Regulatory Submissions, Information, and Document Management Forum

February 11-13 | North Bethesda, MD

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Electronic Submissions
eCTD Submission Metrics and Guidance

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Office of Business Informatics

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AGENDA

- ➢ Guidance
- ➢ eCTD Metrics (FY 2018)
- ➢ Electronic Submission Processing
- ➢ Top 3 Rejections and How to Avoid Them
- ➢ Frequently Asked Question

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Guidance

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Guidance - eCTD

- ➢ 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 the following resources for more information:

eCTD Guidance (Revision 6, posted January 2019)

eCTD Technical Conformance Guide

eCTD Website

Have Questions? Contact eSub@fda.hhs.gov

*Type III Master File requirement effective starting May 5, 2020

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Guidance – Study Data

Study Data Submission Deadlines

➤ Studies that start after December 17, 2016 must be in standardized format for NDA, BLA and ANDA submissions

➤ For Commercial IND submissions, the date is December 17, 2017

See the following resources for more information

[Study Data Standards Resources page](#)

[Technical Rejection Criteria for Study Data](#)

[*The Study Data Guidance*](#)

Have Questions? Contact eData@fda.hhs.gov

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eCTD Guidance – Study Data

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

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Electronic Submissions
Revision 5

D.   The eCTD Specifications

You must submit electronic submissions using the version of eCTD currently supported by FDA. The version of eCTD currently supported is specified in the Data Standards Catalog (available at http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls) and is further described in the following technical specification documents:

- ICH[10] *Electronic Common Technical Document Specification*
- ICH *eCTD Backbone File Specification for Study Tagging Files*
- FDA *eCTD Backbone Files Specification for Module 1*

J.   Datasets and Study Information

Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2. When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files* (see section III.D). Datasets must be referenced in an STF using the appropriate STF *file-tag* describing the document's contents.

For further information regarding the submission of study data, see FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data*.

ECTD SUBMISSION METRICS

CDER receives approximately 200,000 electronic submissions via ESG annually. Nearly 192,000 were in eCTD in FY 2018.

Comparison: Overall Submissions vs. eCTD Submissions

Legend: Overall Submission, eCTD Submissions
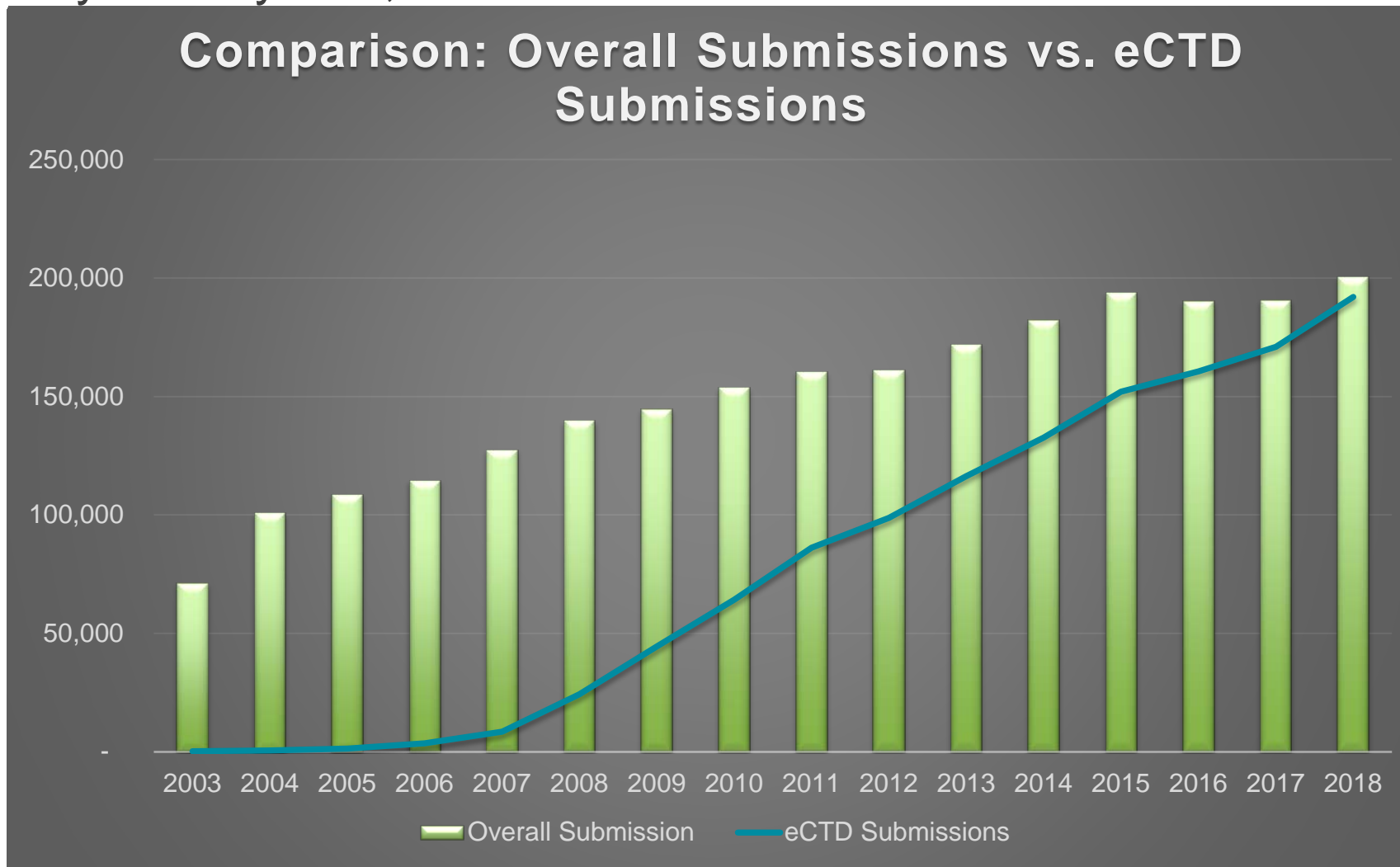
ECTD SUBMISSION METRICS

