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Electronic Submissions Update

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Regulatory Education for Industry (REdI): Annual Conference
July, 2021

- ❖ Electronic Submission Guidance – What's new?
- ❖ Technical Rejection Criteria for Study Data (TRC)
- ❖ Metrics
- ❖ Common eCTD Errors
- ❖ Frequent Asked Questions to ESUB

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, the 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>

“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**
 - ❖ All other submission types to OPDP may be submitted in eCTD format but there is no requirement to do so
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- ▶ Additional resources are available at the OPDP eCTD [webpage](#)
 - ▶ Questions related to eCTD submissions to OPDP can be emailed to OPDPeCTD@fda.hhs.gov

“Study Data Guidance” - *Providing Regulatory Submissions in Electronic Format -- Standardized Study Data (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 March 2021
- ▶ [Study Data Technical Conformance Guide](#) – Latest update June 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



- ❖ **Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data!**
- ❖ **Beginning September 15, 2021, 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

FY 2020: RECEIVED SUBMISSIONS



CDER received approximately **342,000** submissions in FY2020.

85% transmitted via ESG

What about the other 15% ?

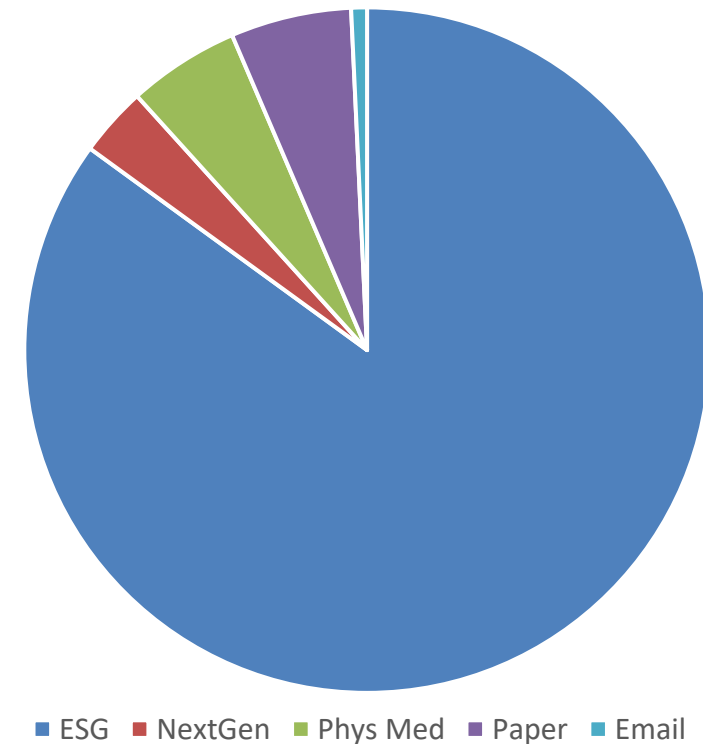
6% Paper

5% Physical media (hard drive, disc)

3% CDER NextGen Portal

<1% Email

All Submissions to CDER in FY 2020



FY 2021: RECEIVED SUBMISSIONS THROUGH JUNE 20, 2021...



CDER received approximately **249,000** submissions so far in FY2021. These numbers are as of June 20, 2021. The FY ends September 30, 2021.

90% transmitted via ESG

What about the other 10% ?

