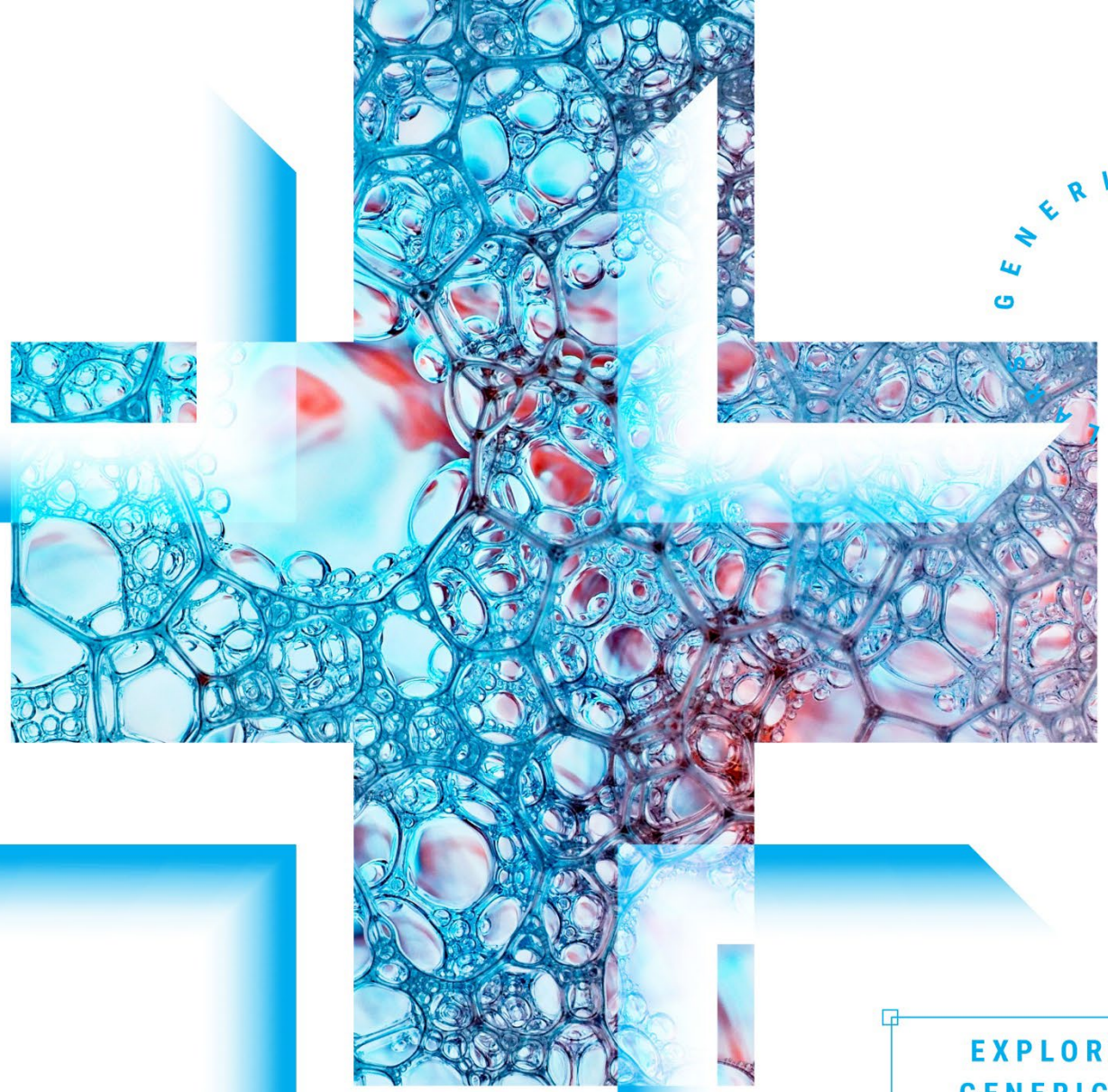


GENERICS AND BIOSIMILARS

GRx+ Biosims™

EXPLORING THE FUTURE OF
GENERICS AND BIOSIMILARS

#GRXBIOSIMS

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Update on eCTD Submissions

Heather Crandall
Business Informatics Specialist
CDER/OSP/OBI

October 21, 2024

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.

