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Generic + Biosimilar Medicines Conference

Electronic Submissions:
eCTD Update

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Project Management Officer, DDMSS, OBI, OSP, CDER, FDA

AGENDA

- Background
- Metrics
- Challenges
- FAQ

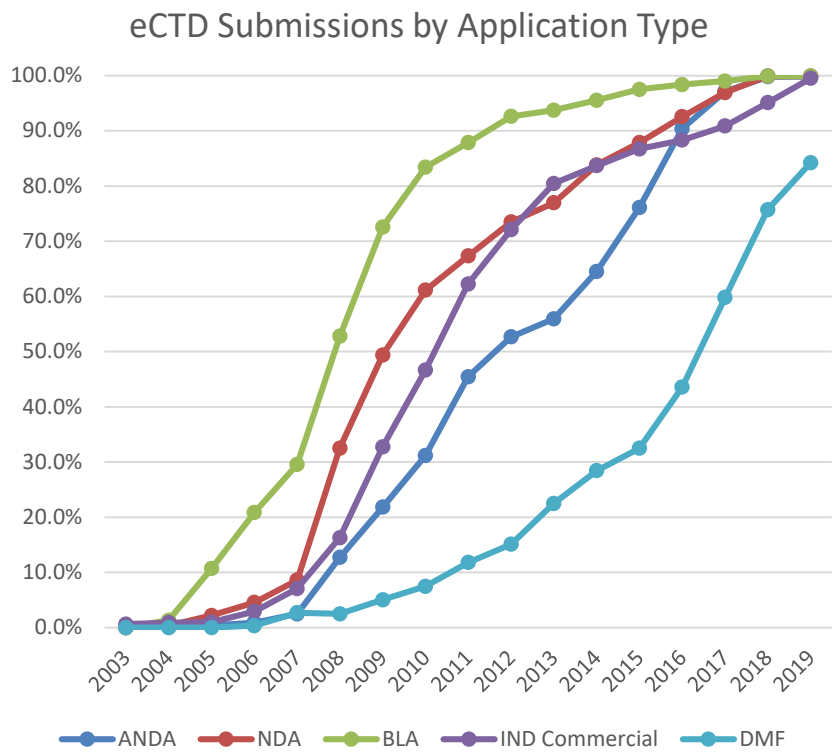
ECTD Background

BACKGROUND

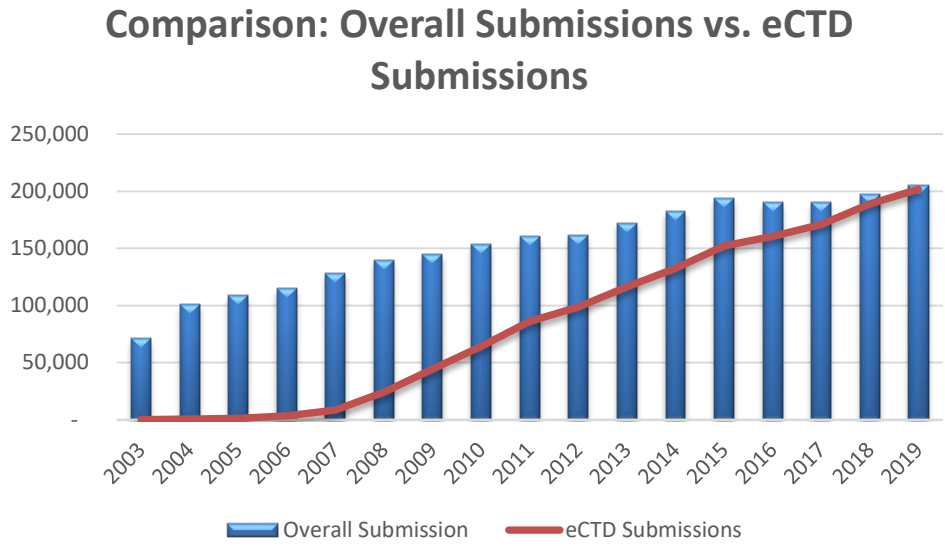
- The number of submissions to the FDA has significantly increased
- eCTD guidance became binding:
  - ✓ May 5, 2017: NDA, BLA, and ANDA must be in eCTD format
  - ✓ May 5, 2018: Commercial IND and Master Files must be in eCTD format
  - ✓ See latest version of guidance at www.fda.gov/ectd

CURRENT STATE: RECEIVED SUBMISSIONS

CDER received approximately 205,000* electronic submissions via ESG in FY19. Nearly 202,000 were in eCTD in FY 2019.



