Regulatory Submissions, Information, and Document Management Forum

February 8-10 | Virtual

FDA Electronic Submissions Update

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Agenda

- Electronic Submission Guidance
- eCTD v4.0 Update
- Submission Metrics
- CDER NextGen Portal – What's New
- CDER Document Room Automation
- Frequently Asked Questions

Electronic Submission Guidance

Guidance - eCTD

- eCTD guidance is binding:
  - Submissions to NDA, BLA, ANDA, Commercial IND and Master Files* must be in eCTD format

- See the following resources for more information:
  - *eCTD Guidance (Revision 7)*
  - *eCTD Technical Conformance Guide*
  - *eCTD Submission Standards*
  - *eCTD Website*

- Have Questions? Contact eSub@fda.hhs.gov

*Type III Master Files are exempt from eCTD requirement

Guidance – eCTD – What's New in Rev 7?

- Section III.C. Types of Submissions That Are Exempted From the eCTD Requirement Described in This Guidance
  - Updated section to include exemption for Type III drug master files
- Section III.D. Types of Submissions That May Qualify for a Long-Term Waiver From the eCTD Requirement Described in This Guidance
  - Added section to include waiver criteria for certain PET drug INDs, NDAs, ANDAs, and BLAs, and waiver criteria for certain Type II DMFs
- Section III.E. Types of Submissions That May Qualify for a Short-Term Waiver From the eCTD Requirement Described in This Guidance
  - Added section to include the criteria to qualify for a waiver and the instructions on how to submit a request for a short-term waiver

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**

Even if your study started prior to the dates above, it will need to include a trial summary file (contains the study start date and/or reason code for standardized data not applicable) if files are submitted under sections listed in the Technical Rejection Criteria for Study Data

- 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

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Guidance – Important Notice about eCTD Module 1

- Starting March 1, 2022, the older version of M1, utilizing DTD 2.01, will no longer be supported. The current version of M1, utilizing DTD 3.3, will be required to pass validation.

- For more information, please see Federal Register Notice located here: https://www.regulations.gov/document?D=FDA-2018-D-1216-0017