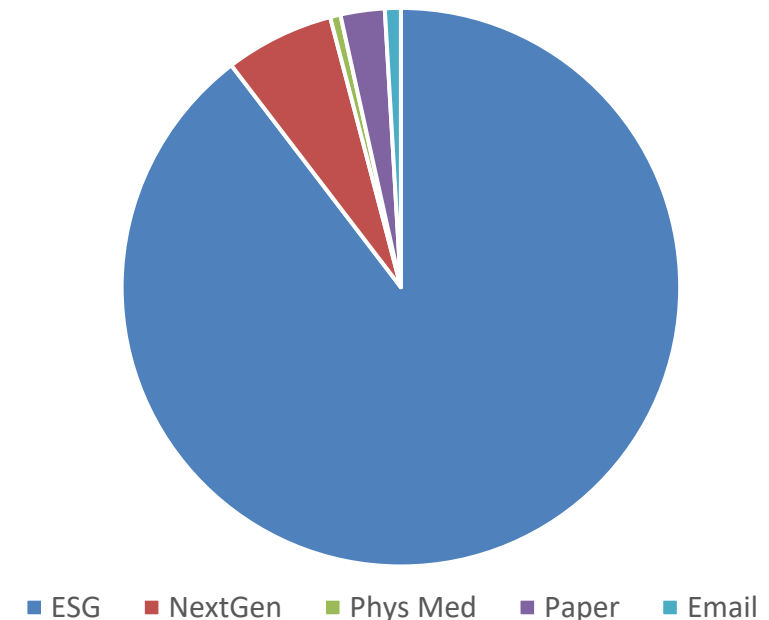
6% CDER NextGen Portal

3% Paper

<1% Email

<1% Physical media (hard drive, disc)

All Submissions to CDER in FY 2021 (partial, thru 6/20/21)



COMMON SUBMISSION ERRORS

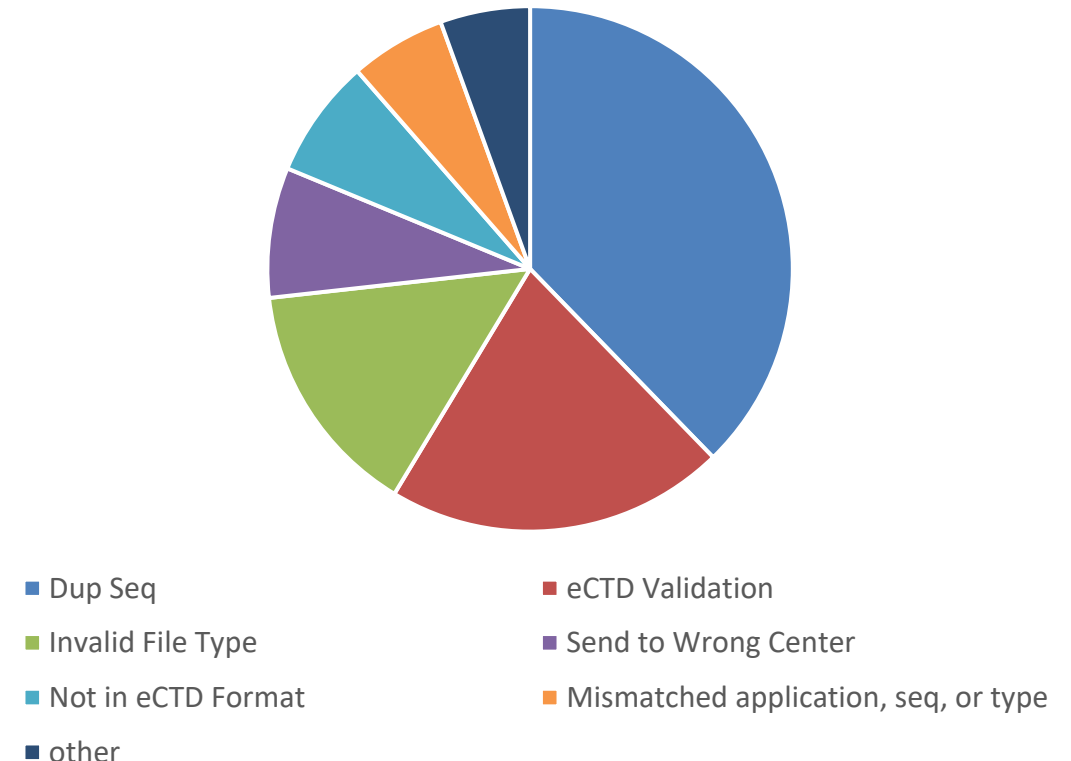


Overall Submission Rejection Rate = 1.4%
Time Period: June 2020 through May 2021

TOP REASONS FOR REJECTION AT CDER

1. Duplicate eCTD Sequence
2. Triggered high severity eCTD Validation Error
3. Invalid file type
4. Sent to wrong Center
5. Not in eCTD Format

How Does the Overall 1.4% Rejection Rate Break Down?