In FY 2018, nearly 100% of the regulatory submissions for NDA, BLA, and ANDA were in eCTD. For Commercial IND and DMF, 96% and 78% (Type II, IV, V)
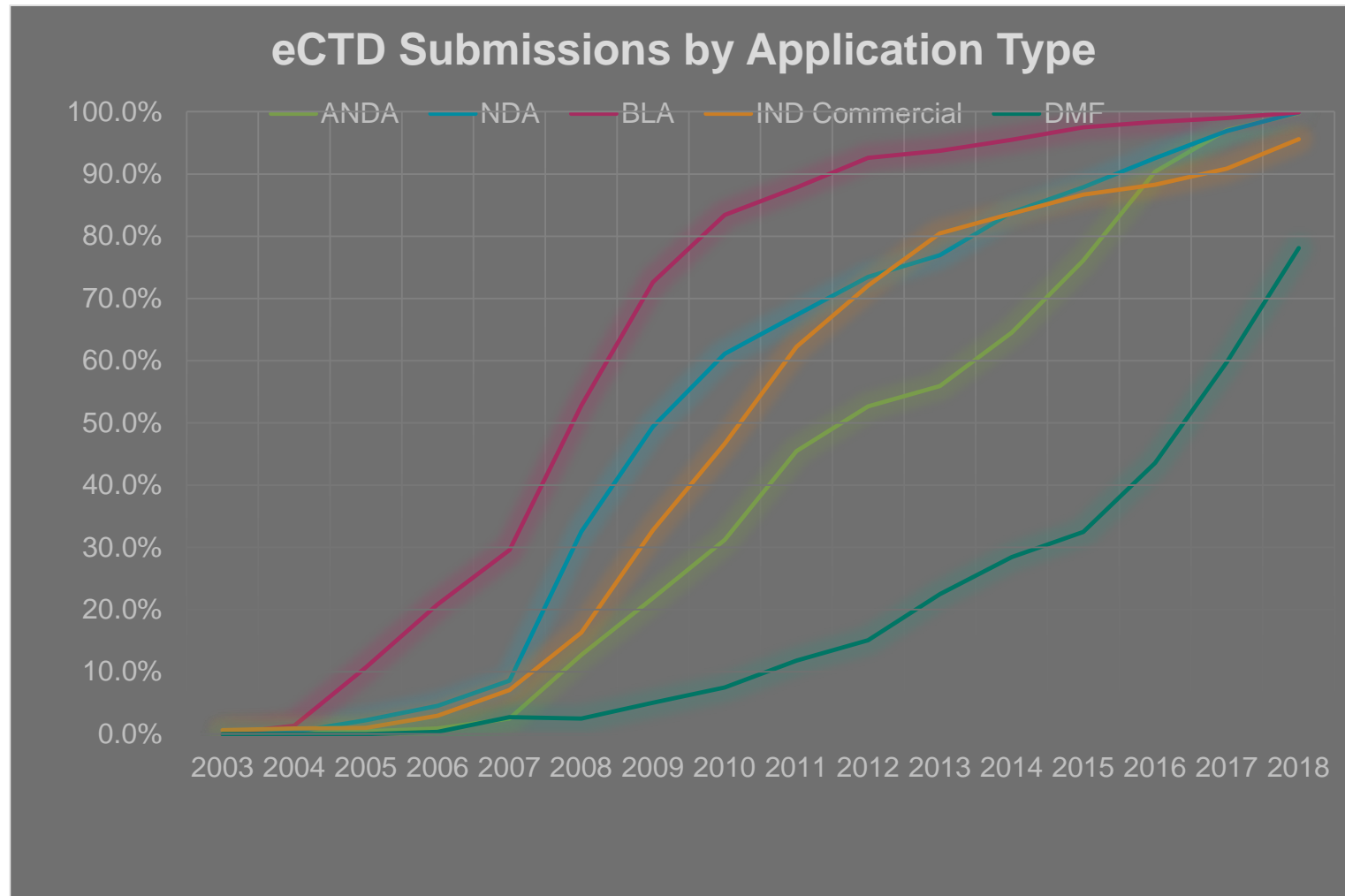
eCTD Submissions by Application Type

