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FDA Electronic Submissions Update

Jonathan Resnick
Cloud Collaboration Capability Team
Office of Business Informatics, CDER

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Agenda

- Electronic Submission Guidance
- eCTD Submission Metrics
- Top 3 Electronic Submission Rejections
- Frequently Asked Questions
- CDER Document Room Automation
- New Way to Request a CDER Application Number

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Guidance

Guidance - eCTD

- 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

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*
  - *Study Data for Submission to CDER and CBER*
  - *Technical Rejection Criteria for Study Data*
  - *The Study Data Guidance*
- Have Questions? Contact eData@fda.hhs.gov

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)

January 2019
Electronic Submissions
Revision 6

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*

Additional technical specification documents are cited throughout this document. For a complete listing of required technical supportive files (e.g., stylesheets and valid values) that you will need in order to submit in the eCTD format, refer to the eCTD web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

J. Datasets and Study Information

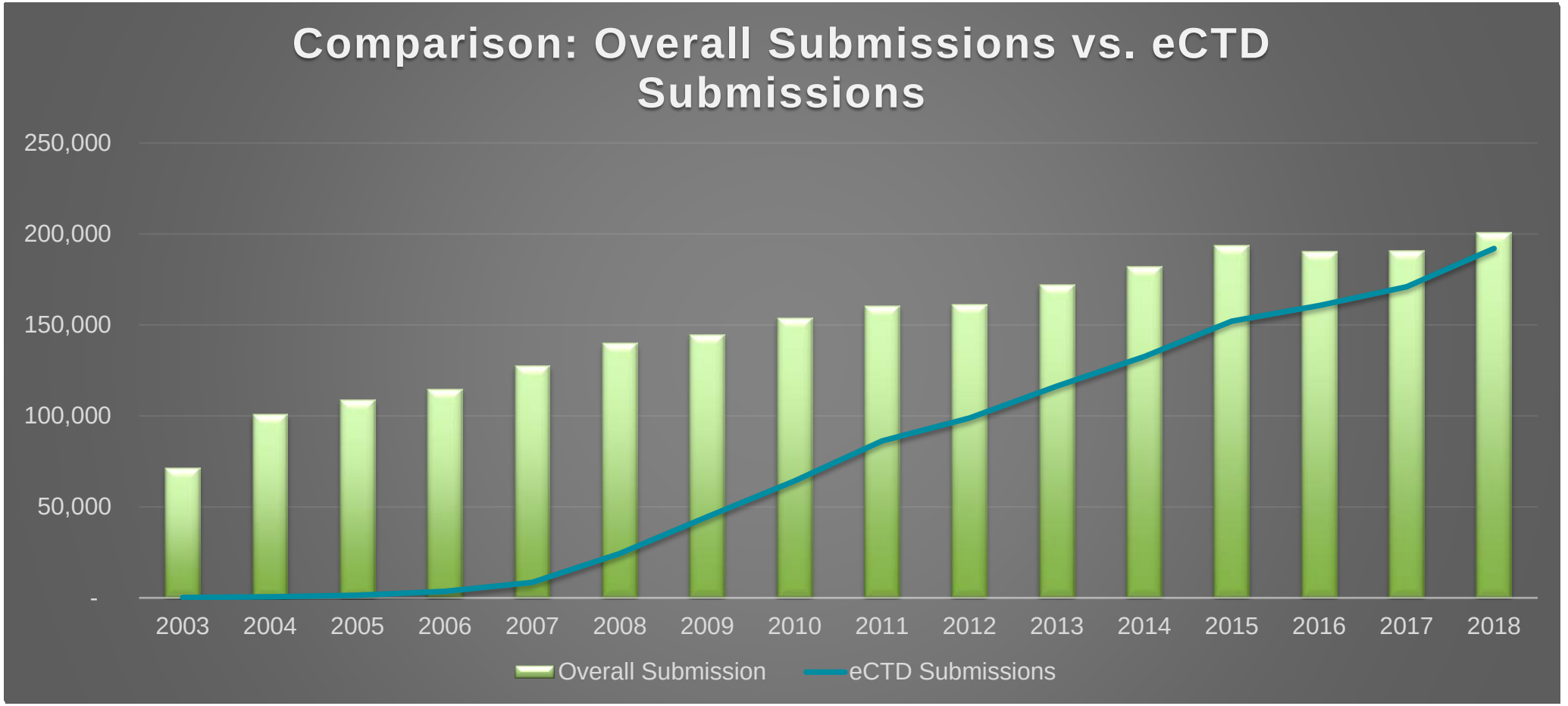
Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2. When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files* (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*.

