FDA DISCLAIMER

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Electronic Submissions Update

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CDER | US FDA

Regulatory Education for Industry (REdI): Annual Conference –
August 26, 2020

AGENDA

- Electronic Submission Guidance – What's new?
- Purpose of eCTD and Study Data Requirements
- CDER processing - A look under the hood
- Frequent Asked Questions to ESUB
- When to use CDER's NextGen Portal

ELECTRONIC SUBMISSION GUIDANCE

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

*"**Study Data Guidance**" - Providing Regulatory Submissions in Electronic Format -- Standardized Study Data*

- **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

For more information on how to submit and what will be validated, see the documents below:

- Technical Rejection Criteria for Study Data – Latest update October 2019
- Study Data Technical Conformance Guide – Latest update July 2020
- Study Data for Submission to CDER and CBER website

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

STUDY DATA TECHNICAL CONFORMANCE GUIDE VS. TECHNICAL REJECTION CRITERIA FOR STUDY DATA

- Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards
- **Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data!**

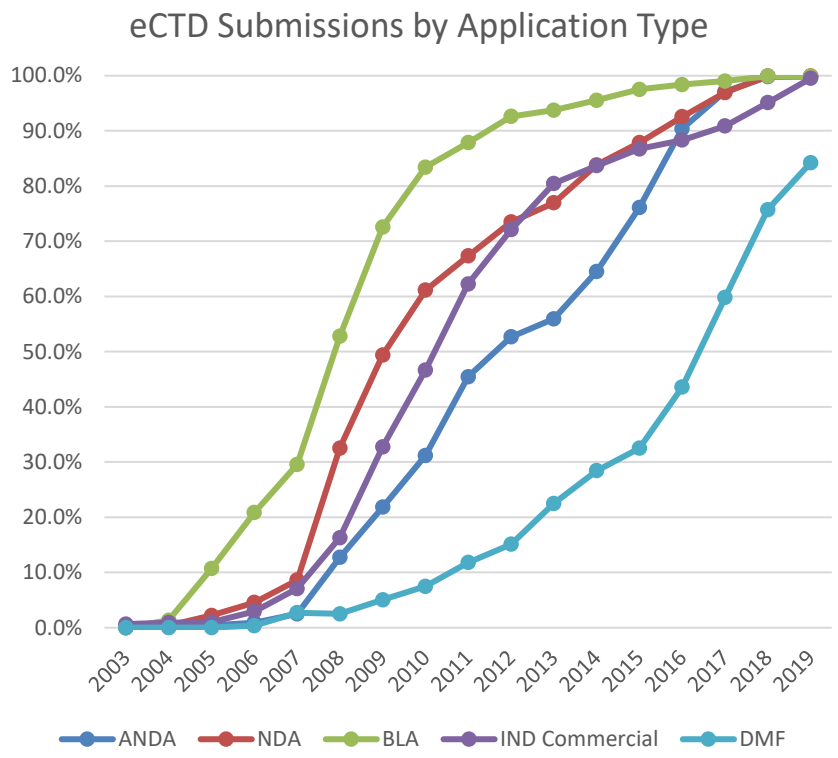
Error	Description (Reference to FDA Technical Rejection Criteria For Study Data Oct. 2019 version)	Severity Level
1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*	**High**
1735	Correct STF file-tags must be used 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