eCTD v4.0 Update

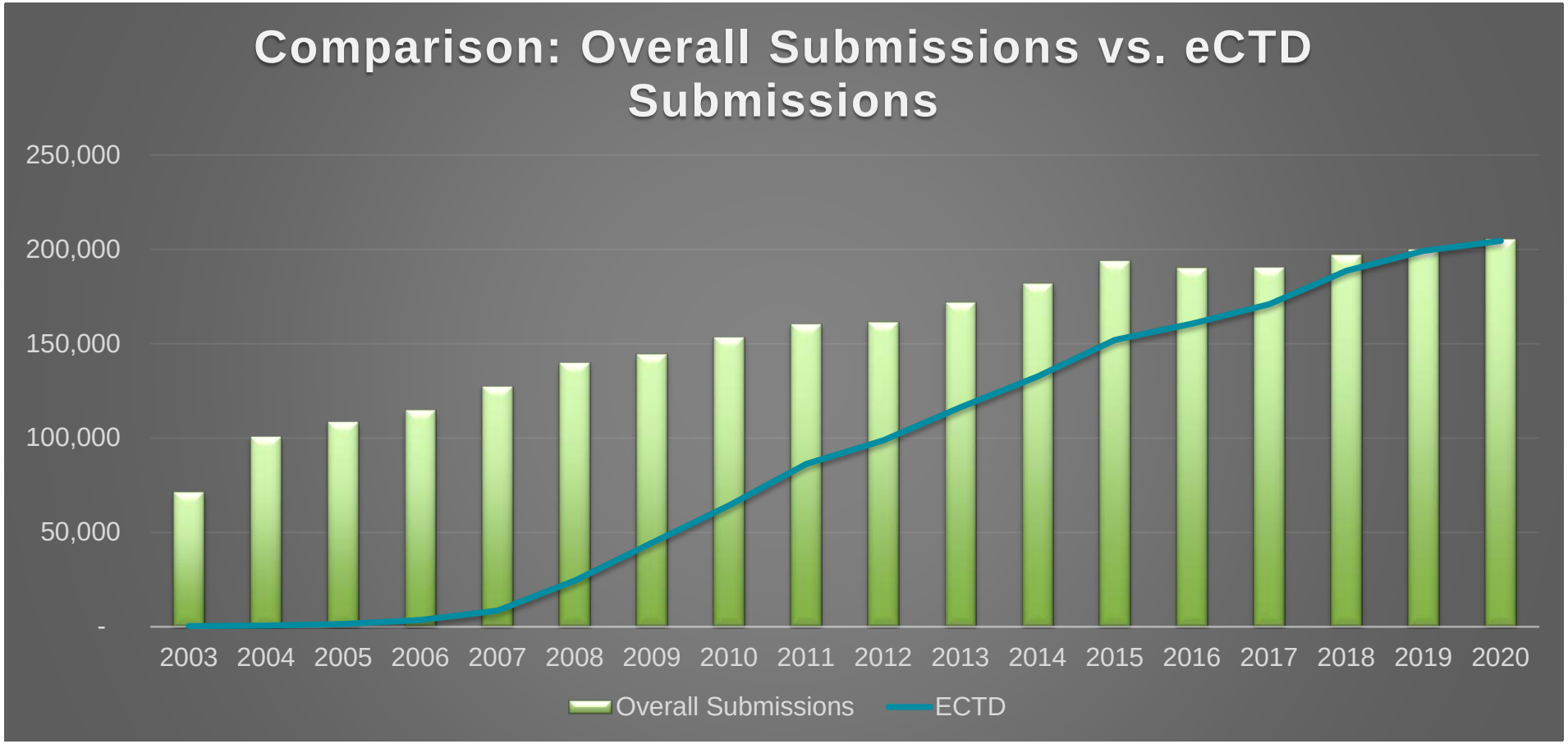
eCTD v4.0 Update

- FDA publishes information about eCTD v4.0 implementation planning here: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40
- The follow documents were posted in 2020 for public comment and revisions are expected to be posted in early 2021:
  - eCTD v4.0 Technical Conformance Guide
  - FDA eCTD v4.0 Module 1 Implementation Package
- Links to the ICH website to access:
  - ICH eCTD v4.0 Implementation Package
  - eCTD v4.0 Q&A Document
- FDA is working with our vendor to incorporate eCTD v4.0 functionality
  - Initial release expected in October 2021
  - If FDA testing is successful, industry testing will be conducted in 2022

Submission Metrics

eCTD Submission Metrics

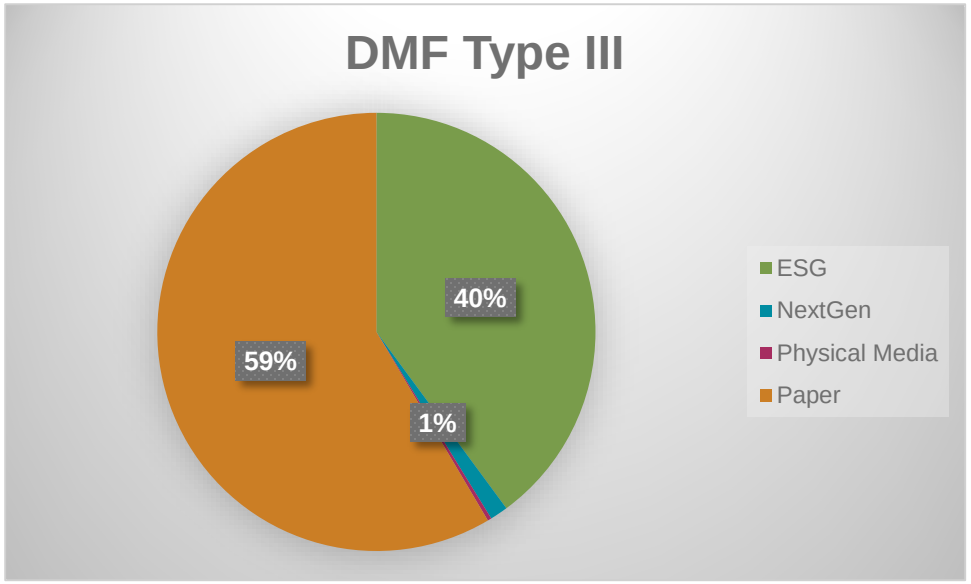
CDER received approximately 205,000* electronic submissions via ESG in FY 2020. Nearly all were in eCTD.