Metrics

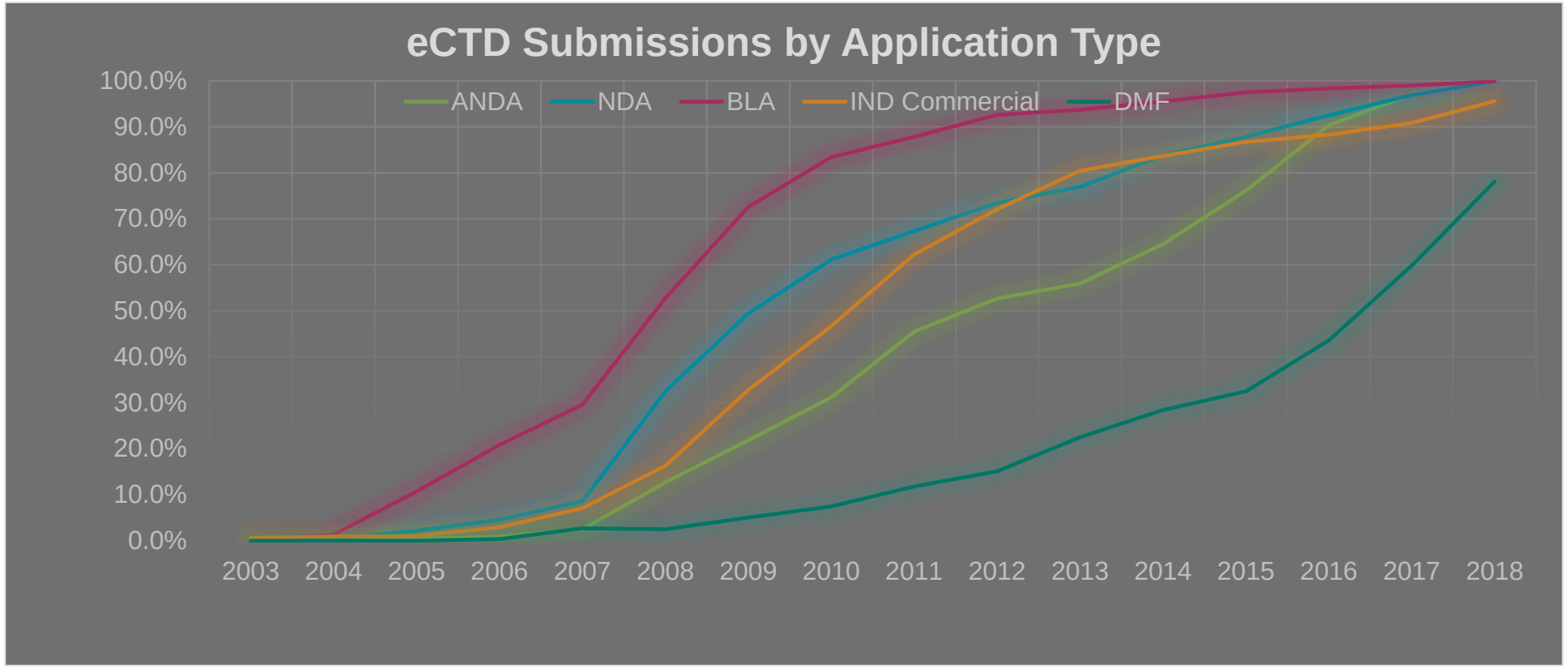
eCTD Submission Metrics

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