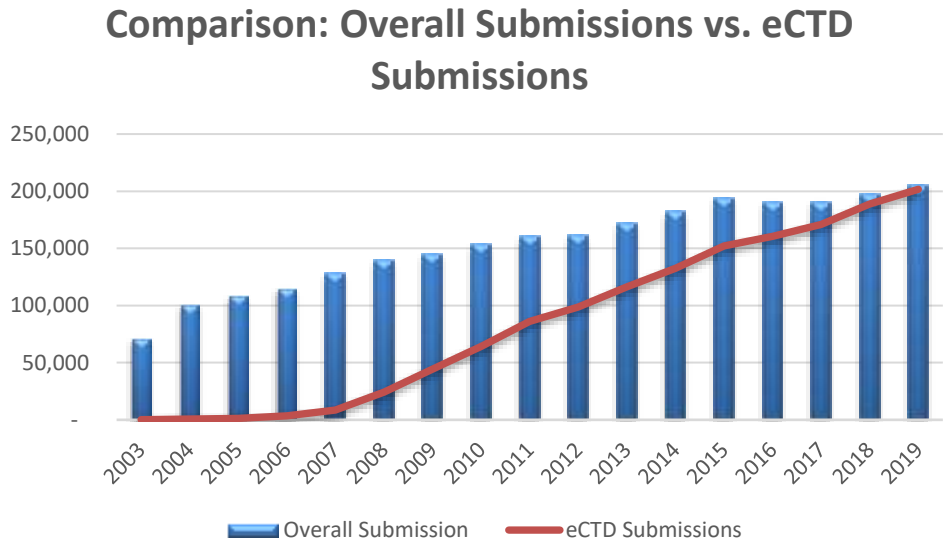
1. * Refer to the latest Technical Rejection Criteria for Study Data for more details

CURRENT STATE: RECEIVED SUBMISSIONS

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



*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 – A LOOK UNDER THE HOOD

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 would still manually process a submission where category cannot be determined and may reject a submission that contains a high validation error