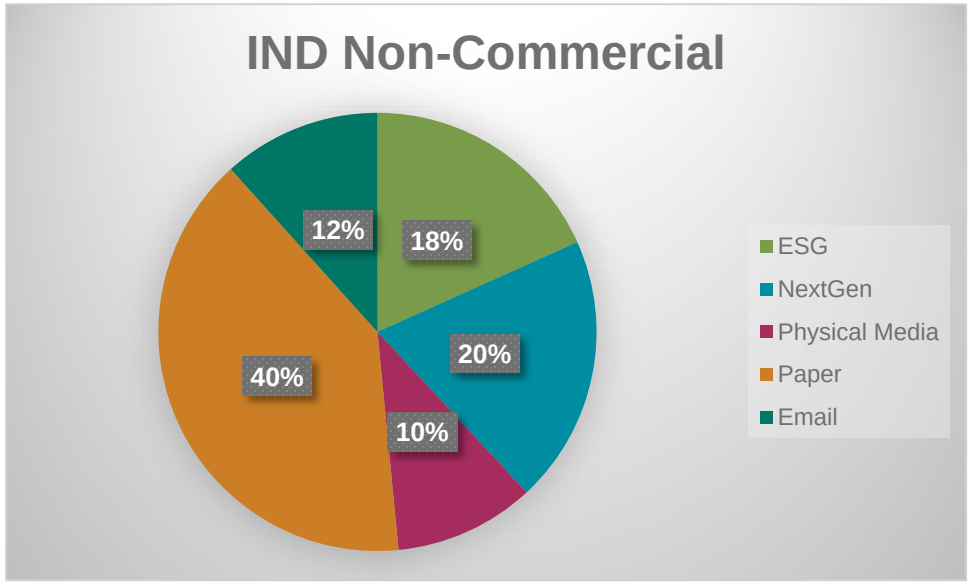


*excludes Non-Commercial IND and DMF Type III

Submission Metrics for Non-Commercial IND and DMF Type III

These application types are not required in eCTD. They are delivered to CDER in a variety of ways