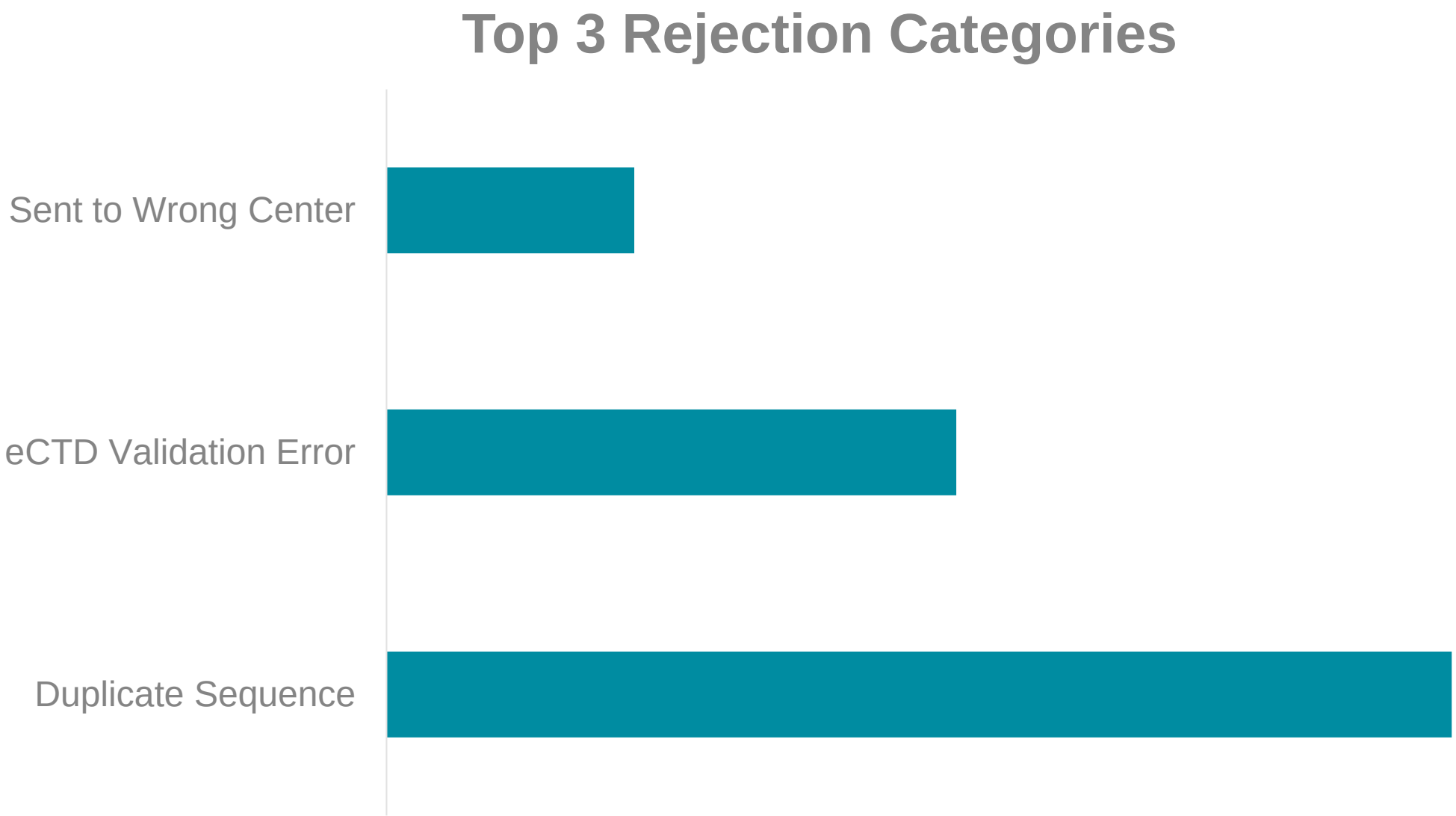
eCTD Submission Metrics

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



Top 3 Rejections

Top 3 Rejections (FY 2018)



