FDA DISCLAIMER

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U.S. FOOD & DRUG ADMINISTRATION

ELECTRONIC SUBMISSIONS

eCTD Metrics and Challenges

Association for Accessible Medicines

GRx + Biosims 2018

Jonathan Resnick
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Business Informatics

September 6, 2018

www.fda.gov

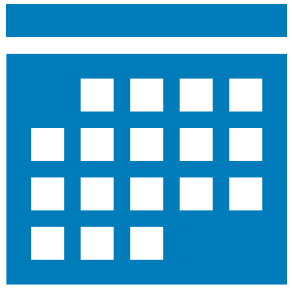
AGENDA

- eCTD Requirement
- Study Data Conformance
- Submit BE Site Information
- Top 3 Rejections and How to Avoid Them
- Frequently Asked Question

ECTD Requirement

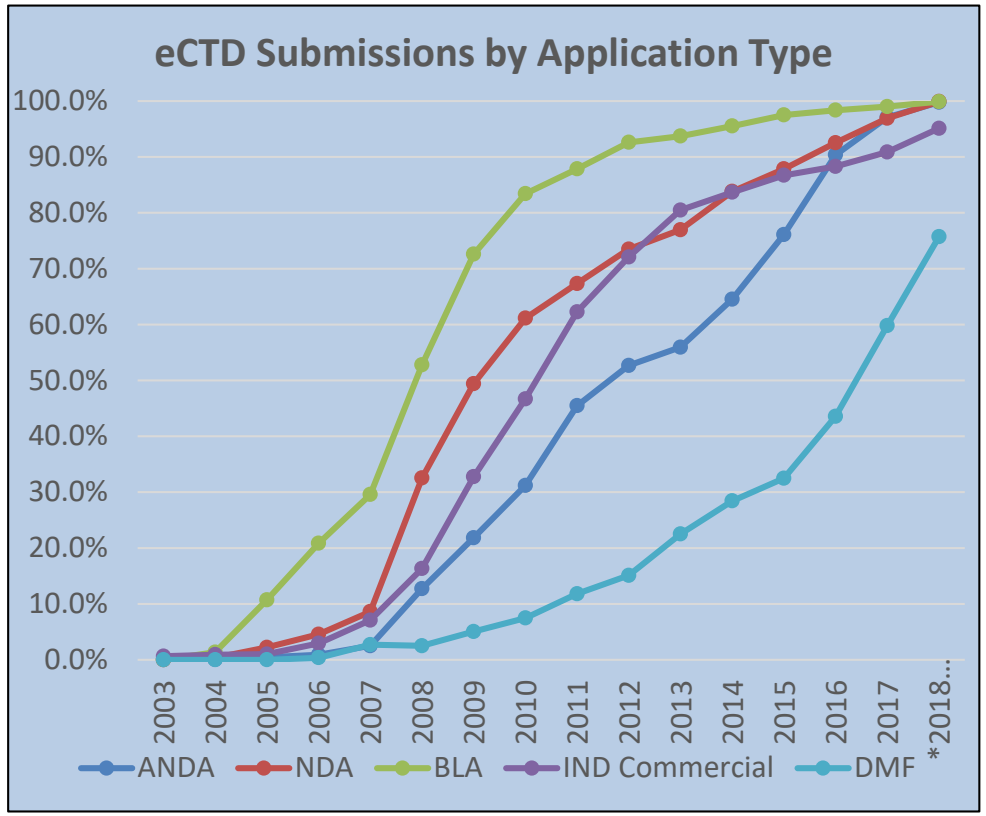
BACKGROUND

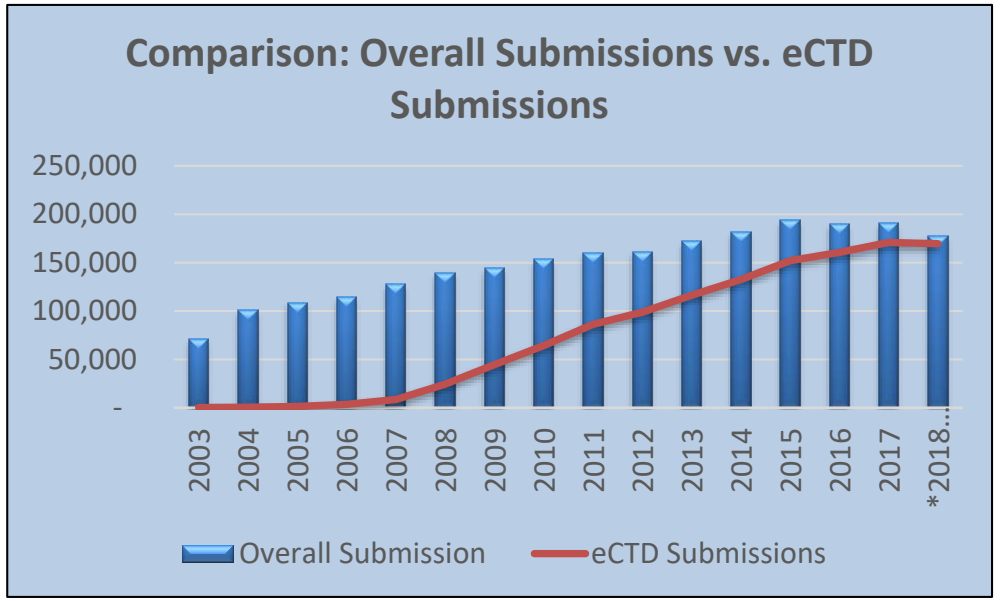
- The number of submissions to the FDA has significantly increased
- eCTD guidance became binding:
  - ✓ May 5, 2017: NDA, BLA, and ANDA must be in eCTD format
  - ✓ May 5, 2018: Commercial IND and Master Files must be in eCTD format



CURRENT STATE: RECEIVED SUBMISSIONS

CDER receives approximately 200,000 electronic submissions via ESG annually. Nearly 180,000 were in eCTD in 2017.