*excludes promotional/advertising



In FY19, 99% of the regulatory submissions (specific to Commercial INDs, NDAs, ANDAs, BLAs, DMFs Type II, IV and V) were submitted in eCTD format

CDER SUBMISSION PROCESSING

Automate process to identify Submission Category

Process:

1. Determine Submission Category based on structured data in eCTD sequence
2. Route to Review Division based on Submission Category

Benefit:

1. Reviewers see submission sooner
2. Reduced manual data entry

Document Room continues to process submissions where category cannot be determined automatically and submissions which contain high validation errors

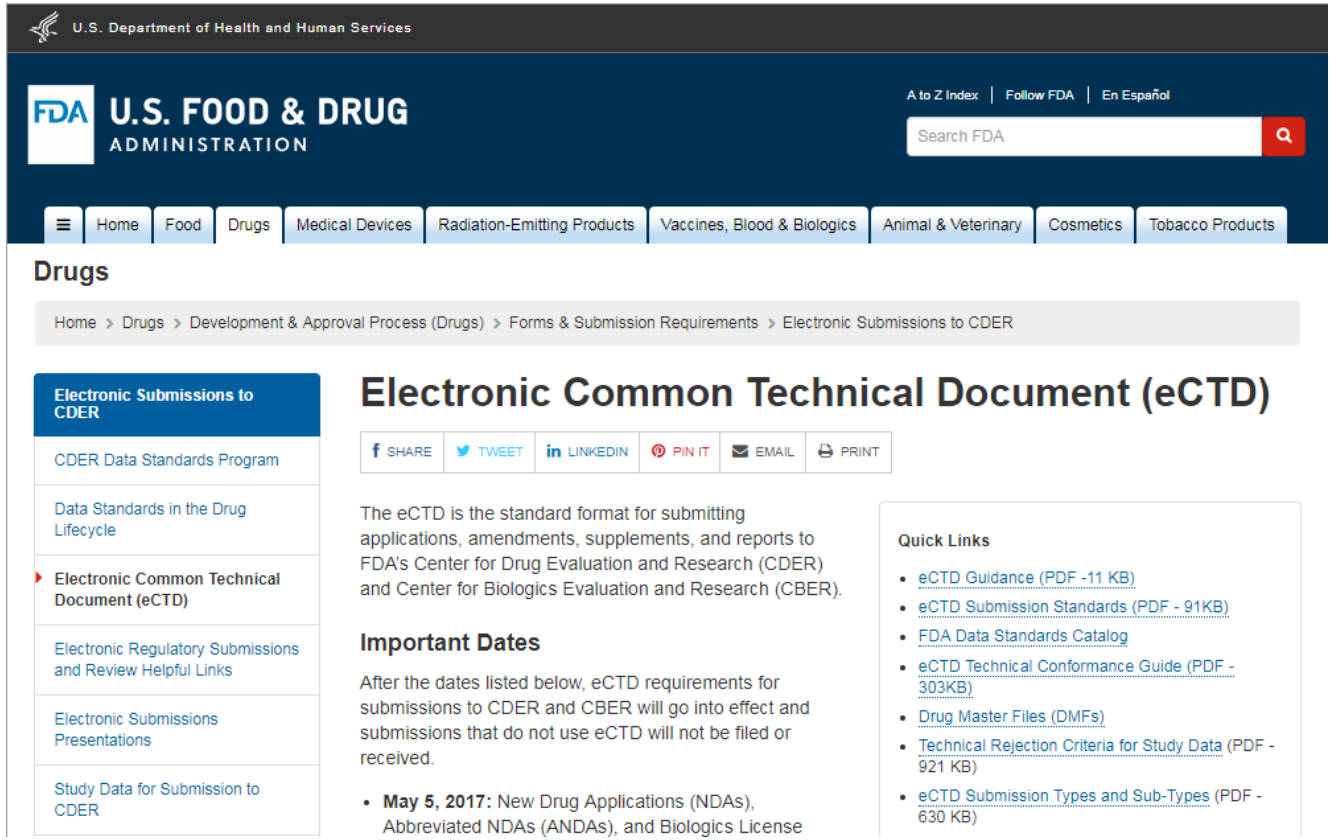
FDA CHALLENGES

- To efficiently and effectively process the increased number of submissions and leverage the submitted structured eCTD and study data, FDA is in the process of automating inbound submissions by using structured data from the eCTD backbone files and Form 356h. **However, data submitted in eCTD backbone files (e.g. us-regional.xml file) and regulatory form (e.g., Form 356h) are not always consistent.**