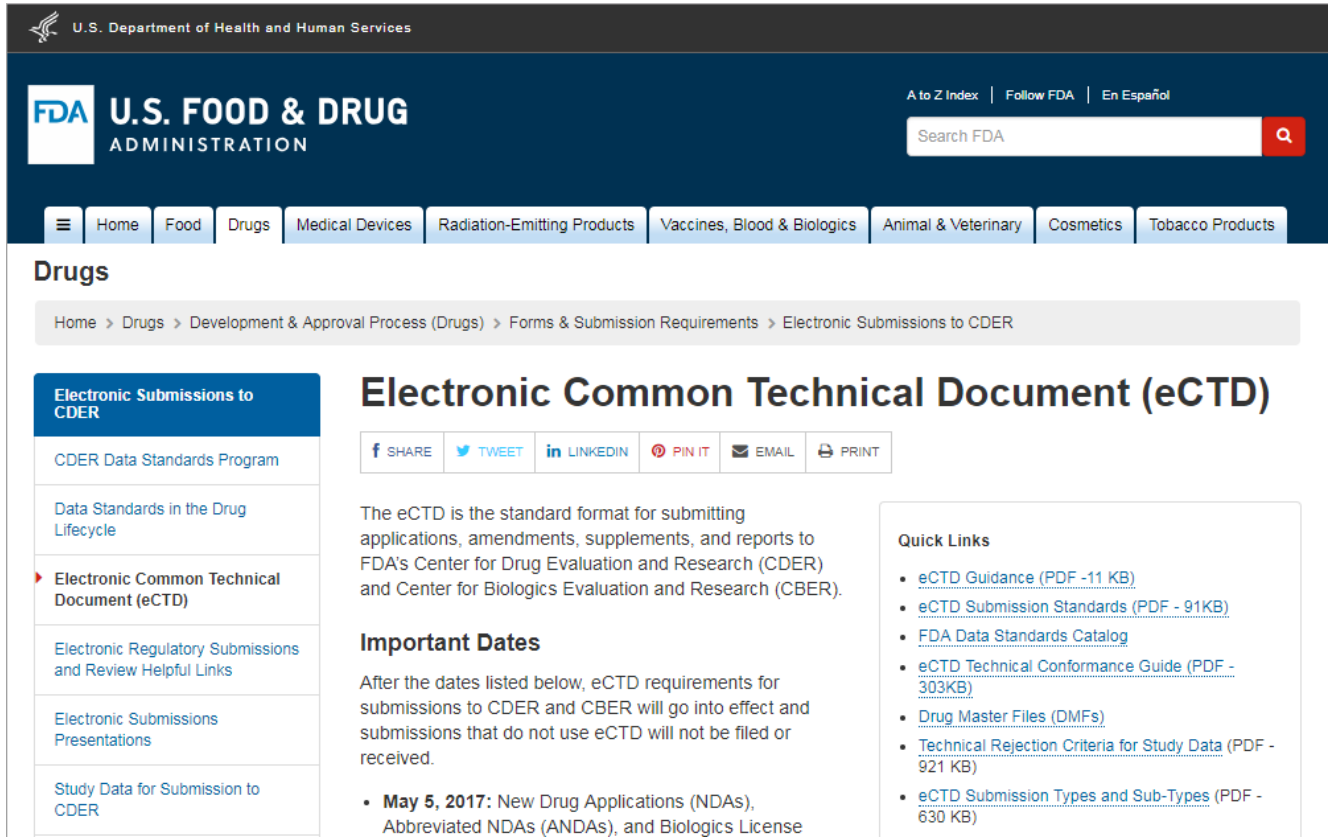
FDA CHALLENGES

- 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:

- 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" (not "Initial Submission")

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)

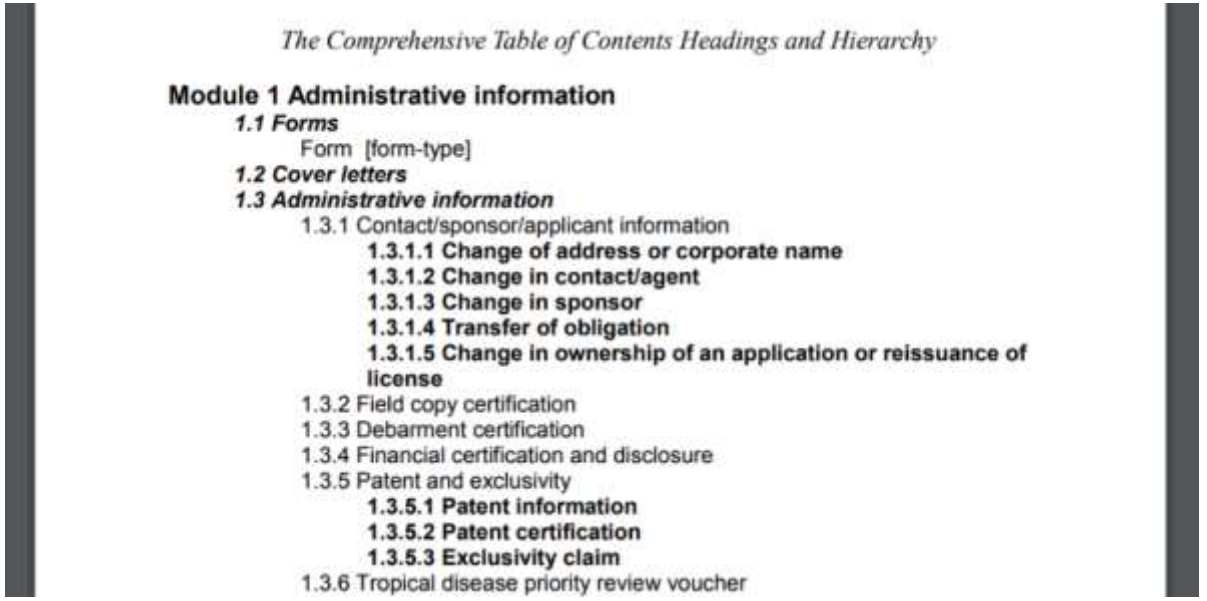
Indicating different Submission Type and/or Submission Sub-Type in us-regional.xml and Form 356h could:

- 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

Frequently Asked Questions to eSub

FREQUENTLY ASKED QUESTIONS

❖ Where do I place my content?



