

FDA DISCLAIMER



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Electronic Submissions Update

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CDER | US FDA

2020 Generic Drugs Forum – April 15, 2020

- ❖ 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

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

“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 October 2019
- ▶ [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 <u>Oct. 2019 version</u>)	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

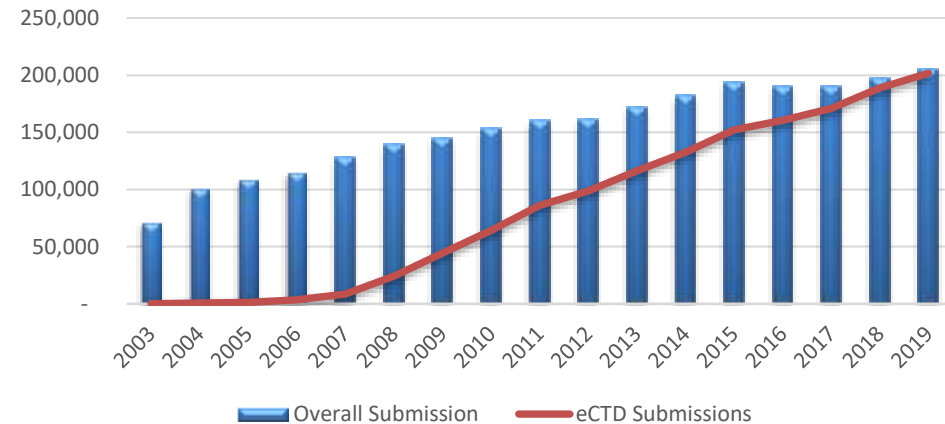
1. * Refer to the latest Technical Rejection Criteria for Study Data for more details

CURRENT STATE: RECEIVED SUBMISSIONS

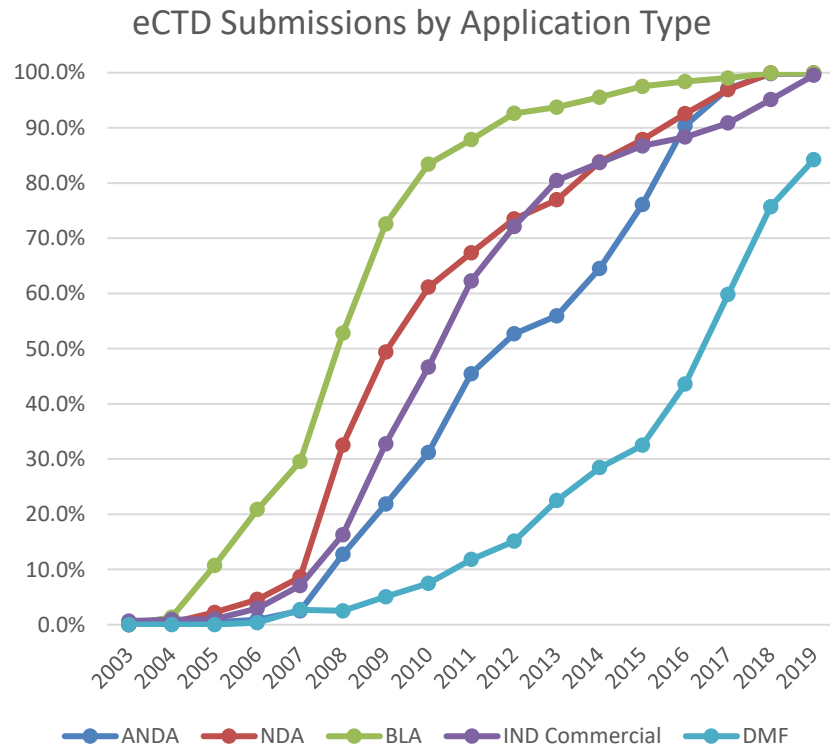


CDER received approximately 205,000* electronic submissions via ESG in FY19. Nearly 202,000 were in eCTD in FY 2019.