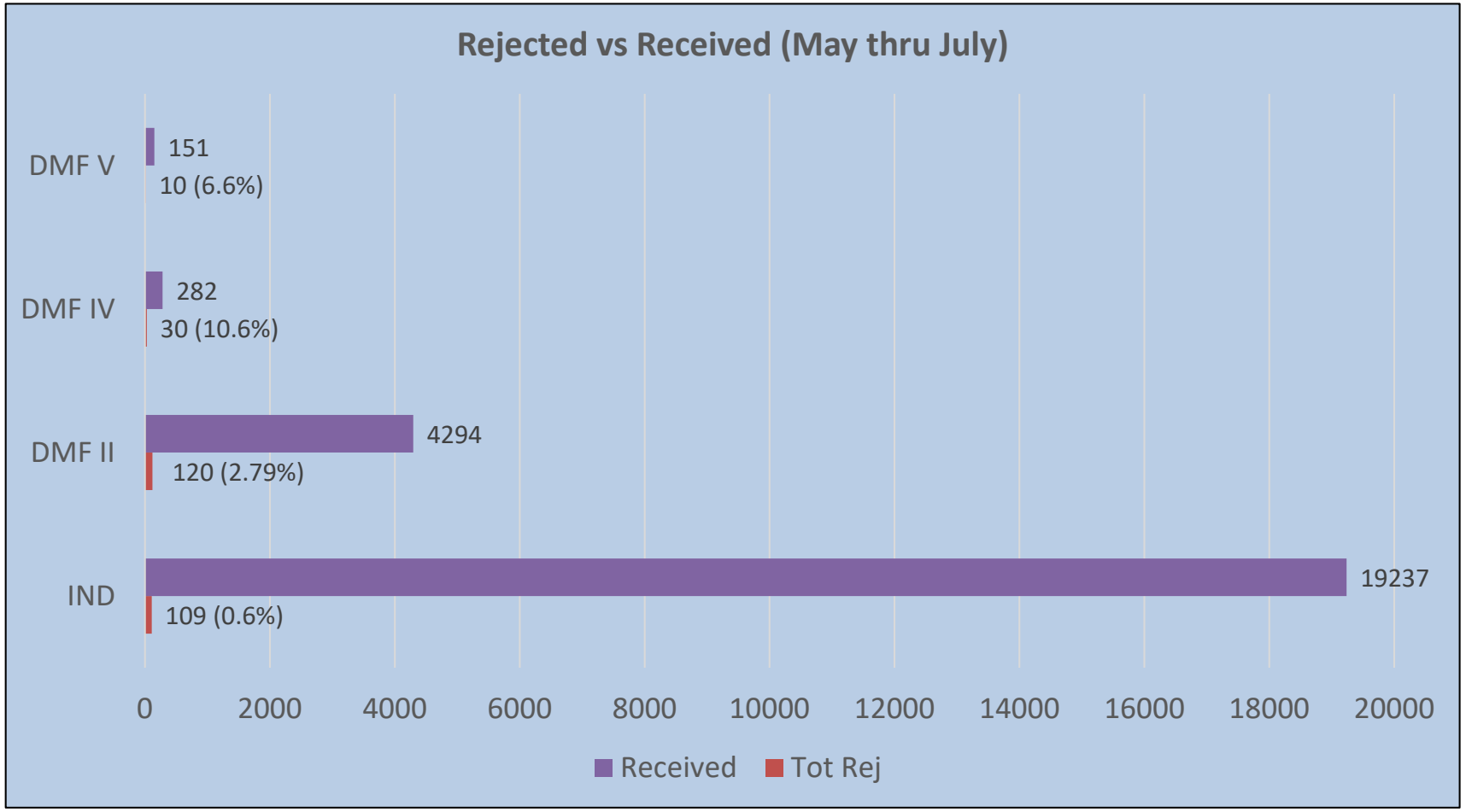




As of August 2018, 98% of the regulatory submissions (specific to Commercial INDs, NDAs, ANDAs, BLAs, DMFs Type II, IV and V) are submitted in eCTD format

ECTD SUBMISSION METRICS – CONT.

May 5, 2018: Master Files (Type II, IV & V) required in eCTD



CURRENT STATE: SUBMISSION PROCESSING

All CDER regulatory submissions received are processed by Document Room.

Current Document Room Process:

1. Manually Review Approx. 200,000 Incoming Submissions
2. Read the Cover Page of every submission (Approx. 850 per day) to determine submission category
3. Code the Submission and route to 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:

1. Reviewers see submission sooner

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

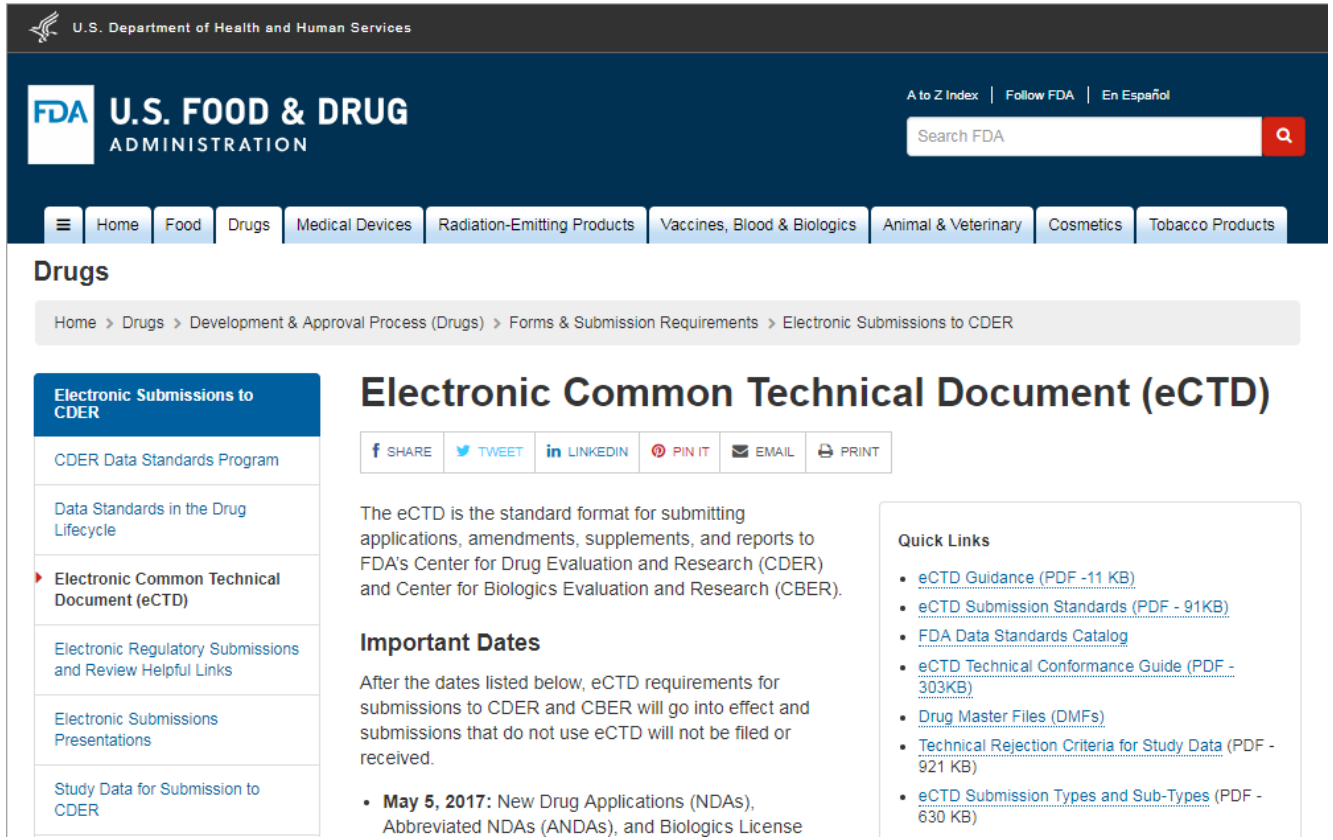
FDA CHALLENGES

- 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 1:

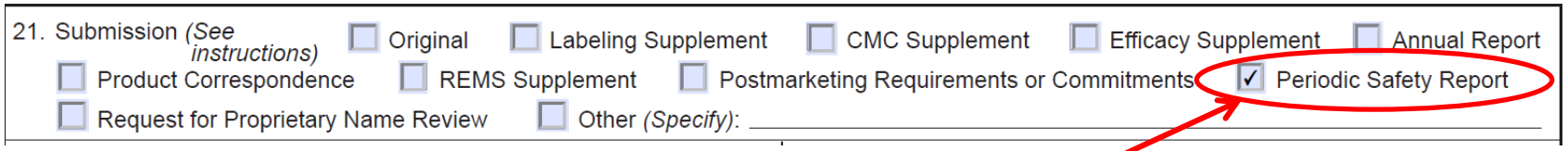
❖ Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```
<submission submission-type="original-application">
  <sequence-number>0022</sequence-number>
</submission>
```

Indicating “Original Application”

Form 356h



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 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

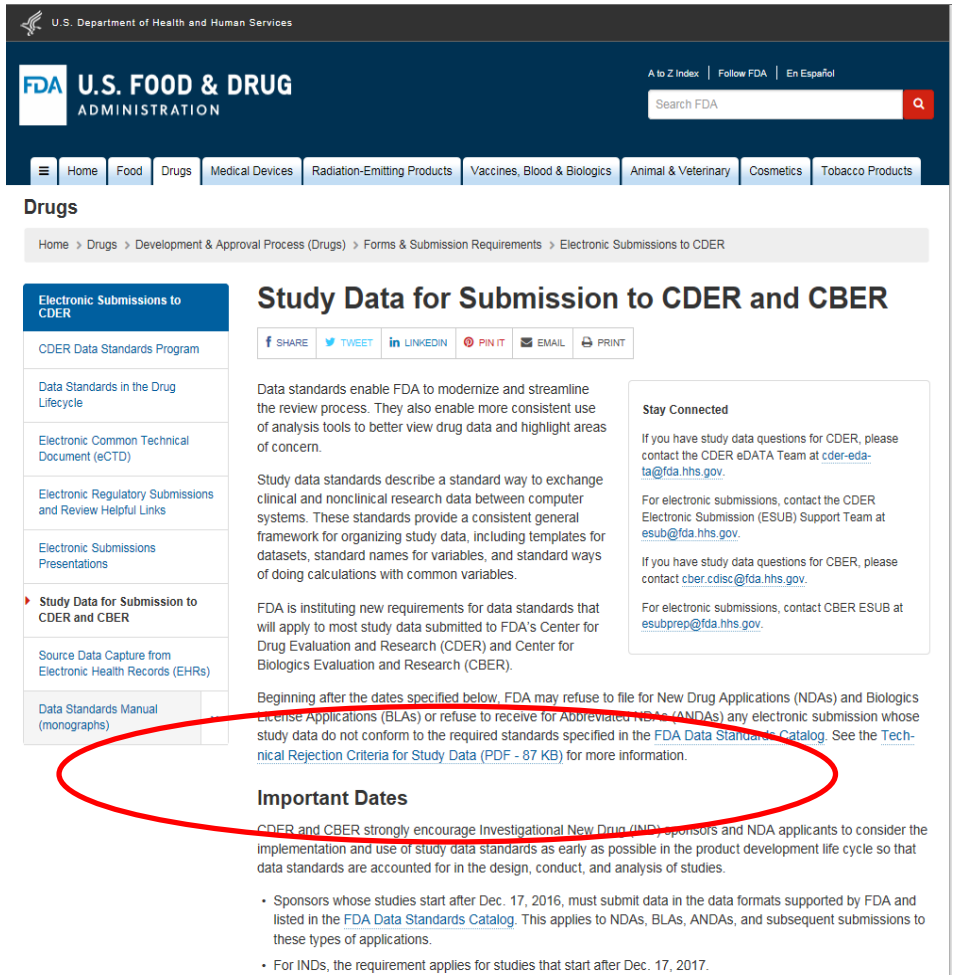
Study Data Conformance

FDA GUIDANCE AND DATA STANDARDS CATALOG

- Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.
- FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014.
- Sponsors must conform to standards in the FDA Data Standards Catalog
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies that started after December 17th, 2017

TECHNICAL REJECTION CRITERIA FOR STUDY DATA

- FDA published "Technical Rejection Criteria for Study Data" which specifies the criteria to be used to assess conformance to the required Study Data Standards.
- When a submission is technically-rejected, the submission sequence is not transferred from the FDA Electronic Submission Gateway into the FDA electronic document rooms.



ANALYSIS OF RECEIVED SUBMISSION WITH STUDY DATA

	All	NDA	ANDA	BLA	Comm. IND
Total Number of Submissions	85,493	24,837	38,346	7,601	14,709
Total Number of Submissions with Study Data	3,221	1,126	1,446	473	176
Total Number Submissions with Critical Errors	1,032	302	551	138	41
Error 1734	968	290	506	137	35
Error 1736 *	84	14	63	1	6
Error Rate (% among submissions with Study Data)	32.04%	26.82%	38.11%	29.18%	23.30%