COMMON SUBMISSION ERRORS

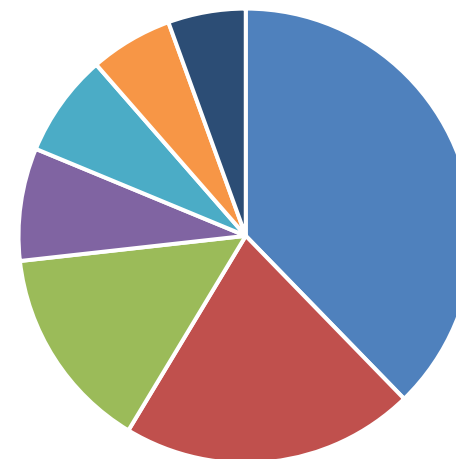


A deeper dive into the top 5...

#1 Duplicate eCTD Sequence

CDER will not process a sequence if the eCTD sequence number already exists under the application

Number:	1697
Group:	M1
Description:	Sequence number was previously submitted
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	6/15/2015
Problem:	The sequence number used in your submission has already been submitted to the application.
Corrective Action:	Resubmit your submission ensuring that you use a 4 numeric digit sequence number that is unique within the application.
Guidance Source:	The eCTD Backbone Files Specification for Module 1 V1.3 and V2.3



- Dup Seq
- eCTD Validation
- Invalid File Type
- Send to Wrong Center
- Not in eCTD Format

COMMON SUBMISSION ERRORS



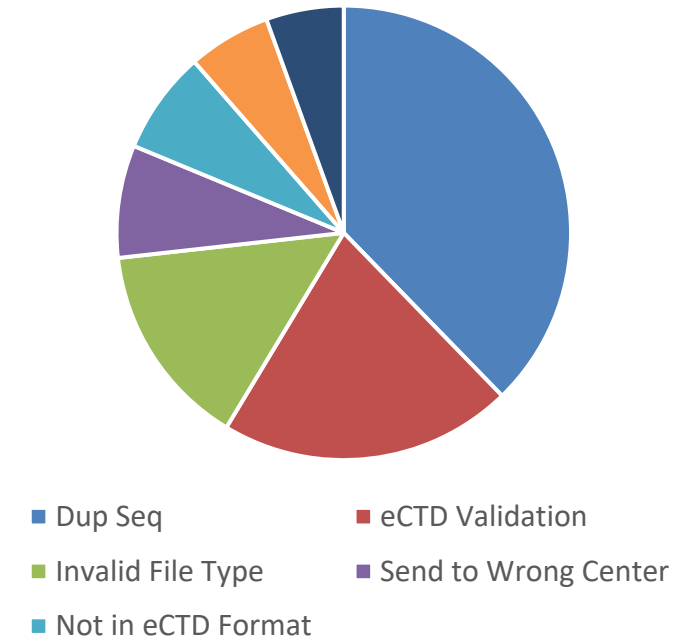
A deeper dive into the top 5...

#2 Triggered high severity eCTD Validation Error Validation codes 2001, 2002, 2022

2001 - An older version of the DTD has been used after a submission to the application used a higher version.

2002 - XML didn't pass validation with the schema (DTD) and attribute files

2022 - Submission-sub-type is invalid for submission-type



COMMON SUBMISSION ERRORS

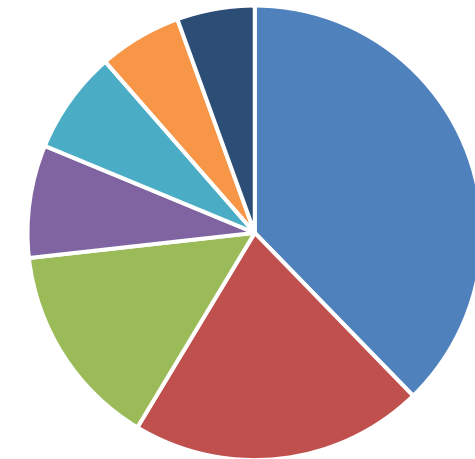


A deeper dive into the top 5...