Comparison: Overall Submissions vs. eCTD Submissions



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



*excludes promotional/advertising

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

- ❖ 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)

The screenshot shows the FDA website's 'Drugs' section. The header includes the U.S. Department of Health and Human Services logo, the FDA logo, and the text 'U.S. FOOD & DRUG ADMINISTRATION'. A search bar is located in the top right corner. Below the header, a navigation bar lists various categories: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The 'Drugs' section is active, and a breadcrumb trail shows the path: Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements > Electronic Submissions to CDER. The main content area is titled 'Electronic Common Technical Document (eCTD)'. It includes a sidebar on the left with links to 'CDER Data Standards Program', 'Data Standards in the Drug Lifecycle', 'Electronic Common Technical Document (eCTD)' (which is highlighted), 'Electronic Regulatory Submissions and Review Helpful Links', 'Electronic Submissions Presentations', and 'Study Data for Submission to CDER'. The main content area contains a description of the eCTD, a list of 'Important Dates' (including May 5, 2017), and a 'Quick Links' section with links to various documents like '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)', and 'eCTD Submission Types and Sub-Types (PDF - 630 KB)'.

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Tobacco Products

Drugs

Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements > Electronic Submissions to CDER

Electronic Submissions to CDER

CDER Data Standards Program

Data Standards in the Drug Lifecycle

Electronic Common Technical Document (eCTD)

Electronic Regulatory Submissions and Review Helpful Links

Electronic Submissions Presentations

Study Data for Submission to CDER

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

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)

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



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 ☒ Initial Submission ☐ Resubmission

23. If a supplement, identify the appropriate category. ☐ CBE ☐ Prior Approval (PA)
☐ CBE-30

Indicating "Initial Submission"

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

-  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

Submit BE Site Information

❖ 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 Information⁹

Study Number	
Study Title	
Study Type	<input type="checkbox"/> In Vivo BE <input type="checkbox"/> In Vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> 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	<input type="checkbox"/> In Vivo BE <input checked="" type="checkbox"/> In Vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Other
Submission Location:	
Study Report	location, ex: 5.3.1.2
Validation Report	location, ex: 5.3.1.2
Bioanalytical Report	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)	a) 20 days
(b) Temperature Range (e.g., -20°C to -80°C)	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	<input checked="" type="checkbox"/> In Vivo BE <input type="checkbox"/> In Vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Other
Submission Location:	
Study Report	location, ex: 5.3.1.2
Validation Report	location, ex: 5.3.1.2
Bioanalytical Report	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)	a) 20 days
(b) Temperature Range (e.g., -20°C to -80°C)	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.

Frequently Asked Questions to eSub

❖ 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

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 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)



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)
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- [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



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](#)