* Error 1736 validation is not performed if a study has Error 1734

Note:
- One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments.
- NDA, BLA, and ANDA submissions received from 12/18/2016 to 3/31/2018
- Commercial IND submissions received from 12/18/2017 to 3/31/2018
- Submission that contains multiple studies can report both Errors 1734 and 1736

Submit BE Site Information

BIOEQUIVALENCE (BE) SITES

- 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 Information[9]

Study Number	
Study Title	
Study Type	☐ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ 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.

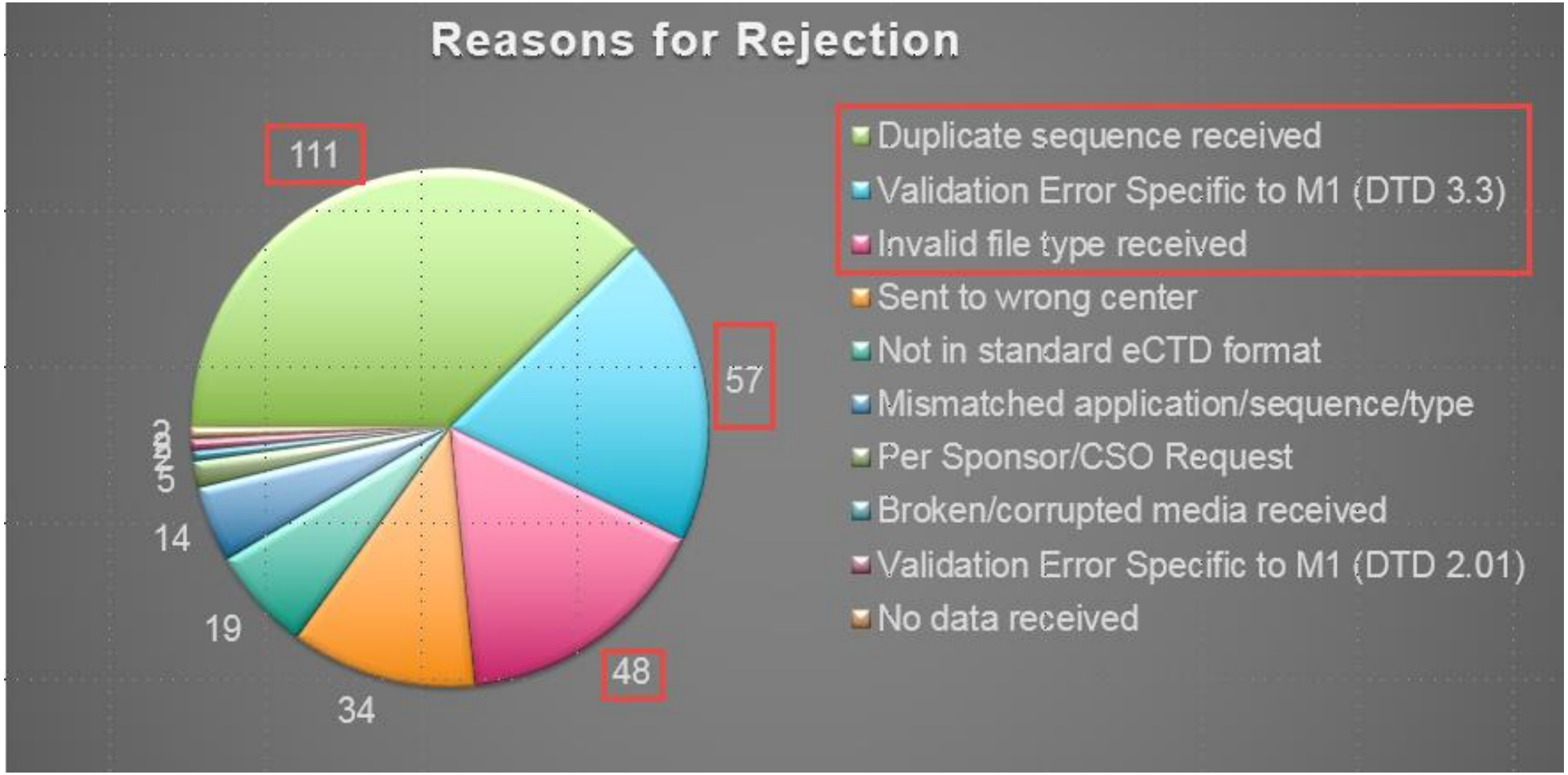
- Provide a separate table for each bioequivalence study.

Model Bioequivalence Data Summary Tables (PDF - 185KB)

Top 3 Rejections and How to Avoid Them

TOP 3 REJECTIONS AND HOW TO AVOID THEM

- A closer look at the 3 most common rejections for eCTD NDA, BLA, IND, MF, ANDA (sample size: 15,765)



TOP 3 REJECTIONS AND HOW TO AVOID THEM

1. Duplicate Sequence Number Received

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 AND HOW TO AVOID THEM

2. Most Common M1 (DTD 3.3) Mistake

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 AND HOW TO AVOID THEM

3. Invalid File Types

- .exe, .zip, and others single file submissions are not allowed

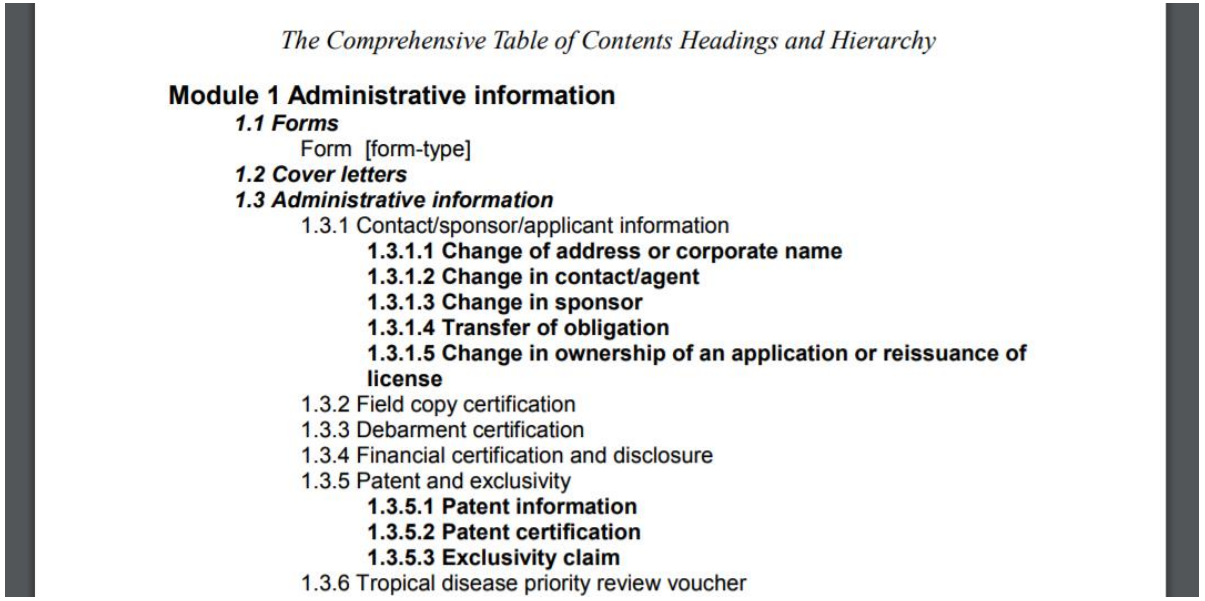
Frequently Asked Questions

FREQUENTLY ASKED QUESTIONS

❖ **Where do I place my content?**

➢ Resources:

✓ The Comprehensive Table of Contents Headings and Hierarchy