Top 3 Rejections

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

Top 3 Rejections

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

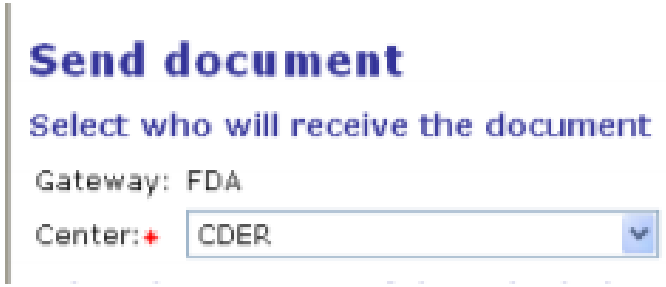
Table 2: Submission Types and Descriptions of Use

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
	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

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



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Frequently Asked Questions

Frequently Asked Questions

Where to place documents in the eCTD?

- Organize content to follow Common Technical Document (CTD) structure

- 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

Frequently Asked Questions

- When do I need to include bookmarks and hyperlinks in a PDF document?
- Is this PDF version acceptable?
- Is a scanned document acceptable?

Answers to above questions and more can be found in FDA's PDF Specifications.

Frequently Asked Questions

- How is my receipt date calculated?
  - Providing Regulatory Submissions in Electronic Format – Receipt Dates
- If I don't have anything to submit in an eCTD section, should I include a document in the section that says not applicable?
  - Placeholder documents are not necessary and discouraged
- Help choosing correct Submission Type and Subtype
  - eCTD Submission Types and Subtypes
- Where should I go to get general guidance on eCTD?
  - eCTD Technical Conformance Guide
  - eCTD website (https://www.fda.gov/ectd)

CDER Document Room Automation

CDER Document Room Automation

Submission Processing: **2018**

All CDER regulatory submissions received are processed by Document Room

Document Room Process:

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

CDER Document Room Automation

Submission Processing: **2019**

Software can now read metadata from eCTD

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

CDER Document Room Automation

Submission Processing Challenges

- Data submitted in eCTD backbone file (e.g. us-regional.xml) and regulatory form (e.g., Form 356h) sometimes contradict each other

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**”.

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 V3.3)

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

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">[redacted]/submission-id>
  <sequence-number submission-sub-type="fdasst3">[redacted]/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	☐ Amendment	23. If a supplement, identify the appropriate category.	☐ CBE	☑ Prior Approval (PA)	
	☑ Initial Submission	☐ Resubmission		☐ CBE-30		

Indicating "Prior Approval"

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

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

New Way to Request a CDER Application Number

New Way to Request Pre-Assigned Application numbers from CDER

- **What** is the new way?
  - Request online via FDA CDER NextGen Portal instead of sending an email
- **When** is it going to be available?
  - Pre-assigned ANDA application requests can be submitted starting from **June 17, 2019**
  - Other application types (CDER only) are planned to be supported in the next few months
- **Where** to get updates?
  - FDA CDER NextGen Portal
  - Requesting Preassigned Application Number Webpage

Tips on Requesting Application Numbers via FDA CDER NextGen Portal

- No need to enter organization information each time an application number is requested
  - Your portal profile information will be used
- Portal questions are designed to ensure all required information is provided on the first request
- To avoid duplication and processing delays, *do not* submit via e-mail if you created a request via portal
  - Portal submissions are encouraged
- Where can I find more information about the FDA CDER NextGen Portal?
  - Frequently asked Portal questions

Thank You

Jonathan Resnick
Cloud Collaboration Capability Team
Office of Business Informatics, CDER

Questions?
eCTD: esub@fda.hhs.gov
Study Data: edata@fda.hhs.gov

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