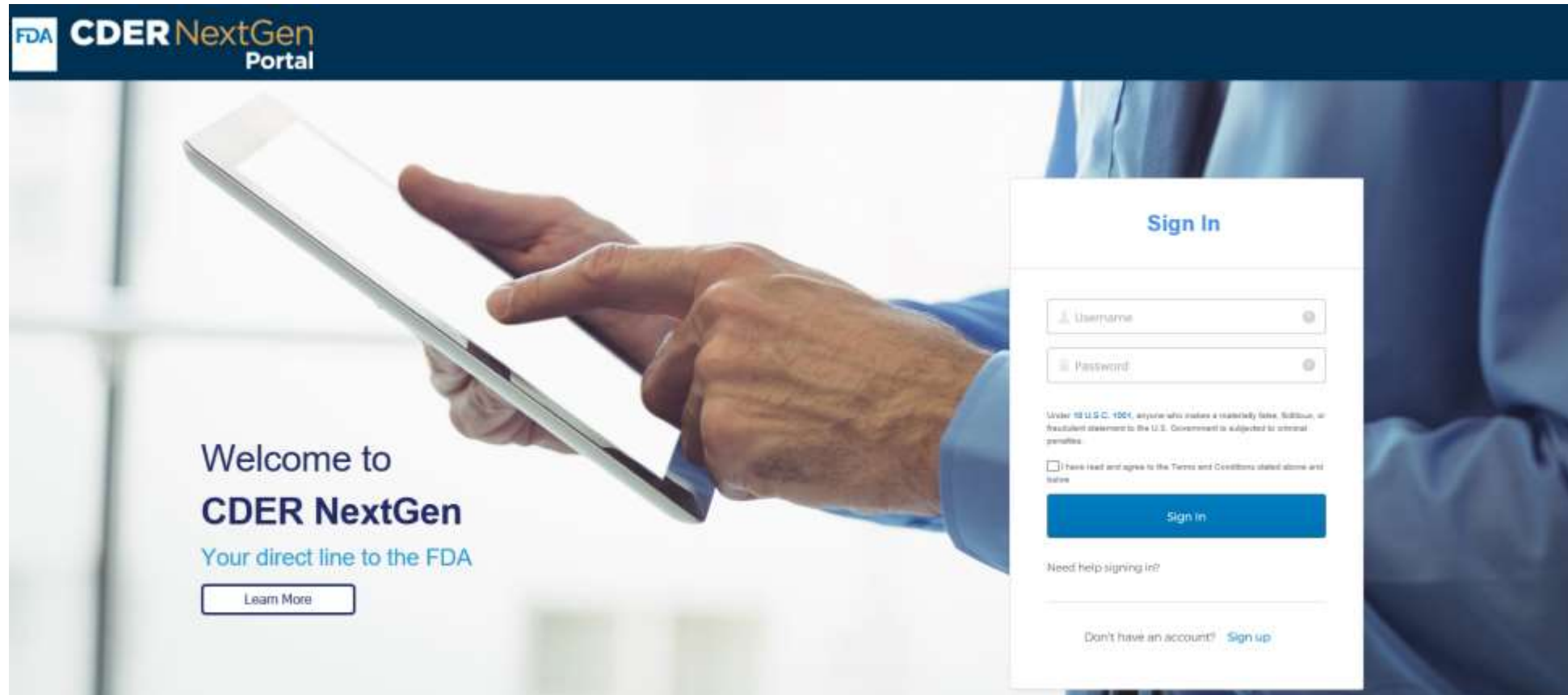
1. Learn About eCTD

- **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](#)

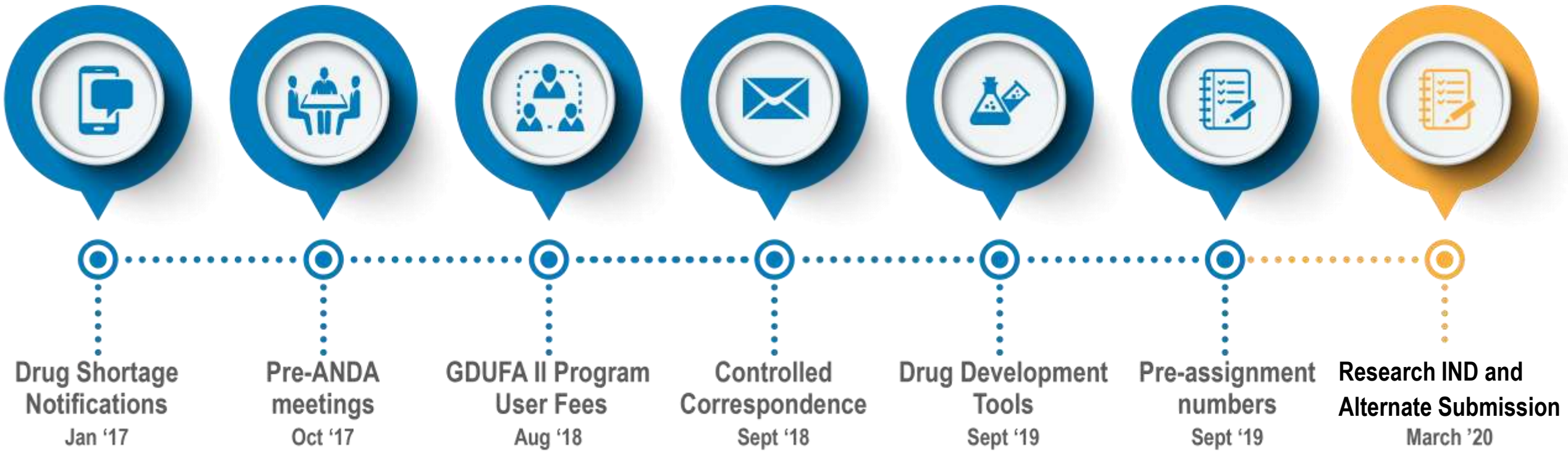
Tip: Build and maintain a knowledge base by staying informed about existing, new, and updated eCTD-related tools and information.

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.



WHAT HAVE WE ALREADY DONE, AND WHAT IS NEW?





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-submissions
- 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>

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



Don't have an account? [Sign up](#)

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
 - Placement of BE Site Information
- CDER NextGen Portal
 - An easy alternative to submitting in paper!