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

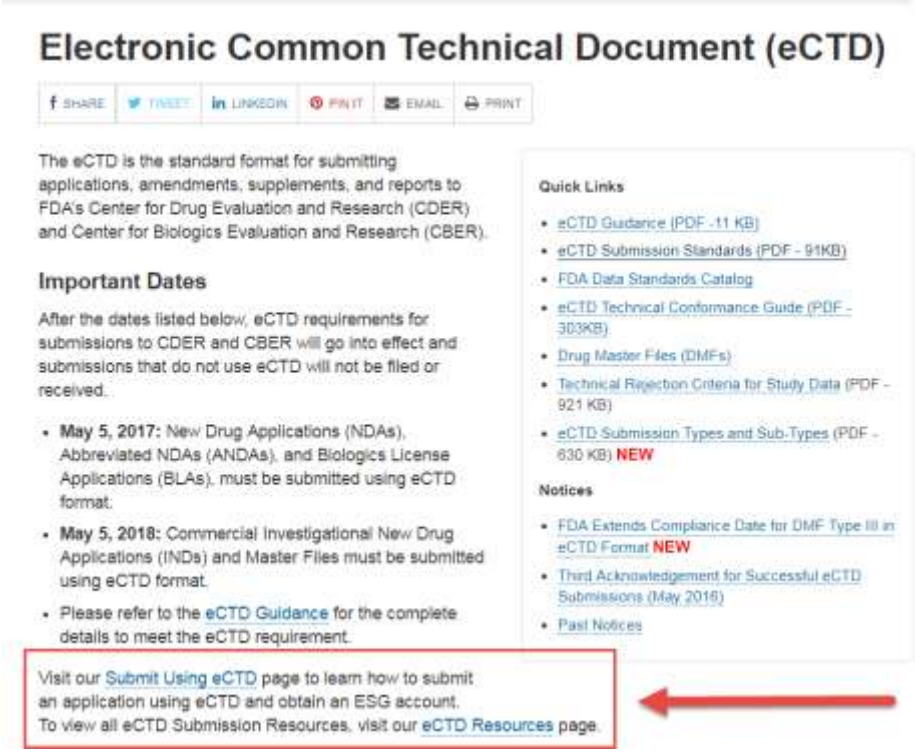
➢ Resources:

- ✓ 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

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)

SHARE | TWEET | 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.