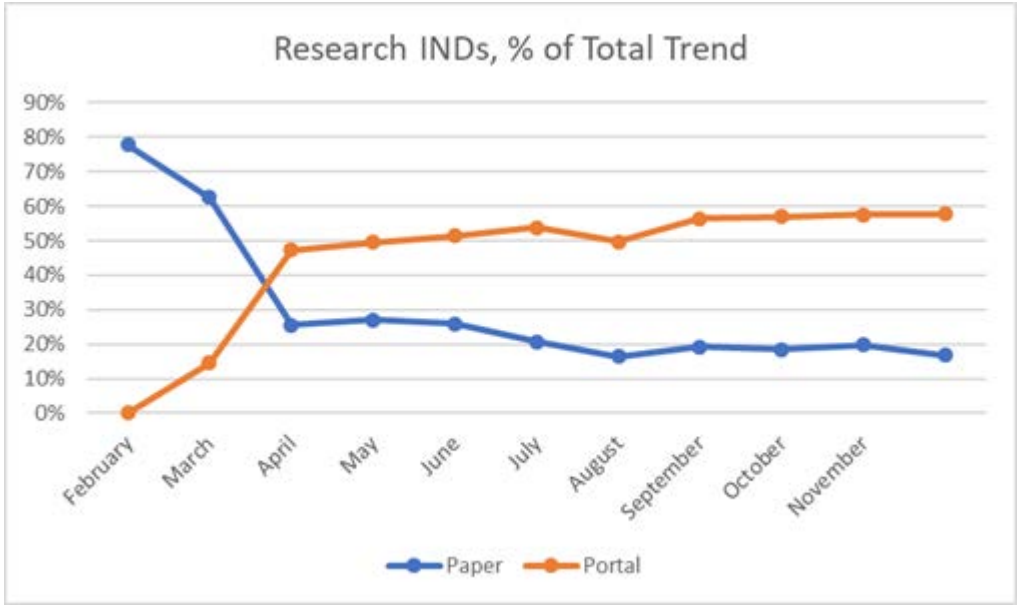


In 2020, CDER expanded electronic options for transmitting non-eCTD submissions. **CDER's NextGen Portal began accepting Non-eCTD submissions to Research IND and DMF Type III applications**. ESG also now accepts non-eCTD DMF Type III. Utilizing CDER NextGen or ESG provides an easier and faster way to transmit a non-eCTD submission compared to paper or physical media (i.e. CD/USB Drive).

Non-eCTD Research IND Submission Trend

Paper Submission of Research INDs dropped from 78% to 17% after the release of CDER NextGen Portal solution in March. The solution sharply decreased the need for staff and RPMs to come to the campus and physically engage, thus improving safety.

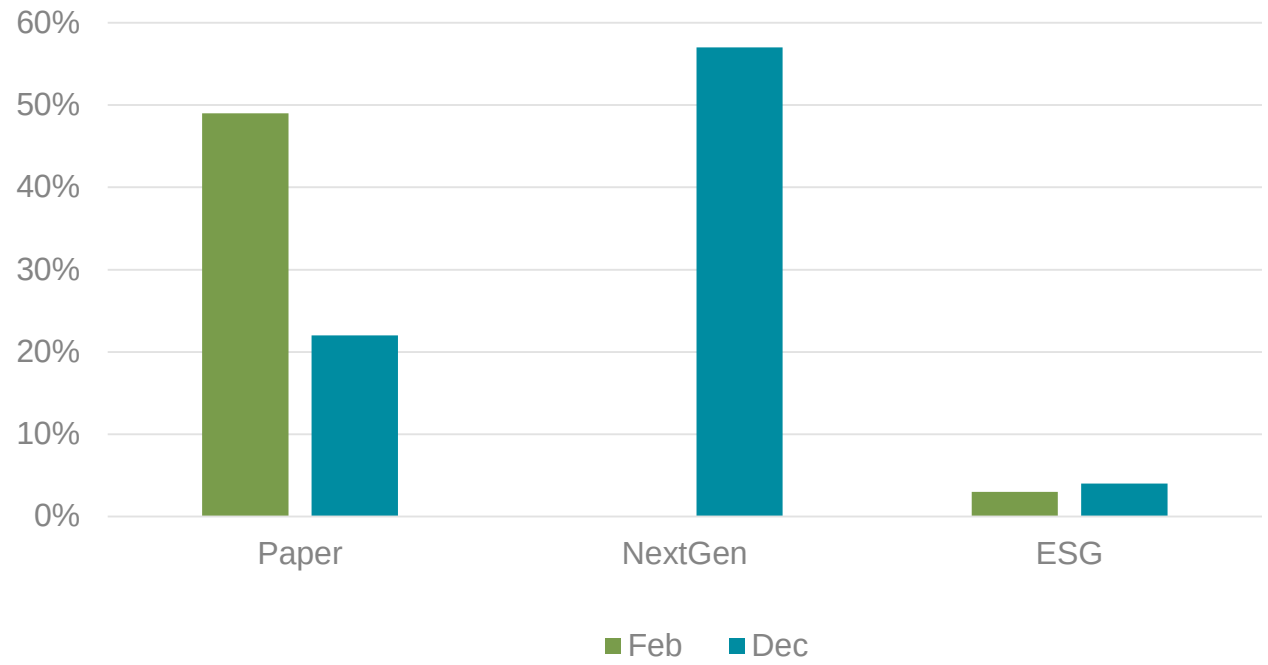
2020	Feb	Dec
Paper	78%	17%
NextGen Portal	0%	58%
ESG	22%	25%