- FDA reviewers use the state-of-the-art review tools (e.g. JMP Clinical) to support analyzing submitted study data. **However, study data submitted do not always conform with the published FDA Data Standards Catalog.**

ECTD BACKBONE FILES SPECIFICATION

- The *eCTD Backbone Files Specification for Module 1* explains how to build regulatory activities using M1 elements and attributes such as submission-type, submission-id and submission-sub-type (if DTD version 3.3)



ECTD DATA DISCREPANCY EXAMPLE 1:

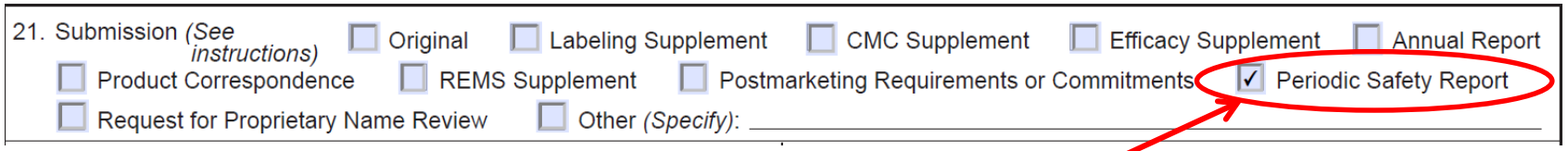
- Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```
<submission submission-type="original-application">
  <sequence-number>0022</sequence-number>
</submission>
```

Indicating “Original Application”

Form 356h



Indicating “Periodic Safety Report”

This submission was a periodic safety report.
The appropriate eCTD “**submission-type**” would have been “**other**”.

ECTD DATA DISCREPANCY EXAMPLE 2:

- Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```
<application-information application-type="[redacted]">
  <submission submission-type="amendment">
    <sequence-number>[redacted]</sequence-number>
    <related-sequence-number>[redacted]</related-sequence-number>
  </submission>
</application-information>
```

Indicating "Amendment"

Form 356h

Indicating "Initial Submission"

21. Submission *(See instructions)*	☑ Original	☐ Labeling Supplement	☐ CMC Supplement	☐ Efficacy Supplement	☐ Annual Report	
☐ Product Correspondence	☐ REMS Supplement	☐ Postmarketing Requirements or Commitments	☐ Periodic Safety Report			
☐ Request for Proprietary Name Review	☐ Other *(Specify)*: _____					
22. Submission Sub-Type	☐ Presubmission	☐ Amendment	23. If a supplement, identify the appropriate category.	☐ CBE	☐ Prior Approval (PA)	
	☑ Initial Submission	☐ Resubmission		☐ CBE-30		

This submission was an amendment containing patent information.
The appropriate "Submission Sub-Type" on Form 356h would have been "Amendment"

ECTD DATA DISCREPANCY EXAMPLE 3:

❖ Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```
<application-information application-type="ind">
  <submission submission-type="chemistry-manufacturing-controls-supplement">
```

Indicating "Chemistry-Manufacturing-Controls-Supplement"

Form 1571

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☑ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Indicating "Chemistry/Microbiology Information Amendment"

This submission was an amendment to Original submission.
The appropriate eCTD "**submission-type**" would have been "**Amendment**".

ECTD DATA DISCREPANCY IMPACT

When data is submitted correctly in eCTD backbone files (e.g. us-regional.xml file) and regulatory form (e.g., Form 356h), submission can be efficiently routed to the assigned review division and/or reviewer(s)

Indicating different Submission Type and/or Submission Sub-Type in us-regional.xml and Form 356h could:

- Impact FDA's ability to automate the submission process
- Require addition effort to read the Cover Letter in order to resolve the discrepancy
- May require Request(s) for Information that may otherwise not be necessary

Submit BE Site Information

BIOEQUIVALENCE (BE) SITES

- Current Challenges
  - Key components of BE site information is missing (name & address)
  - BE sites appear in various formats (Tables, Study Reports, etc.)
  - BE sites not consistently placed in the correct location of the eCTD submission

- Implication
  - **Potential delayed issuance of an action letter due to misplaced or missing BE sites and relevant information.**

WE NEED YOUR HELP…

To improve the access to quality data.

- Submit a complete list of **all** BE sites on Table 10 – Study Information
- Place BE Summary Tables in section 2.7.1 of the eCTD

Additional information about the ANDA submissions is available on the ANDA Forms and Submission Requirements Web page located at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm

TABLE 10 – BE STUDY INFORMATION

Table 10 Study Information[9]

Study Number	
Study Title	
Study Type	☐ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other