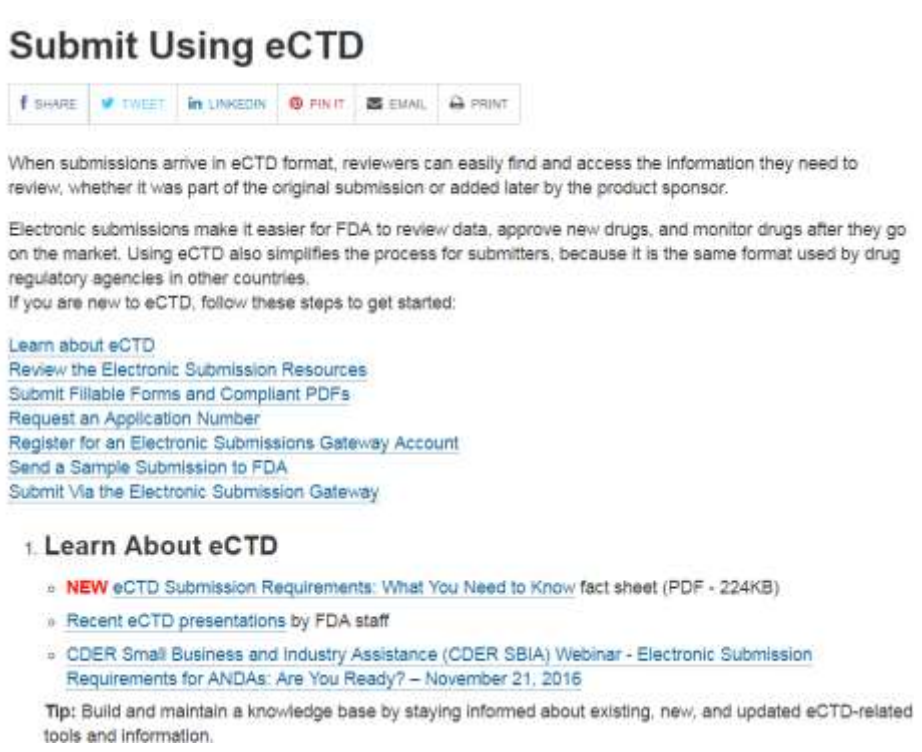
Quick Links

- 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

SHARE | TWEET | 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

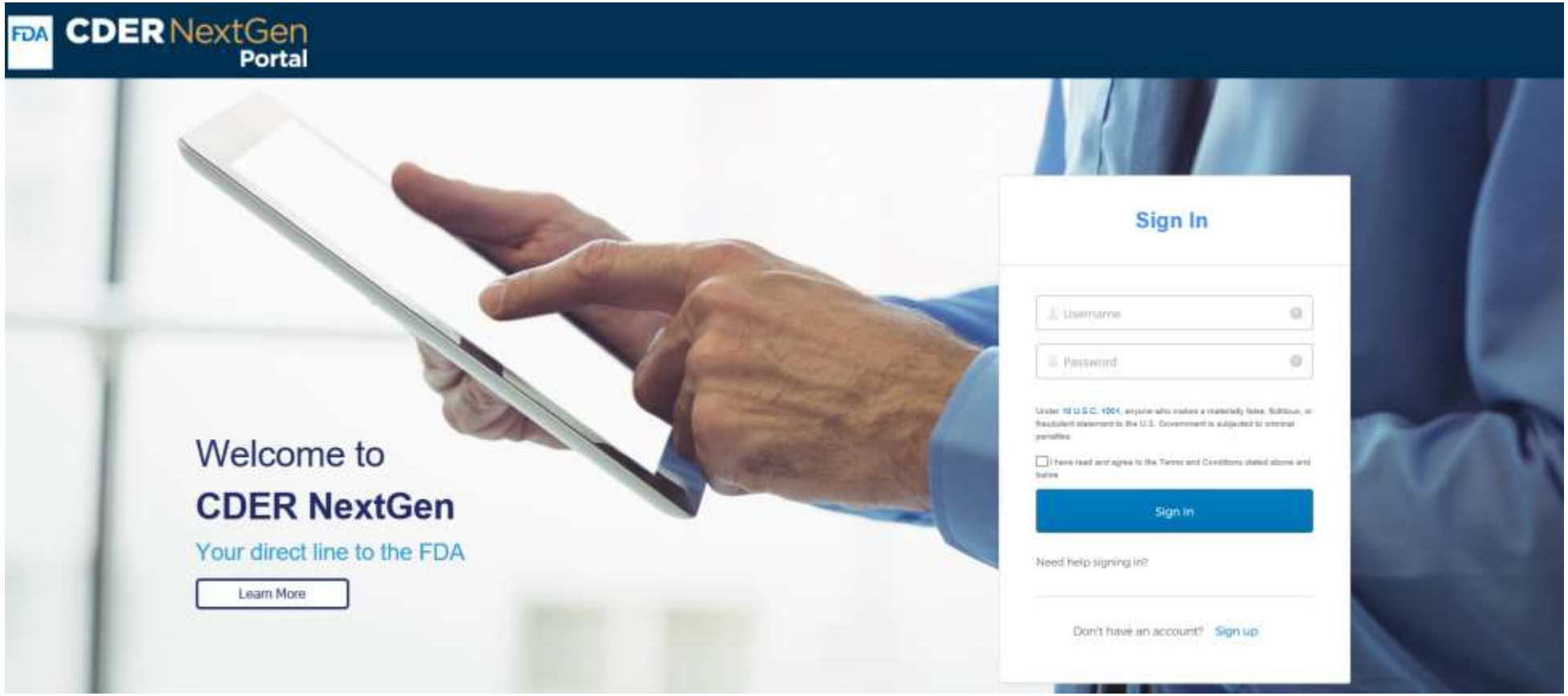
1. Learn About eCTD

- **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.

When To Use CDER's NextGen PORTAL

The CDER NextGen **Collaboration Portal** is a **cloud-based** system that has enabled a transformation in the way CDER and industry work together.



ELECTRONIC SUBMISSION PATHS TO CDER

CDER NextGen
(CDER Only except for DDT)

- Request an Application Number
- Drug Shortage Notifications
- Non-eCTD submission to DMF Type III, Research IND
- Non-eCTD submission to application granted eCTD Waiver
- Pre-ANDA Meetings
- GDUFA II Program User Fees
- Controlled Correspondence
- Drug Development Tools (DDT)
- Non-eCTD submission of Medical Gas, Promotional Material, EUA, or Presubmission correspondence

ESG (All Centers)

- eCTD submission to NDA, BLA, ANDA, IND, DMF applications
- Non-eCTD submission to DMF Type III, Research IND
- Non-eCTD submission to application granted eCTD Waiver
- E2B Postmarket Safety Reports (submitting to FAERS)
- SPL Submissions

CDER Direct (CDER Only), SPL Submissions

- NDC Labeler Code Requests
- Product Listing and Reporting
- Establishment Registrations and annual updates
- GDUFA Facility Self-ID Product Listing
- 503 Outsourcing Facility – registration and product reporting
- Wholesale Drug Distributors and Third Party Logistic Providers (WDD/3PL)

WHAT HAVE WE ALREADY DONE, AND WHAT IS NEW?