#3 Invalid file type

Single file submitted via ESG instead of a folder

Number:	3
Group:	File Check
Description:	Single file submission
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	5/31/2016
Problem:	You have a submitted a single file
Corrective Action:	Resubmit folder containing file(s)/subfolders
Guidance Source:	FDA Presentations



- Dup Seq
- eCTD Validation
- Invalid File Type
- Send to Wrong Center
- Not in eCTD Format

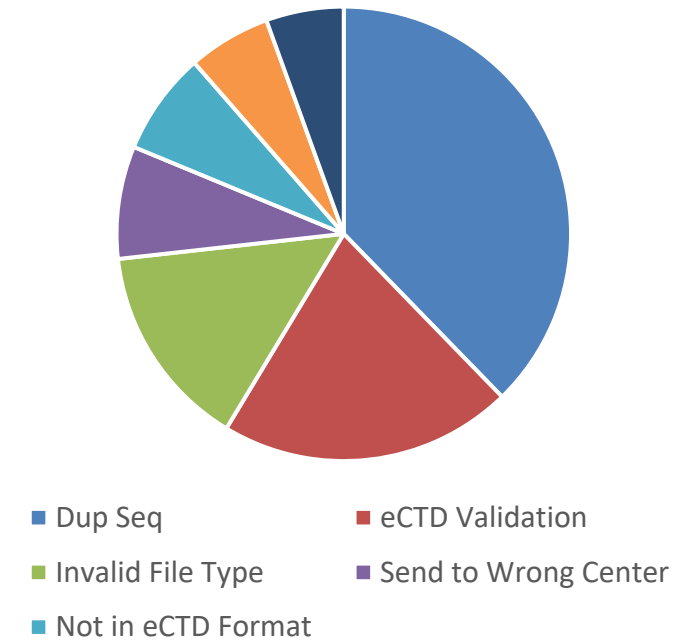
COMMON SUBMISSION ERRORS



A deeper dive into the top 5...

#4 Sent to wrong Center

CBER submission sent to CDER



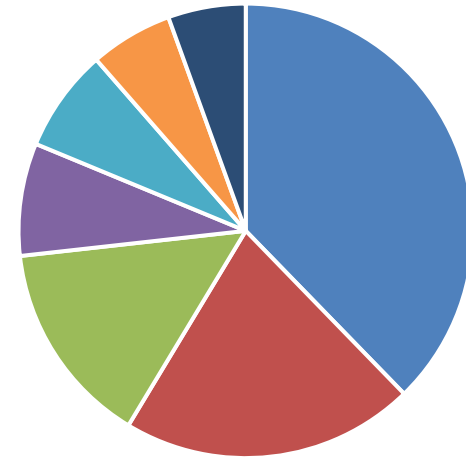
COMMON SUBMISSION ERRORS



A deeper dive into the top 5...

#5 Not in eCTD Format

Submission does not follow eCTD specifications



- Dup Seq
- eCTD Validation
- Invalid File Type
- Send to Wrong Center
- Not in eCTD Format

Number:	6
Group:	General
Description:	Submission is not in eCTD format
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	5/5/2017
Problem:	You are required to submit in eCTD format
Corrective Action:	Resubmit using eCTD format
Guidance Source:	eCTD Guidance

COMMON SUBMISSION ERRORS



Caution! eCTD Validation 1306 and 1323 will become high severity
March 1, 2022

1306 - No leaf element for file

You have submitted the file(s) without a corresponding reference in the index.xml or us-regional.xml.

1323 - No file for leaf element

You have referenced the file(s) from the us-regional.xml or index.xml files without providing the actual file(s).

Frequently Asked Questions to eSub

FREQUENTLY ASKED QUESTIONS

❖ Where do I place my content?

➤ Resources:

- ✓ [The Comprehensive Table of Contents Headings and Hierarchy](#)
- ✓ [M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry](#)
- ✓ FDA Regulatory Project Manager
- ✓ esub@fda.hhs.gov

The Comprehensive Table of Contents Headings and Hierarchy

Module 1 Administrative information

1.1 Forms

Form [form-type]

1.2 Cover letters

1.3 Administrative information

1.3.1 Contact/sponsor/applicant information

1.3.1.1 Change of address or corporate name

1.3.1.2 Change in contact/agent

1.3.1.3 Change in sponsor

1.3.1.4 Transfer of obligation

1.3.1.5 Change in ownership of an application or reissuance of license

1.3.2 Field copy certification

1.3.3 Debarment certification

1.3.4 Financial certification and disclosure

1.3.5 Patent and exclusivity

1.3.5.1 Patent information

1.3.5.2 Patent certification

1.3.5.3 Exclusivity claim

1.3.6 Tropical disease priority review voucher

FREQUENTLY ASKED QUESTIONS



- ❖ How do I get started with eCTD?
 - ❖ How do I request an application number?
 - ❖ How do I get a gateway account?
- These questions and more are answered on the eCTD website:

Electronic Common Technical Document (eCTD)

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The 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).