Submission Location: Study Report Validation Report Bioanalytical Report	location, ex: 5.3.1.2 location, ex: 5.3.1.2 location, ex: 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax#)	
Principal Clinical Investigator (Name, Email)	
Analytical Site (Name, Address, Phone #, Fax#)	
Principal Analytical Investigator (Name, Email)	
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte 1: Analyte 2: (if applicable) Note: The LTSS should be conducted at the upper limit of the storage temperature range.
LTSS Data Location	Specify the exact location of the LTSS study reports and data, including Module, Section, Subsection, and page(s). Provide hyperlink(s) to the locations as appropriate.

- Provide a separate table for each bioequivalence study.

Model Bioequivalence Data Summary Tables (PDF - 185KB)

TABLE 10 – BE STUDY INFORMATION EXAMPLES

In Vitro BE Analytical Site

Study Number	XYZ.123.000
Study Title	In Vitro Test for XYZ Tablets for 500 mg strength
Study Type	☐ In Vivo BE ☒ In Vitro BE ☐ Permeability ☐ Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	 location, ex: 5.3.1.2 location, ex: 5.3.1.2 location, ex: 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax#)	N/A
Principal Clinical Investigator (Name, Email)	N/A
Analytical Site (Name, Address, Phone #, Fax#)	ABC Analytical 789 Park Rd., New York, NY USA 50000 Telephone: 555-555-5555 Fax: 999-999-9999
Principal Analytical Investigator (Name, Email)	Jane Doe Janedoe@abcanalytical.com
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	a) 20 days b) -20°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte 1: Analyte 2: (if applicable) Note: The LTSS should be conducted at the upper limit of the storage temperature range.
LTSS Data Location	Specify the exact location of the LTSS study reports and data, including Module, Section, Subsection, and page(s). Provide hyperlink(s) to the locations as appropriate.

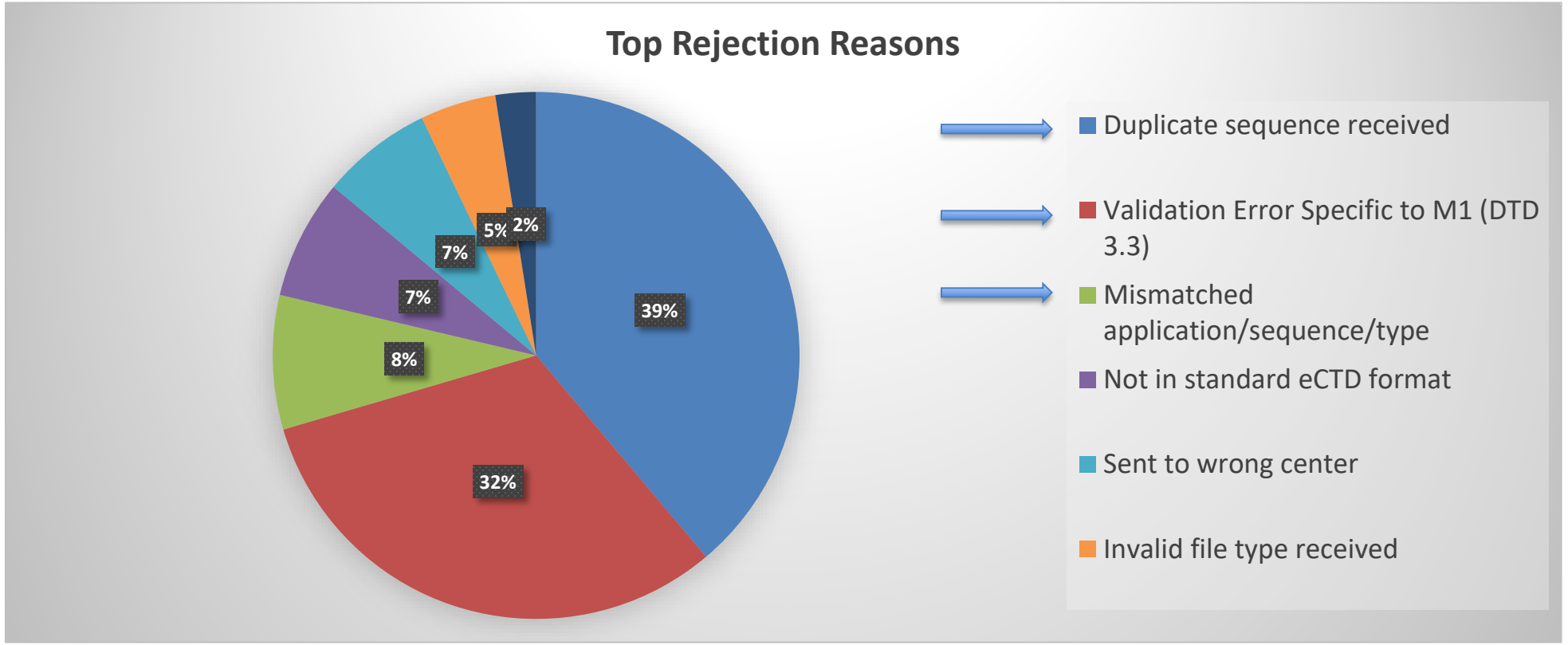
In Vivo BE Clinical and Analytical Sites

Study Number	ABC.789.000
Study Title	Fasting Bioequivalence Study of 500 mg ABC Capsules
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	 location, ex: 5.3.1.2 location, ex: 5.3.1.2 location, ex: 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax#)	ABC Clinical 123 Main St., New York, NY USA 50000 Telephone: 555-555-5555 Fax: 999-999-9999