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

✓ M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry

✓ FDA Regulatory Project Manager

FREQUENTLY ASKED QUESTIONS

- **Can I submit a xyz file format?**
  - 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

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)

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.

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

U.S. FOOD & DRUG ADMINISTRATION

COLLABORATION IN THE CLOUD

Modernizing interactions between CDER and industry

Association for Accessible Medicines

GRx + Biosims 2018

Jonathan Rappaport, MBA
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Business Informatics

September 6, 2018

www.fda.gov

WHAT OPPORTUNITIES DO WE HAVE TO IMPROVE COMMUNICATIONS BETWEEN CDER AND INDUSTRY?

Much of today's regulatory communication is sent through a collection of **emails** and submissions to the **Electronic Submission Gateway**.

WHAT OPPORTUNITIES DO WE HAVE TO IMPROVE COMMUNICATIONS BETWEEN CDER AND INDUSTRY?

Reduced administrative overhead on companies

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Simplified tracking for CDER personnel

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Reduced administrative overhead on companies

Increased automation of data validation checks

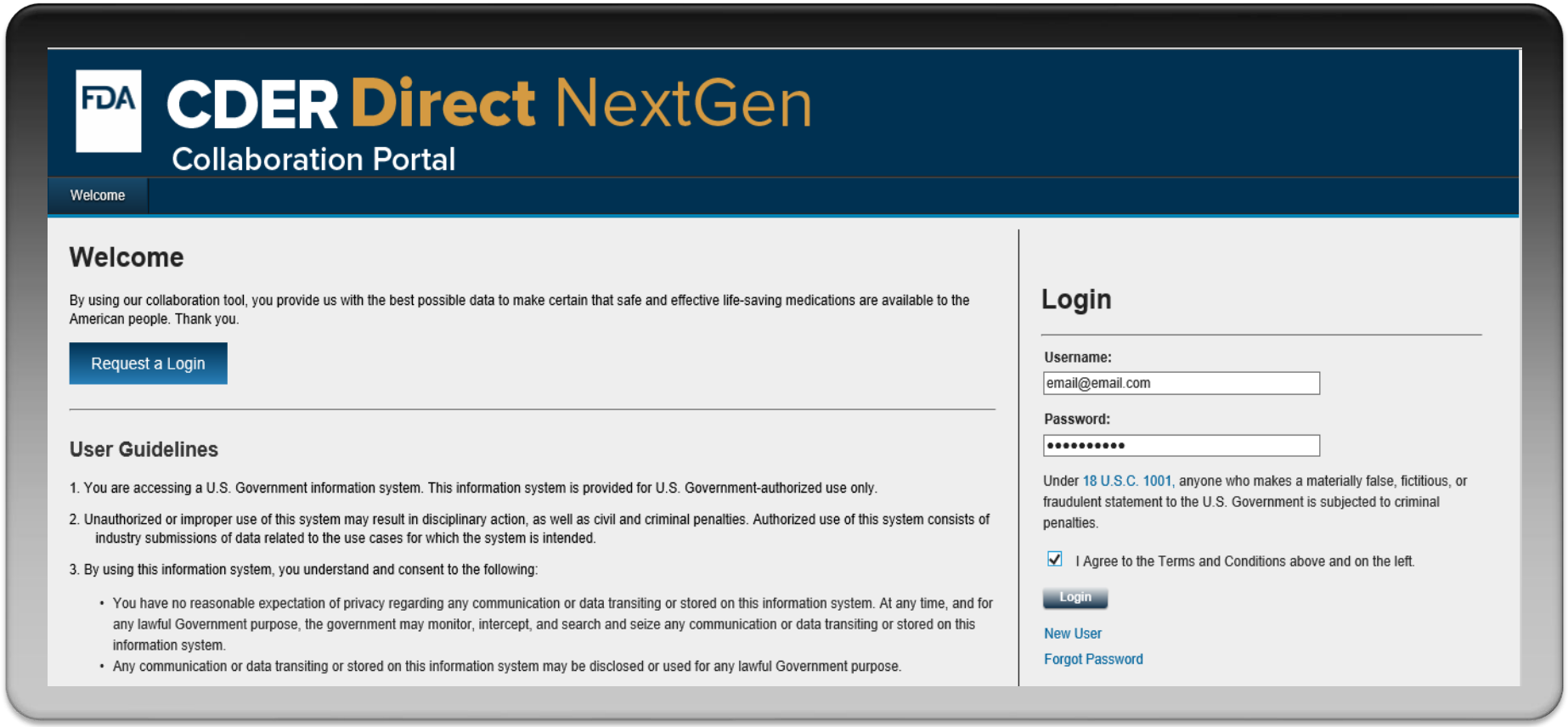
Centralized and coherent view of complex interactions

Simplified tracking for CDER personnel

More flexible architecture

WHAT ARE WE DOING TO SHIFT THE PARADIGM?

