systems

eCTD Viewing Tool

- 1 Administrative Information and Prescribing Information
- 2 Common Technical Document Summaries
- 5 Clinical Study Reports
  - 5.2 Tabular Listing of all Clinical Studies
    - 5.2 Tabular List of Clinical Studies
  - 5.3 Clinical Study Reports
    - 5.3.5 Reports of Efficacy and Safety Studies
      - 5.3.5.1 Study Reports of Controlled Clinical Studies Per
        - 8-Year Efficacy Study XYZ-123
          - 16.2.9 Other Safety
          - Study Report Body Chapter
          - 16. APPENDICES
          - Datasets
            - Analysis Datasets
            - Tabulation Datasets
              - Tabulation Datasets (SDTM)
                - define1-0-0
                - Define - XML
                - Define - PDF
                - Datasets
                  - ADAE
                  - ADCM
                  - ADSL
                  - AE
                  - CE



eCTD Viewer Error:



eCTD v4.0 Update

ICH eCTD v4.0 Materials

- 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 Materials

- 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 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 its tool vendor to incorporate eCTD v4.0 functionality
    - Received/installed software update – December 2021
  - Perform testing in 2022 (testing has begun!)
  - 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 v4.0 Update

- FDA 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

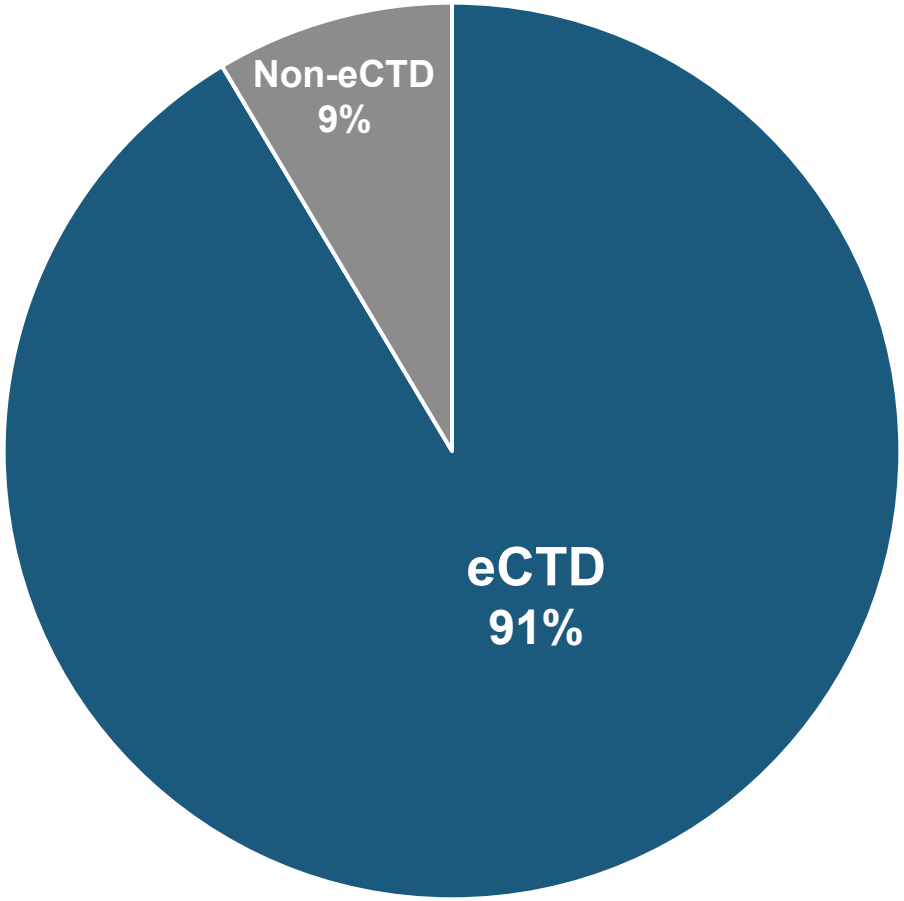
eCTD v4.0 Enhancements

- **Complete standard**
  - Regional model/xml
  - Simplified submission management
- **Message is managed through controlled vocabularies**
- **Enhanced control of dossier**
  - Document Reuse, Document Ordering, Keyword/Attribute Mods, Lifecycle, Group Title
- **Enhanced identification of information contained within a submission**
  - Document metadata level