Principal Clinical Investigator (Name, Email)	John Doe Johndoe@abcclinical.com
Analytical Site (Name, Address, Phone #, Fax#)	ABC Analytical 789 Park Rd., New York, NY USA 50000 Telephone: 555-555-5555 Fax: 999-999-9999
Principal Analytical Investigator (Name, Email)	Jane Doe Janedoe@abcanalytical.com
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	a) 20 days b) -20°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte 1: Analyte 2: (if applicable) Note: The LTSS should be conducted at the upper limit of the storage temperature range.
LTSS Data Location	Specify the exact location of the LTSS study reports and data, including Module, Section, Subsection, and page(s). Provide hyperlink(s) to the locations as appropriate.

Top 3 Rejections and How to Avoid Them

TOP 3 REJECTIONS AND HOW TO AVOID THEM

- Overall, under 2% rejected in FY2019
- A closer look at the 3 most common rejections for eCTD NDA, BLA, IND, MF, ANDA (FY 2019)



TOP 3 REJECTIONS AND HOW TO AVOID THEM

1. Duplicate Sequence Number Received

Issue	Resolution
Submitting revised content under same sequence number (e.g. trying to swap out a sequence)	Content should be updated by submitting changes in the next available sequence
Transfer of application but new owner is not aware of sequence numbers used	Recommend obtaining full sequence history from prior owner
Re-using a sequence number if submission has been withdrawn	Even if a submission is withdrawn, FDA continues to keep the sequence

TOP 3 REJECTIONS AND HOW TO AVOID THEM

2. Most Common M1 (DTD 3.3) Mistake

Issue

Validation Code 2022: You have used a submission-sub-type which is not allowed for the submission-type and/or type of application.
Ex: **Original Application/Correspondence**

Resolution

See list of valid **Submission Type** and **Sub-Type** combinations.
Resource: eCTD Backbone Files Specifications for Module 1, Table 2: Submission Types and Descriptions of Use

Table 2: Submission Types and Descriptions of Use

Submission Type	Submission Sub-Type	Supplement Effective Date Type (if applicable and *submission-sub-type* = "application")	Valid For Application Types