Current State: Submission Processing

All CDER regulatory submissions received are processed by Document Room.

Current Document Room Process:

Staff reads the Cover Page of every submission (Approx. 850 per day) to categorize and route to correct Review Divisions

Future: 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:

Reviewer gets submission faster

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

Future: Submission Processing 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 FDA Forms. **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.**

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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**

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): _____

Indicating "Periodic Safety Report"

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

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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=█████>
    <submission submission-type="amendment">
        <sequence-number>████</sequence-number>
        <related-sequence-number>████</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**"

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eCTD Data Discrepancy Example 3:

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

us-regional.xml (DTD V3.3)

```
<submission-information>
  <submission-id submission-type="fdast1">     </submission-id>
  <sequence-number submission-sub-type="fdasst4">     </sequence-number>
```

Indicating "Amendment"

Form 356h

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	

Indicating "Initial Submission"

This submission was an amendment to an original application.
The appropriate "**Submission Sub-Type**" on Form 356h would have been "**Amendment**"

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eCTD Data Discrepancy Example 4:

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

✅ **us-regional.xml (DTD V3.3)**

```
<submission-information>
    <submission-id submission-type="fdast3" supplement-effective-date-type="fdasedt2"     ██</submission-id>
    <sequence-number submission-sub-type="fdasst3">██</sequence-number>
```

Indicating "CBE"

❌ **Form 356h**

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 ☑ Initial Submission	☐ Amendment ☐ Resubmission	23. If a supplement, identify the appropriate category.	☐ CBE ☐ CBE-30	☑ Prior Approval (PA)

Indicating "Prior Approval"

> This submission was an Initial CMC Supplement CBE.
> The appropriate "**Supplement Category**" on Form 356h would have been "**CBE**"

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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 additional effort to read the Cover Letter in order to resolve the discrepancy
  ➢ May require Request(s) for Information that may otherwise not be necessary

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Top 3 Rejections and How to Avoid Them

Top 3 Rejections and How to Avoid Them (FY 2018)