Non-eCTD (excluding Research IND) Submission Trend

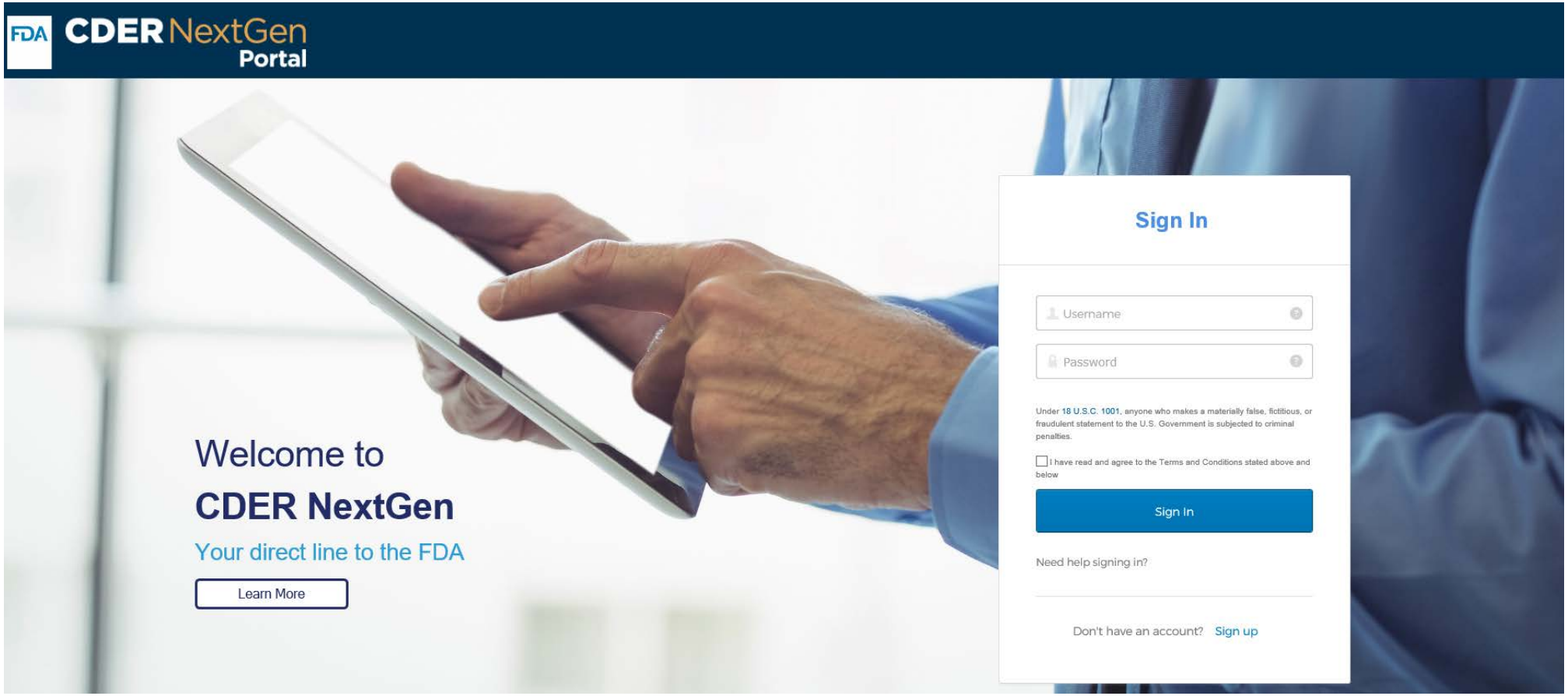
The non-eCTD (excluding Research IND) submission trend for other submissions (DMF Type III, Pre-IND, and various types of correspondence) dropped from 49% to 22% after the release of CDER NextGen **Portal** solution in March.