The CDER Direct NextGen **Collaboration Portal** is a **cloud-based** system that has enabled a transformation in the way CDER and industry work together. It serves as a "**one-stop-shop**" for your communications.



HOW IS THE COLLABORATION PORTAL ENHANCING COMMUNICATION PROCESSES?

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Streamlined step-by-step guidance through the submission process with dropdown menus and fillable fields

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Full integration with CDER's internal work management systems

HOW IS THE COLLABORATION PORTAL ENHANCING COMMUNICATION PROCESSES?

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Live validation against CDER's master data with instant discrepancy reconciliation requests

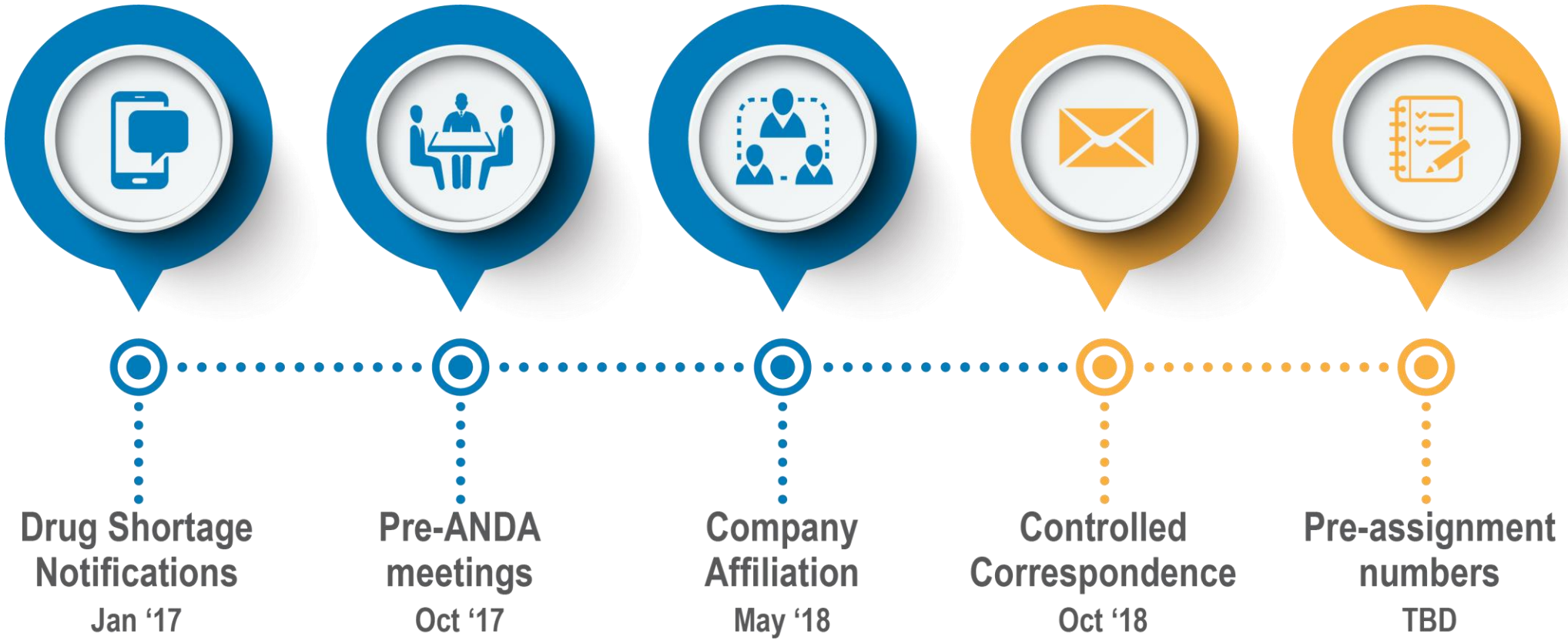
Real-time status updates and notifications to submission owners

Centralized chronological view of all communications and documents

Full integration with CDER's internal work management systems

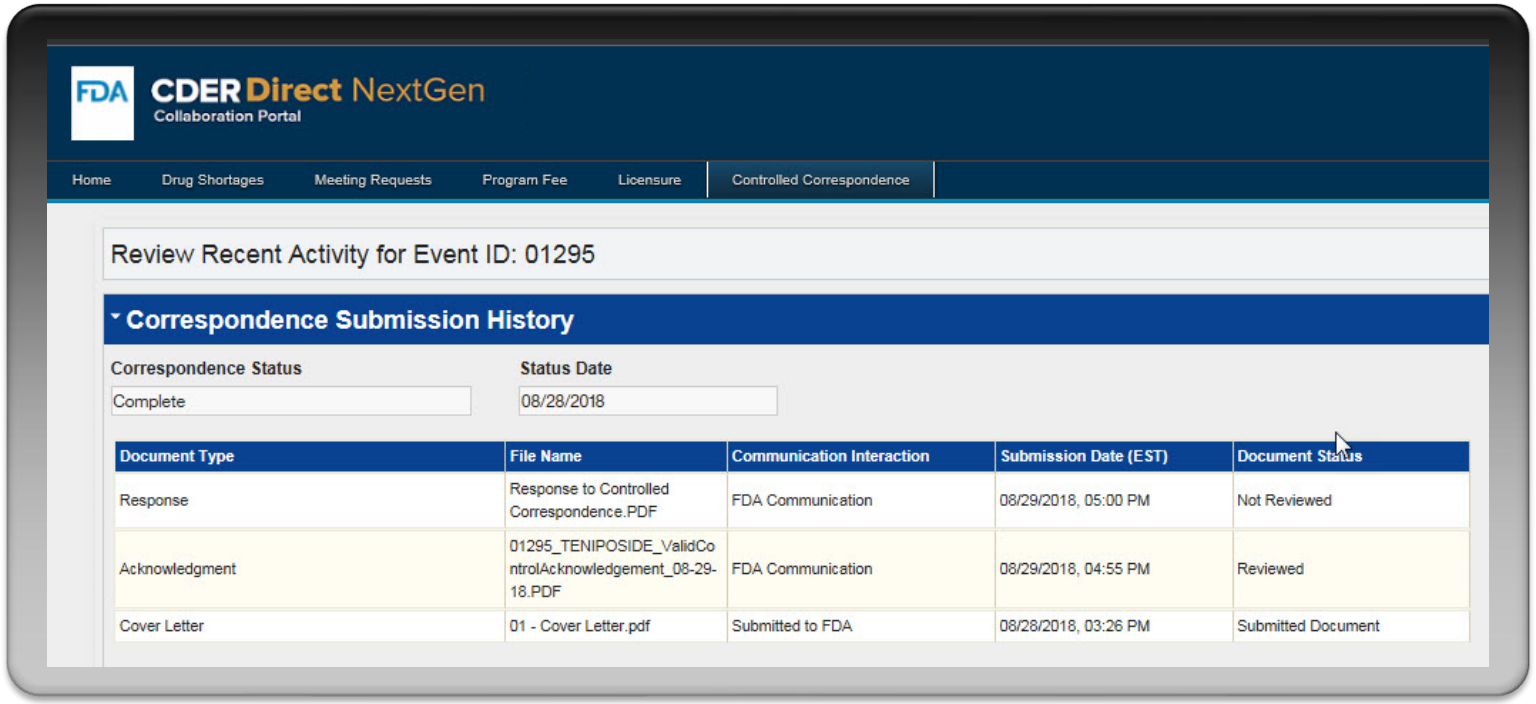
Scalable cloud architecture to accommodate future growth

WHAT HAVE WE ALREADY DONE, AND WHAT COMES NEXT?



WHAT CAN YOU EXPECT FOR CONTROLLED CORRESPONDENCE?

Email announcement from CDER in the coming weeks informing you that the Collaboration Portal will be ready to receive your Controlled Correspondences



Go to edm.fda.gov to request an account

HOW ARE WE SECURING YOUR INFORMATION?

Current

Basic User Validation

User Registration and validation occurs to gain access

Future

Advanced Authentication