Benefits of eCTD

Electronic Submissions to CDER

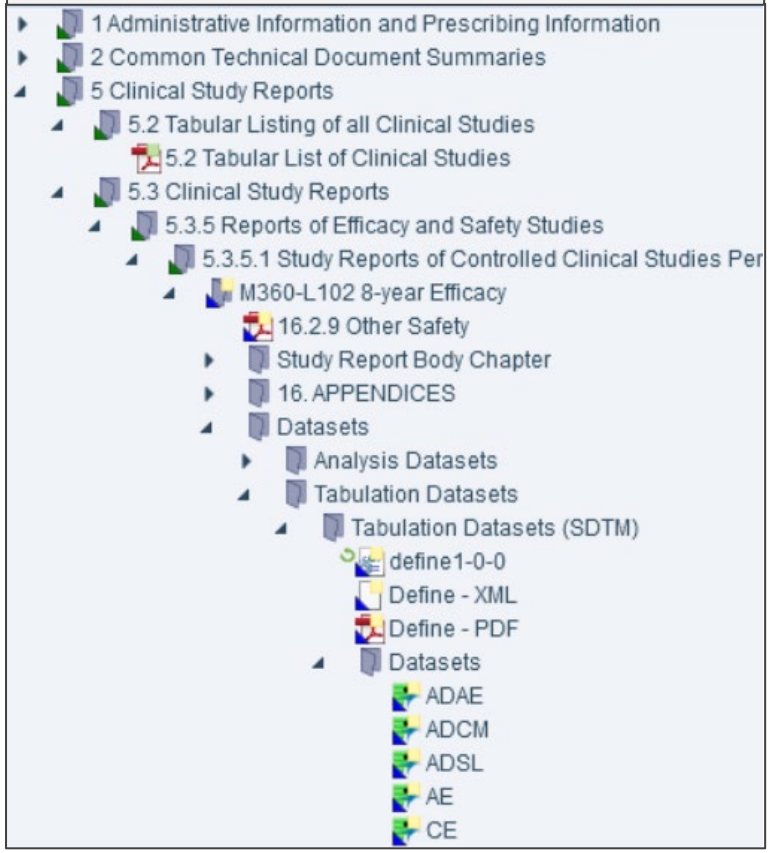
- In 2021, CDER received 91% of submissions in eCTD format
- Most non-eCTD submissions were Research INDs



FDA Tools & Systems to Support Reviews

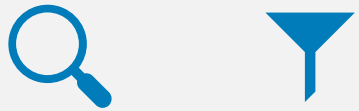
eCTD formatted submissions support reviewers to locate and view submission content *in context*

eCTD Viewing



Standardized submission data and metadata can be leveraged to enable more complex search and analytics capabilities as well as reviewing structured documents