WHAT IS PREASSIGNMENT APPLIATION NUMBER?

What's New: FDA added a new event in the CDER NextGen Portal in 2019 for requesting an application number

Target Audience: Applicants that need a CDER assigned application number for NDA, BLA, ANDA, IND or Master Files

Benefits of CDER NextGen: Streamlined approach to submit and track a request for application number

For more information, please go to the FDA website at:
https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number

WHAT ARE ALTERNATE SUBMISSIONS IN CDER NEXTGEN?

Submissions that do not fall under the FDA eCTD Guidance*, exempted under the guidance, or have received a waiver from the guidance

- EUAs
- DMF Type III
- Marketing and Advertising**
- Pre-submission correspondence
- Applications which received a waiver from the eCTD Guidance
- Medical Gas

The goal is to provide a way for industry to send submissions, which are not required in eCTD, without the need for paper or electronic media (i.e. hard drive, DVD).

*FDA eCTD Guidance: https://www.fda.gov/media/135373/download

** Certain types of Marketing and Advertising submissions will be required in eCTD in June 2021. See FDA Promotional Labeling and Advertising Materials Guidance: https://www.fda.gov/media/128163/download

WHAT IS RESEARCH IND IN CDER NEXTGEN?

What's New: FDA recently added a new event in the CDER NextGen Portal for submission of Research INDs

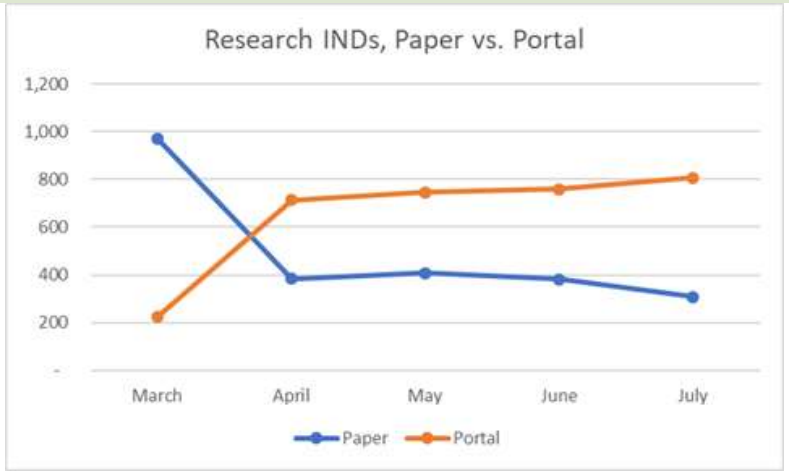
Target Audience: Sponsors who currently submit Research INDs in paper (non-eCTD)*

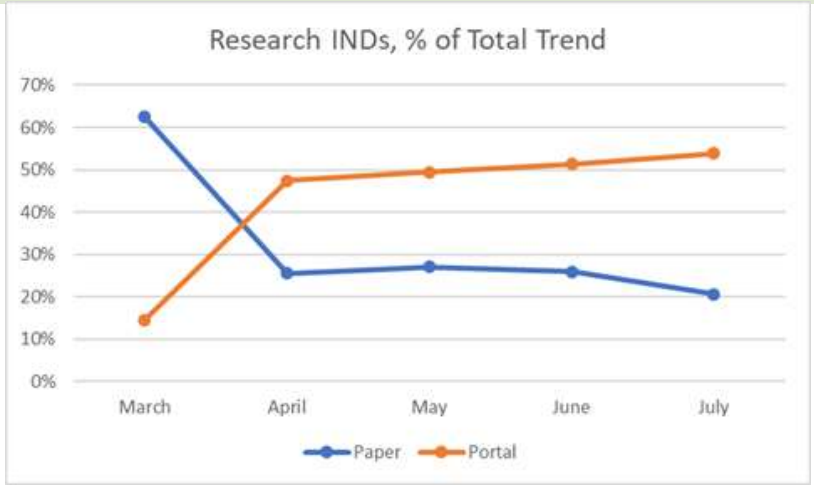
Benefits of CDER NextGen:
https://www.fda.gov/media/136301/download