Achieve assurance levels using self service “identity proofing”

- User Registration and Validation
- User Profile
- User Login and Password

- NIST Level 3
- ✔ Two Factor Authentication
- ✔ Lock out after 15 minute of inactivity
- ✔ Remote Identity Proofing

The Collaboration Portal is compliant with FedRAMP cloud service security requirements.

amazon web services AWS GovCloud

FedRAMP Authorized

EARLY SUCCESS FOR THE COLLABORATION PORTAL

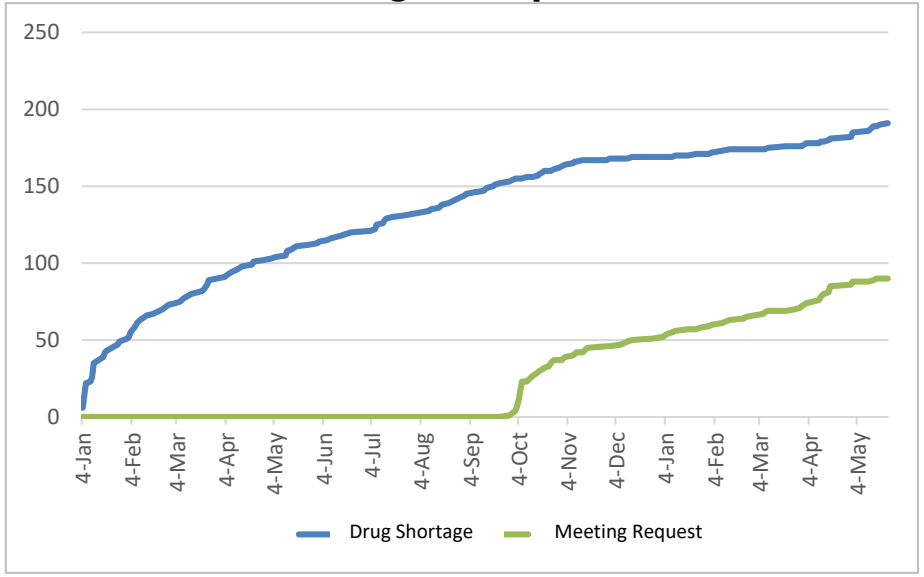
248
Unique Users

148
Registered Companies

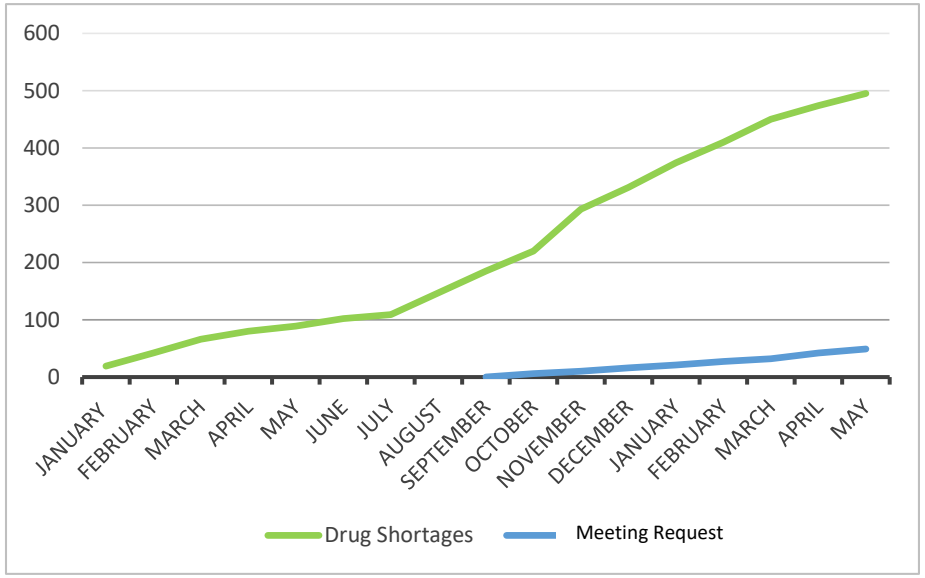
495
Drug Shortages Notifications

49
Meeting Requests

Login Requests



Submissions

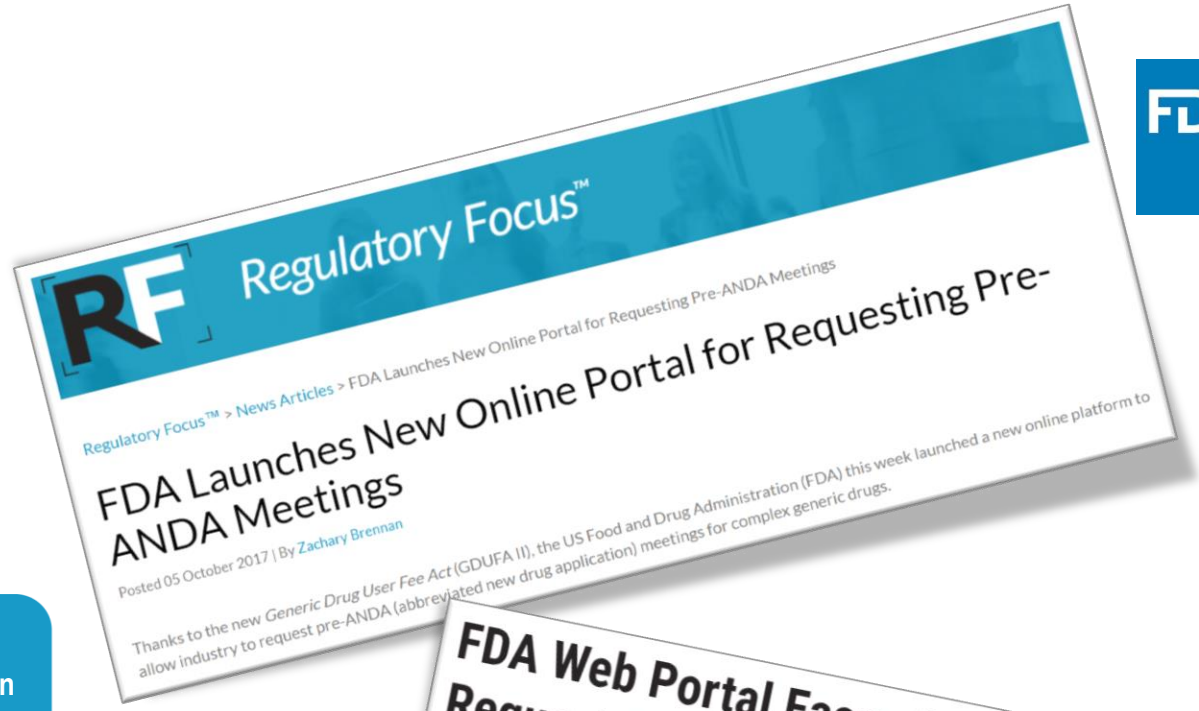


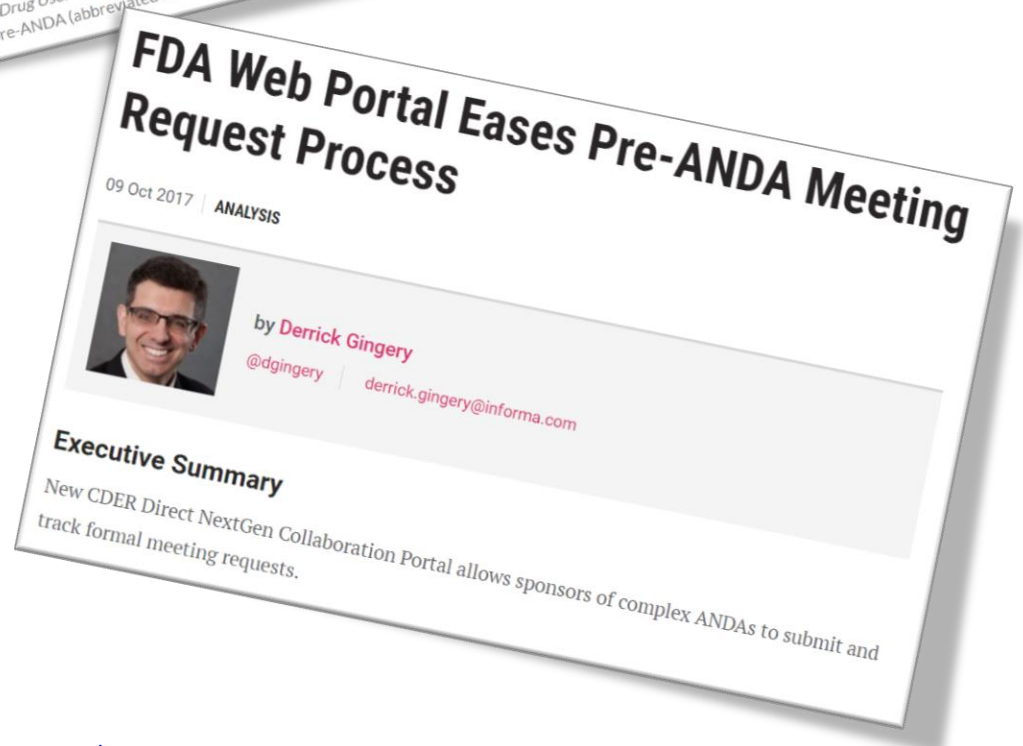
WHAT ARE PEOPLE SAYING?

"This tool seems really helpful and like it will change how we communicate with Industry."

"This is really impressive and could be used for so many other communications."

"I love that all communications are in one place for the user."





https://pink.pharmaintelligence.informa.com/PS121719/FDA-Web-Portal-Eases-PreANDA-Meeting-Request-Process

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CDER'S VISION – WHERE CAN THE COLLABORATION PORTAL TAKE US?

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- **Administrative changes:** use a tailored interface to update responsible official, address, etc., rather than a using a "one size fits all" form
- **Information request:** capture the complete chronological view of the back-and-forth involved in information requests and responses

THANK YOU