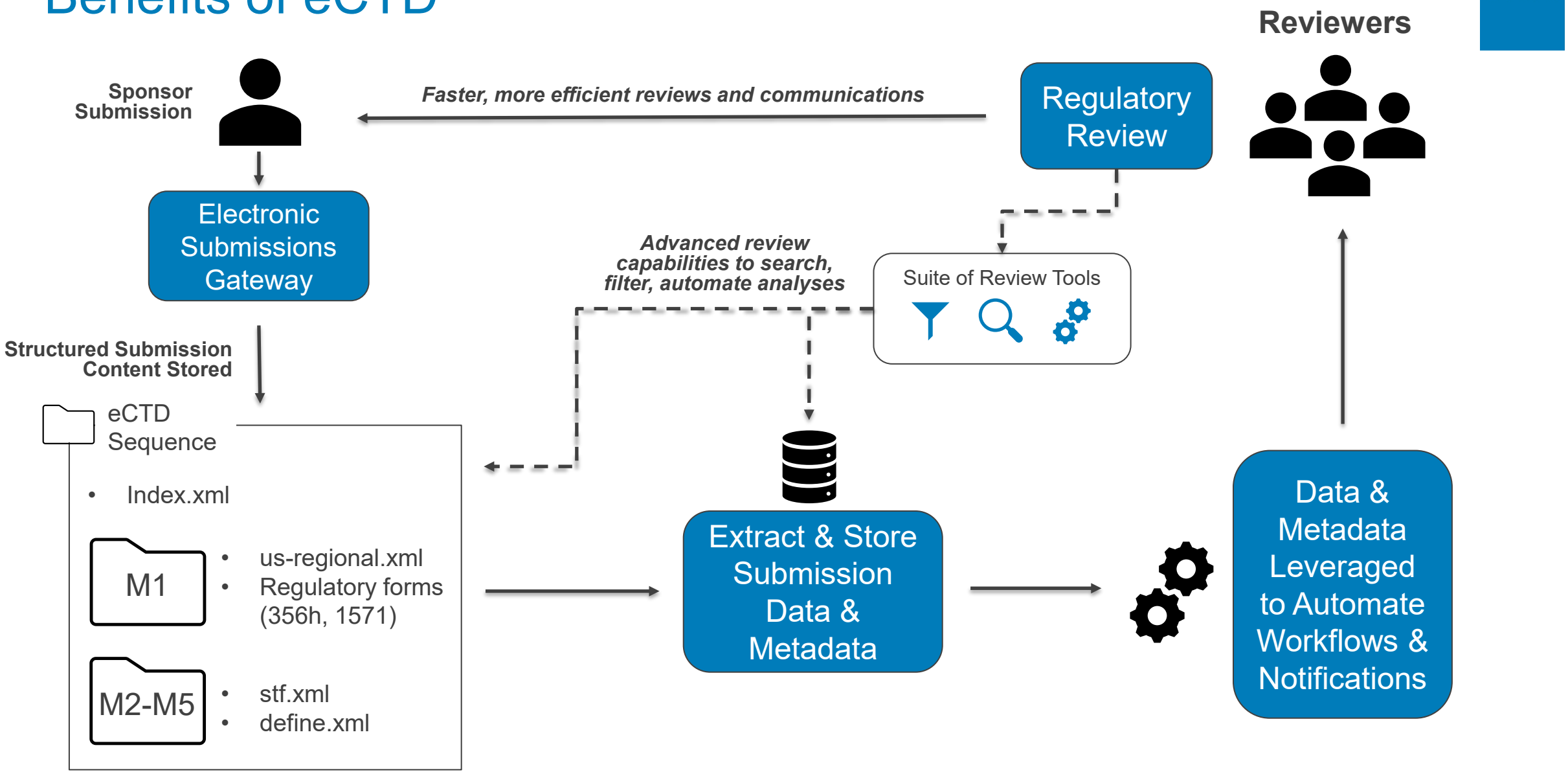
Advanced Search & Filtering



- History of application and submission content
- Searching across applications
- Searching information within documents
- Searching trials based on key attributes across applications and studies
- Searching information linked to external data sources
- Aggregating similar application and study information

Advanced tools and capabilities improves efficiency and consistency of review decisions

Benefits of eCTD



Existing Challenges and Path Forward

Challenge in 1990s/Early 2000s

Transform Drug Applications from paper to electronic

Electronic submissions follow the ICH Electronic Common Technical Document Standard (eCTD)

- eCTD submissions contain a standardized message
  - Structured data is used to identify key information for each file in the submission
    - Document Name, File Path, Life Cycle, Standardized Heading Placement, Study it belongs to, and more..

Today's Challenge

Many files contained within an eCTD submission do not conform to a data standard. Some submissions (i.e. Research IND) are not in eCTD. The more files we can transition from "paper on glass" to structured data, the more dynamic the analytic tools can be for review workflow and data analysis.

Solving Today's Challenge

FDA is focusing on applying data standards and structured content to more documents within submissions

- ***CDER NextGen Portal - Application Builder for Research IND***
- ***Revisiting content and structure in FDA Fillable Forms***
- ***Specify data format/standard for files submitted in Module 3***
- ***Continue focus on Study Data in Standardized Format***

Summary

- Stay Informed! Starting March 1, 2022 the following mistakes will result in rejection:
  - Using FDA's old version of Module 1 (DTD v2.01)
  - Triggering eCTD validation error 1306 or 1323
- ECTD v4 is coming
  - Voluntary submission planned for 2023
  - FDA webpage dedicated to eCTD v4 to obtain guides, specifications, and more
- Benefits of eCTD
  - Standardized view and elements are used in downstream tools for analytics and reviewer workflow
  - Analytical tools developed can leverage quality data to perform advanced data analysis in supporting regulatory review operations
- Challenges and Path Forward
  - While eCTD has successfully standardized the format a submission and CDISC has helped to standardize studies, these submissions still contain many non-standardized PDF documents ("paper on glass")
    - CDER has projects under way such as PQ/CMC to address
  - Many Research INDs come in non-eCTD (one or few PDF documents)
    - CDER developed an "application builder" for Research INDs in the CDER NextGen Portal to collect key structured data to associate with individual files a sponsor uploads

Thank You

Resources:

- FDA eCTD Website: https://www.fda.gov/ectd
- FDA CDER eSub Team: esub@fda.hhs.gov
- FDA CDER eData Team: edata@fda.hhs.gov