Top 3 Rejection Categories

- Sent to Wrong Center
- eCTD Validation Error
- Duplicate Sequence

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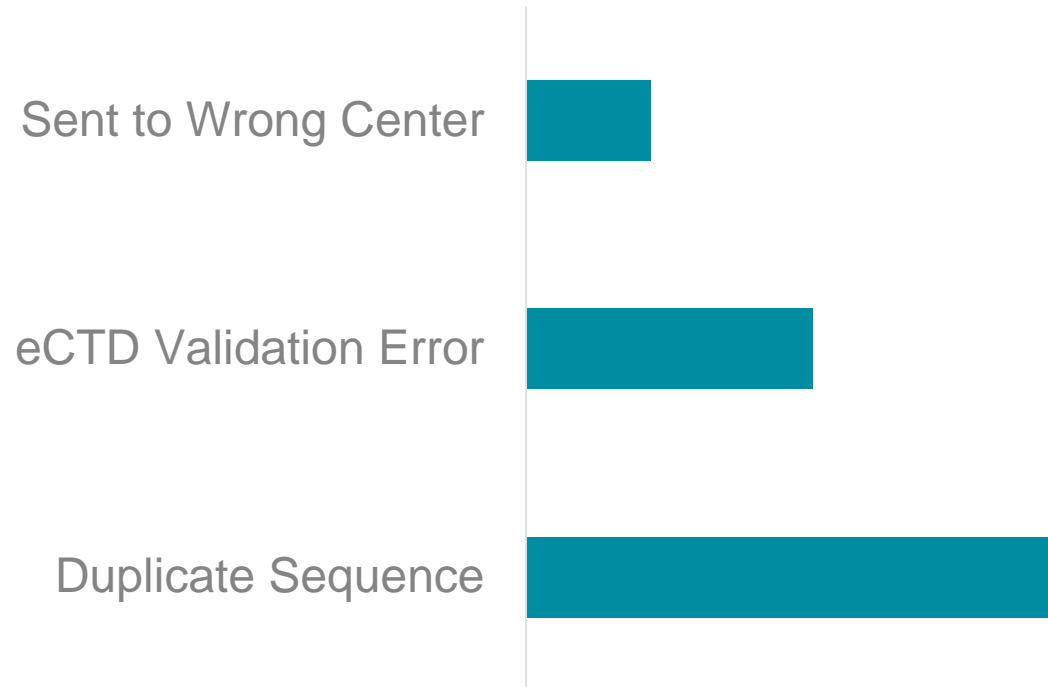
Top 3 Rejections and How to Avoid Them

Duplicate Sequence Number Received (Most Common, Nearly 50% of All Errors)

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

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eCTD Validation Error (Most common was 2022)

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
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

Submission Sent To Wrong FDA Center

Issue	Resolution
Sequence submitted to wrong FDA Center (e.g., CBER BLA submitted to CDER)	Select appropriate FDA Center in ESG/Webtrader

Send document

Select who will receive the document

Gateway: FDA

Center: + CDER

Frequently Asked Questions

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

Note: *Do not send empty sections or provide placeholders for files*

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

- **Can I submit a particular file format? (e.g, .docx, xpt, etc.)**

  - When creating content, follow the [Specifications for File Format Types Using eCTD Specifications](#) for guidance on file formats FDA expects under the different CTD headings

- **Questions related to PDF files (e.g. hyperlinks, bookmarks, font, etc)**

  - Follow FDA's [PDF Specifications](#) and communicate to vendors the need to follow these specifications

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➤ **If I receive a successful third acknowledgement, does that mean the review office finds my submission to be complete?**

– No, the successful third acknowledgement means the submission has passed technical validation and is now available to the review office to conduct their processing (e.g, Filing review).

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➢ **What is the relevance of the ESG timestamp?**

– The ESG timestamp (e.g., date and time on Official Center Acknowledgment (second acknowledgment)) is used to calculate the official receipt date of the submission.

– If submission arrives through the ESG on a weekend, a federal holiday, or another day on which the FDA office that will review the submission is not open for business, it is deemed to have arrived at FDA on the next day when that office is open for business.

– Please see the FDA Guidance* for complete details

*Guidance for Industry Providing Regulatory Submissions in Electronic Format — Receipt Dates

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Frequently Asked Questions

➢ **How to get started with eCTD?**

➢ **How to request an application number?**

➢ **How to get a gateway account?**

These questions and more are answered on the eCTD website:

Electronic Common Technical Document (eCTD)

f SHARE   TWEET   in LINKEDIN   PIN IT   EMAIL   PRINT

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

f SHARE   TWEET   in LINKEDIN   PIN IT   EMAIL   PRINT

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.

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WHERE TO GET HELP

Specification documents are posted on www.fda.gov/ectd in the *eCTD Submission Standards*

Validation Documents Include:
- ➢ eCTD Validation Specifications
- ➢ Technical Rejection for Study Data Criteria

CDER submissions, contact:
- ➢ EDATA@fda.hhs.gov
- ➢ ESUB@fda.hhs.gov

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THANK YOU

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