Important Dates

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or received.

- **May 5, 2017:** New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs), must be submitted using eCTD format.
- **May 5, 2018:** Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format.
- Please refer to the [eCTD Guidance](#) for the complete details to meet the eCTD requirement.

Visit our [Submit Using eCTD](#) page to learn how to submit an application using eCTD and obtain an ESG account. To view all eCTD Submission Resources, visit our [eCTD Resources](#) page.

Quick Links

- [eCTD Guidance](#) (PDF - 11 KB)
- [eCTD Submission Standards](#) (PDF - 91KB)
- [FDA Data Standards Catalog](#)
- [eCTD Technical Conformance Guide](#) (PDF - 303KB)
- [Drug Master Files \(DMFs\)](#)
- [Technical Rejection Criteria for Study Data](#) (PDF - 921 KB)
- [eCTD Submission Types and Sub-Types](#) (PDF - 630 KB) **NEW**

Notices

- [FDA Extends Compliance Date for DMF Type III in eCTD Format](#) **NEW**
- [Third Acknowledgement for Successful eCTD Submissions](#) (May 2016)
- [Past Notices](#)

Submit Using eCTD

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When submissions arrive in eCTD format, reviewers can easily find and access the information they need to review, whether it was part of the original submission or added later by the product sponsor.

Electronic submissions make it easier for FDA to review data, approve new drugs, and monitor drugs after they go on the market. Using eCTD also simplifies the process for submitters, because it is the same format used by drug regulatory agencies in other countries.

If you are new to eCTD, follow these steps to get started:

Learn about eCTD

[Review the Electronic Submission Resources](#)
[Submit Fillable Forms and Compliant PDFs](#)
[Request an Application Number](#)
[Register for an Electronic Submissions Gateway Account](#)
[Send a Sample Submission to FDA](#)
[Submit Via the Electronic Submission Gateway](#)

1. Learn About eCTD

- **NEW** [eCTD Submission Requirements: What You Need to Know](#) fact sheet (PDF - 224KB)
- [Recent eCTD presentations](#) by FDA staff
- [CDER Small Business and Industry Assistance \(CDER SBIA\) Webinar - Electronic Submission Requirements for ANDAs: Are You Ready? – November 21, 2016](#)

Tip: Build and maintain a knowledge base by staying informed about existing, new, and updated eCTD-related tools and information.

CHALLENGE QUESTION #1



When will FDA begin rejecting submissions for failing eCTD validations listed in the Technical Rejection Criteria for Study Data (TRC):

- A. September 15, 2021
- B. October 1, 2021
- C. March 1, 2022
- D. FDA is already rejecting when a submission fails these validations

Which of the following statements is **NOT** true?

- A. Even if my study is not required in standardized format, I need to read the TRC to see if a simplified TS.XPT will be required in the Study's STF (study tagging file)
- B. eCTD Validation 1306 and 1323 will become HIGH on March 1, 2022
- C. The old eCTD M1 (DTD v2.01) will no longer be supported starting March 1, 2022
- D. Starting June 24, 2021, Promotional 2253 submissions to CDER will be allowed in non-eCTD format

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 Updates; M1 DTD v2.01 will be retired
 - Promotional Guidance is active as of June 24, 2021 making certain submission types required in eCTD
 - Submitting Study Data? It's critical to read the TRC even if your study is not required to follow standardized format
- FDA CDER Submission Metrics FY 2021 (as of June 2021)
 - 90% Electronic Submission Gateway
 - 6% CDER Direct NextGen Portal
- Common eCTD Errors
 - Re-using the same sequence number is the biggest reason for rejection
 - 1306 and 1323 validations will be HIGH severity March 1, 2022