2020	Feb	Dec
Paper	49%	22%
NextGen Portal	0%	57%
ESG	3%	4%



What is CDER NextGen Portal?

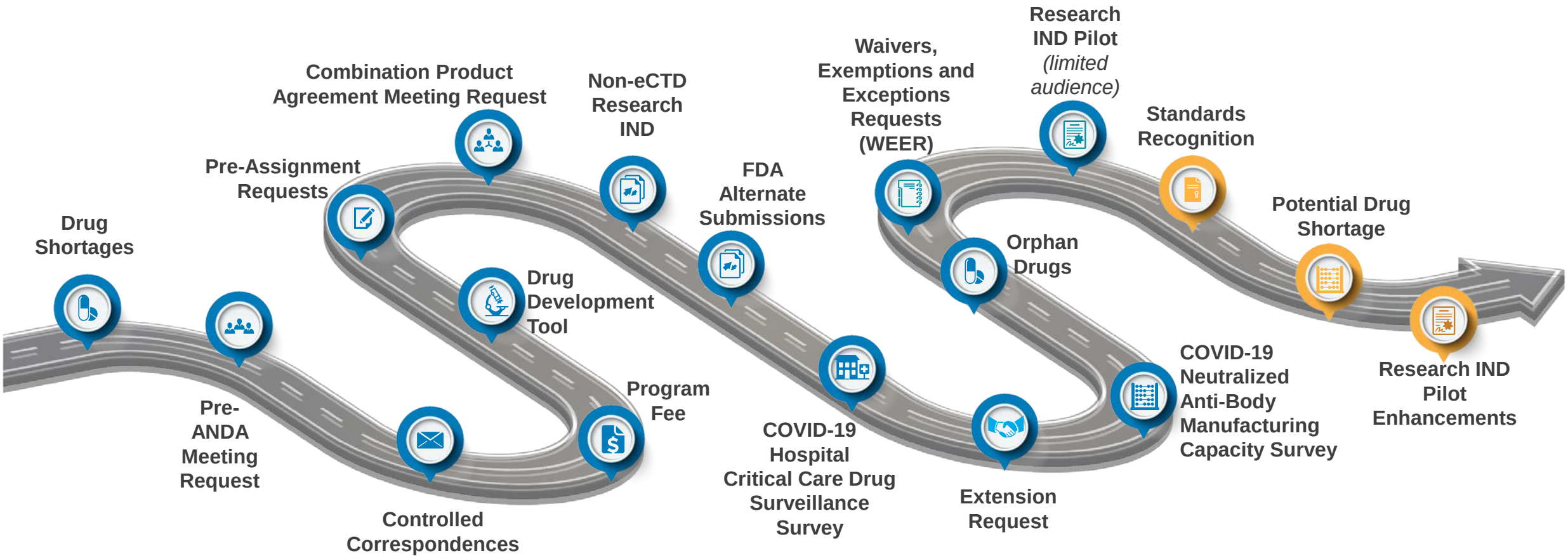
The CDER NextGen **Portal** is a **cloud-based** system that has enabled a transformation in the way CDER and industry work together.



CDER NextGen Portal – What's New

CDER NextGen Portal

What have we already done and what comes next?



Additional details can be found here: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/improving-regulatory-communication-cder-nextgen-portal-december-19-2019-issue

What can you do on CDER NextGen Portal?