Original Application	Presubmission Application Amendment Resubmission		IND, NDA, ANDA, BLA, DMF, EUA
Efficacy Supplement	Presubmission		NDA, BLA
	Application	Prior Approval Supplement (PAS)	
	Amendment Resubmission		
Chemistry Manufacturing Controls Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS), Changes Being Effected (CBE-0), or Changes Being Effected 30 (CBE-30)	
	Amendment Resubmission		
Labeling Supplement	Presubmission		NDA, ANDA, BLA
	Application	Prior Approval Supplement (PAS) or Changes Being Effected (CBE-0)	
Annual Report	Report Amendment		IND, NDA, ANDA, BLA, DMF
Product Correspondence	Correspondence Amendment		IND, NDA, ANDA, BLA, DMF

TOP 3 REJECTIONS AND HOW TO AVOID THEM

3. Mismatched Application/Sequence/Type

Issue	Resolution
The Sequence Number specified in the US-Regional file does not match the Sequence Number Folder	Main submission folder must be named using a four-digit sequence number; Same number must be used in usregional.xml file
The application number specified in the US-Regional file does not match the Application Number in the fillable form (356h/1571)	Prior to submitting, confirm application number in usregional.xml file matches number on 356h/1571 form
The application type specified in the US-Regional file does not match the application type in the fillable form	Prior to submitting, confirm application type in usregional.xml file matches type on 356h/1571 form

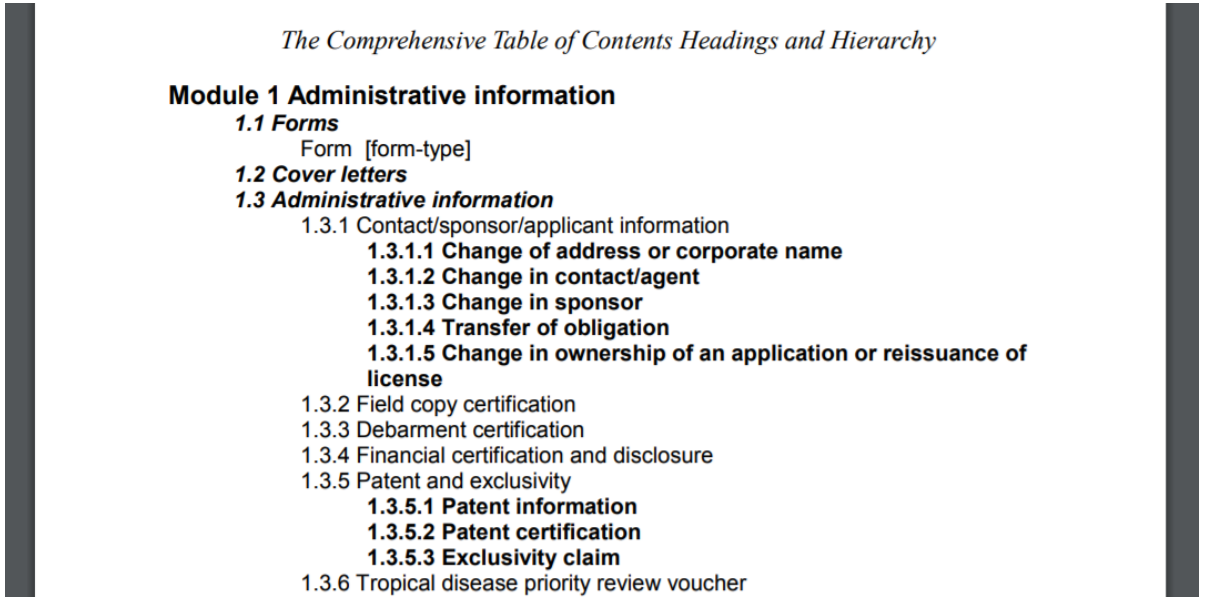
Frequently Asked Questions

FREQUENTLY ASKED QUESTIONS

❖ Where do I place my content?

➢ Resources:

✓ The Comprehensive Table of Contents Headings and Hierarchy



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

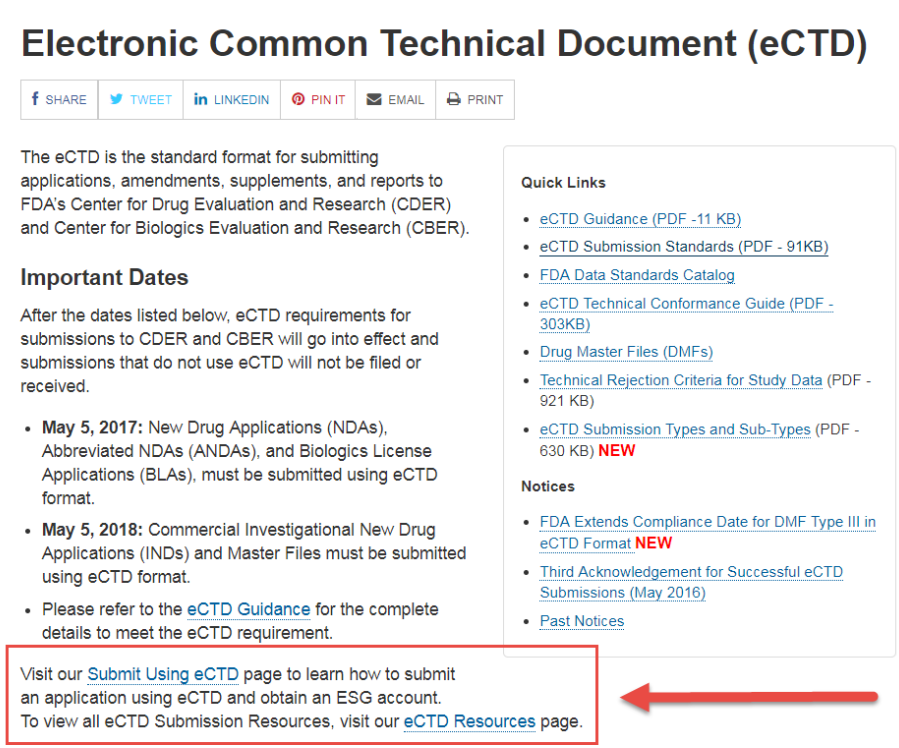
✓ M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry

✓ FDA Regulatory Project Manager

FREQUENTLY ASKED QUESTIONS

- How do I get started with eCTD?
- How do 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.

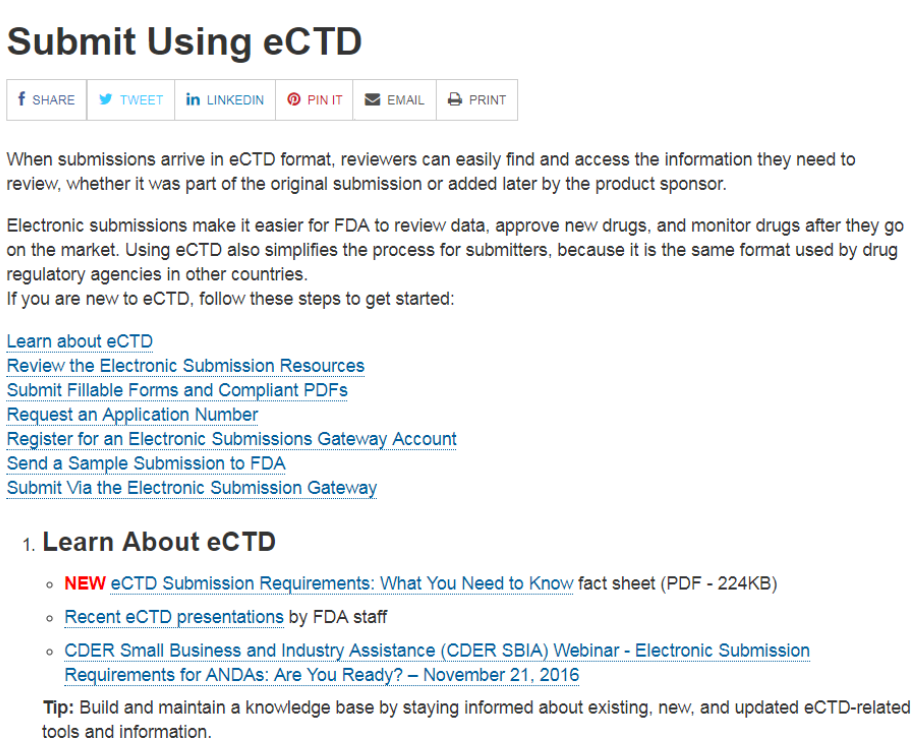
Quick Links

- 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

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.



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.

THANK YOU