*This is for Research INDs only. Commercial INDs must be in eCTD and may not use the CDER NextGen Portal unless granted an eCTD waiver. See *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry* (eCTD Guidance) for more information.

RESEARCH IND METRICS (NON-ECTD)

Research IND counts (standardized)	March		April		May		June		July	
	Count	% of total	Count	% of total	Count	% of total	Count	% of total	Count	% of total
Paper	969	62%	384	26%	408	27%	382	26%	309	21%
CDER NextGen Portal	225	15%	713	47%	746	50%	758	51%	807	54%
Gateway	357	23%	408	27%	353	23%	336	23%	382	25%
Total	1,551	100%	1,505	100%	1,507	100%	1,476	100%	1,498	100%





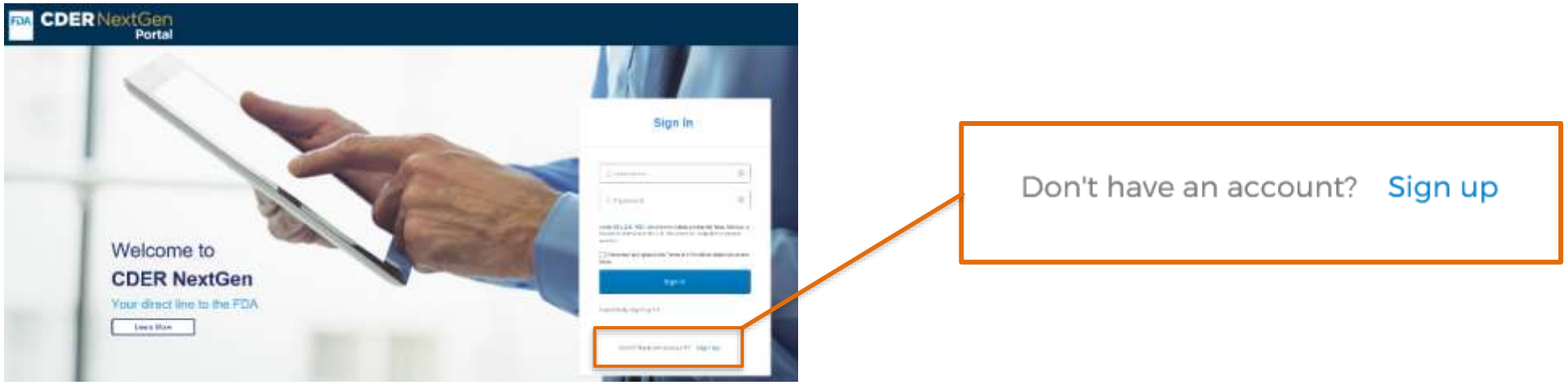
HOW DO I GAIN ACCESS TO THE PORTAL?

Existing Portal Users

Alternate Submission tab was added to your account automatically – click on it when you are ready to submit a request

New Users

To register for an account with the CDER NextGen Portal, navigate to https://edm.fda.gov and follow the signup instructions



SUPPORT FOR YOUR ELECTRONIC SUBMISSION

- eCTD and General Electronic Submission Questions – esub@fda.hhs.gov
- Study Data Submissions – edata@fda.hhs.gov
- CDER NextGen Portal Submissions – edmsupport@fda.hhs.gov

SUMMARY

- FDA Electronic Submission Guidance
  - eCTD Guidance Feb 2020 Updates
  - Submitting Study Data? What you Need to Know to Avoid a Technical Rejection!
- Help CDER Process Submissions Efficiently
  - Align submission type in eCTD metadata with the submission type selected on FDA form
- CDER NextGen Portal
  - When to use it
  - An easy alternative to submitting in paper!