- **Drug Shortages (Jan'17)** – submit information regarding a drug shortage and the reason for the shortage to the Agency
- **Pre-ANDA Meeting Request (Oct'17)** - request pre-ANDA meetings for complex generic drugs
- **Controlled Correspondence (Sept'18)** – submit correspondence to the Agency, requesting information on a specific element of generic drug product development.
- **Program Fee (Aug'18)** – submit company and affiliate portfolio to the Agency to be assessed for the annual program fee, depending on the number of approved ANDAs in the portfolio
- **Drug Development Tool (Sept'19)** – submit all Drug Development Tools (DDT) submissions (e.g., Letter of Intent, Qualification Plan, Full Qualification Package) including those that are CDER-specific, CBER-specific or applicable across both Centers to a DDT Qualification Program.
- **Pre-Assignment Requests (June'19 and Aug'19)** – submit pre-assigned ANDA, NDA, BLA, IND, and MF number requests

What can you do on CDER NextGen Portal?

- **Combination Product Agreement Meeting (CPAM) Request (Feb'20)** – request a pre-submission Combination Product Agreement meeting
- **Non-eCTD Research IND (March'20)** – provide an electronic pathway for submitting Research IND new and subsequent submissions previously submitted in paper
- **FDA Alternate Submissions (March'20)** - submit various types of submissions through an electronic submission pathway that can be used for submissions that are not covered under the eCTD requirement (i.e. Marketing and Advertising, EUAs, pre-submissions).
- **COVID-19 Hospital Critical Care Drug Surveillance Survey (May'20)** – allows hospitals and organizations to submit COVID-19 Critical Care Drug Surveillance Surveys
- **Extension Request (Aug'20)** - request to extend the expiration date for drug stockpile that has been stored in a controlled environment and tested for viability.

What can you do on CDER NextGen Portal?

- **COVID-19 Neutralized Anti-Body Manufacturing Capacity Survey (Oct'20)** - provide the Agency with information about the specific investigational new drug (IND) application and the manufacturer, along with details about rates of production, treatment courses, clinical trials and allocations of the drug.
- **Orphan Drugs (Nov'20)** – submit Orphan Drug Designation requests
- **Waivers, Exemptions and Exceptions Requests (WEER) (Dec'20)** – submit and correspond about waivers, exceptions and exemptions from section 582 requirements of the Federal Food, Drug, and Cosmetic Act related to the traceability and security of certain prescription drugs as they are distributed in the United States
- **Research IND Pilot (Dec'20)** - pilot program for more comprehensive application to investigate if a drug is reasonably safe
  - Research IND applications are strictly for research and may result in publications in peer-reviewed journals

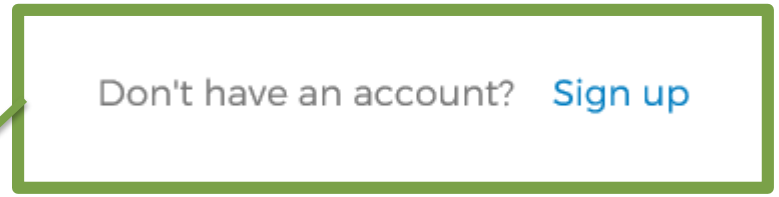
What comes next?

- **Standards Recognition** – request to informally recognize voluntary consensus standards related to pharmaceutical quality
- **Potential Drug Shortage** – provide FDA with notifications about changes in production of certain drug and biologic products
- **Research IND Pilot Enhancements** – additional functionality for the Research IND Pilot

How do I gain access to the Portal?

New Users

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



CDER Document Room Automation

CDER Document Room Automation

Submission Processing: 2020

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: 2020

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)

```
<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 2:

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 3:

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

Frequently Asked Questions

Frequently Asked Questions

Where to place document 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
  - M4 The CTD — Quality Questions and Answers/ Location Issues 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)

DIA

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

Join the conversation
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