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
eCTD Metrics and Challenges

Association for Accessible Medicines
GRx + Biosims 2018

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

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

Rejected vs Received (May thru July)

- **DMF V**: 151 (10%)
  - 10 (6.6%)
- **DMF IV**: 282 (30)
  - 30 (10.6%)
- **DMF II**: 120 (2.79%)
- **IND**: 109 (0.6%)

**Tot Rej**: 19237

**Received**: 4294
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
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.
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)
Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```xml
<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)**

```xml
<application-information application-type="">
  <submission submission-type="amendment">
    <sequence-number>123</sequence-number>
    <related-sequence-number>456</related-sequence-number>
  </submission>
</application-information>
```

**Form 356h**

- Indicating “Amendment”
- Indicating “Initial Submission”

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)**

```xml
<submission-information>
  <submission-id submission-type="fdast1">XXXX</submission-id>
  <sequence-number submission-sub-type="fdasst4">XXXX</sequence-number>
</submission-information>
```

**Form 356h**

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
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.


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
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

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

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

**Note:**
- One drug application could contain multiple submissions throughout its review lifecycle, 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
**TABLE 10 – BE STUDY INFORMATION**

- Provide a separate table for each bioequivalence study.
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

<table>
<thead>
<tr>
<th>Issue</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitting revised content under same sequence number (e.g. trying to swap out a sequence)</td>
<td>Content should be updated by submitting changes in the next available sequence</td>
</tr>
<tr>
<td>Transfer of application but new owner is not aware of sequence numbers used</td>
<td>Recommend obtaining full sequence history from prior owner</td>
</tr>
<tr>
<td>Re-using a sequence number if submission has been withdrawn</td>
<td>Even if a submission is withdrawn, FDA continues to keep the sequence</td>
</tr>
</tbody>
</table>
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
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

✔ 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 I request an application number?
- How do I get a gateway account?

These questions and more are answered on the eCTD website:
WHERE TO GET HELP

- Specification documents are posted on [www.fda.gov/ectd](http://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
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
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**. CDER aims to reshape these interactions.

- 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?

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

**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?

Drug Shortage Notifications
Jan ‘17

Pre-ANDA meetings
Oct ‘17

Company Affiliation
May ‘18

Controlled Correspondence
Oct ‘18

Pre-assignment numbers
TBD
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

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

**Future**

**Advanced Authentication**

Achieve assurance levels using self service “identity proofing”

- 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.
EARLY SUCCESS FOR THE COLLABORATION PORTAL

248
Unique Users

148
Registered Companies

495
Drug Shortages Notifications

49
Meeting Requests

Login Requests

Submissions

Drug Shortages
Meeting Request

Drug Shortages
Meeting Request
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.”
Collaboration in the cloud is an evolution for efficiency in our communications. It’s an enabling technology that paves the way for significant improvements in the regulatory process.

Some aspirational business process transformations:

- **356h online**: enter key data once rather than re-sending with each submission
- **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