Agenda

- What's New?
- Common Errors for ANDAs

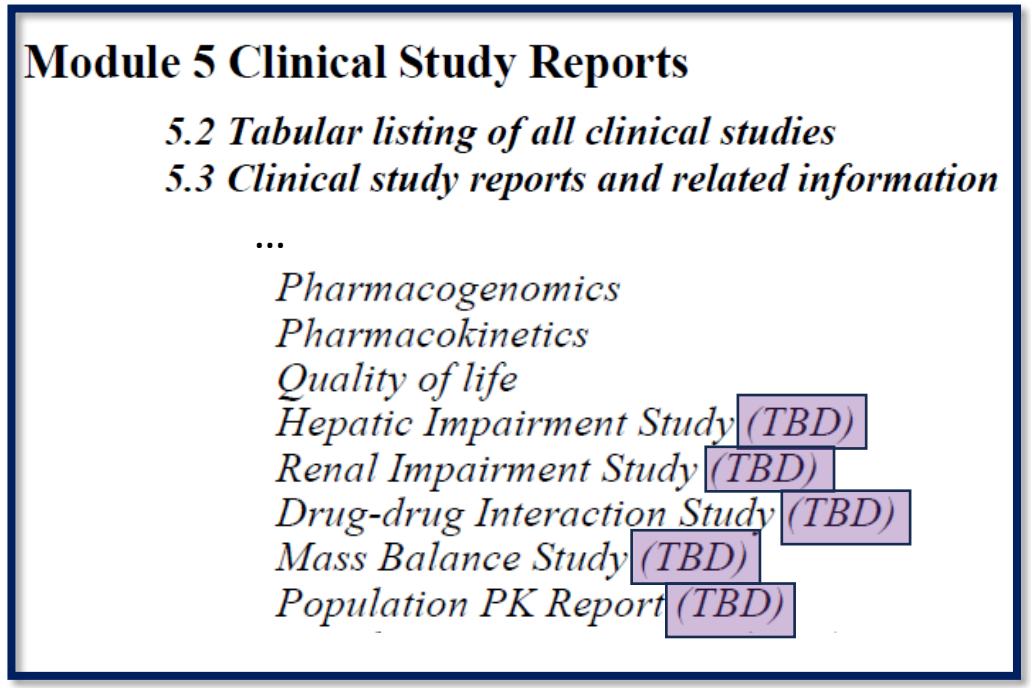
What's New for 2024?

What's New?

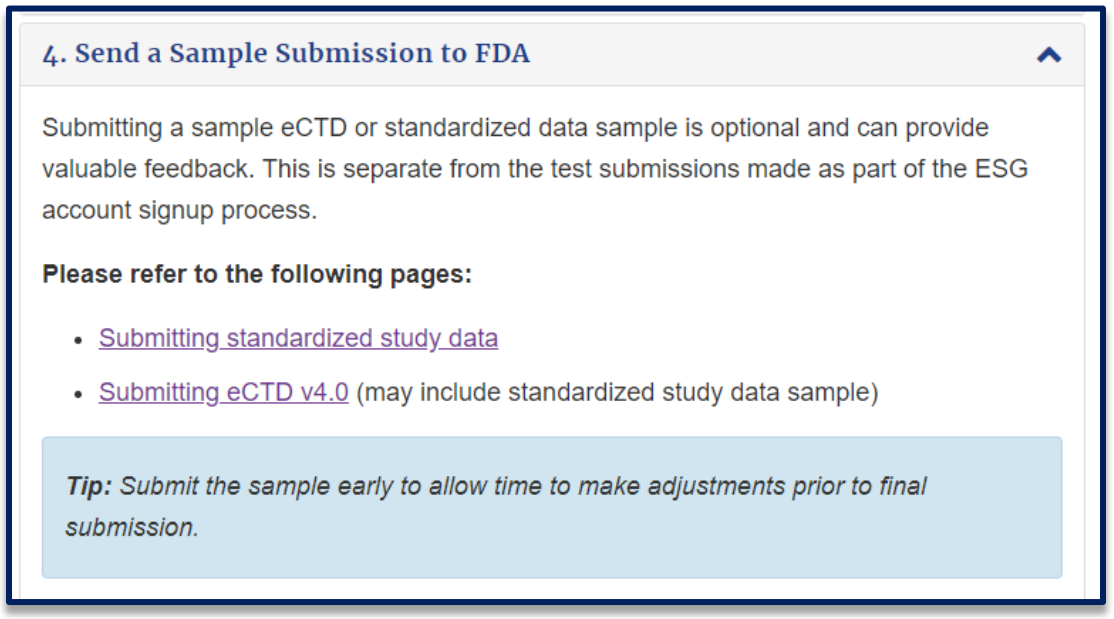
eCTD Submission Standards for eCTD v3.2.2 and Regional M1

- 03/20/2024 – Updates to File Format Specification
  - **Removed recommendation to include PDF archive format copy** when submitting .doc/.docx, .xls/.xlsx
  - Updated file format added:
    - Modeling & Simulation file types: .pumascp, .jmd, .qmd

- 09/09/2024 – Updates to
  - Version of Lorenz tool
  - eCTD Technical Conformance Guide
    - As of April 1, 2024, FDA published final guidance "Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry", which provides a new method to submit these reports
  - Comprehensive Table of Contents Headings and Hierarchy
    - adding Valid-Values.xml v6.0 (support date TBD)



What's New?



4. Send a Sample Submission to FDA

Submitting a sample eCTD or standardized data sample is optional and can provide valuable feedback. This is separate from the test submissions made as part of the ESG account signup process.

Please refer to the following pages:

- Submitting standardized study data
- Submitting eCTD v4.0 (may include standardized study data sample)

***Tip:** Submit the sample early to allow time to make adjustments prior to final submission.*

Submit a Standardized Data Sample to FDA

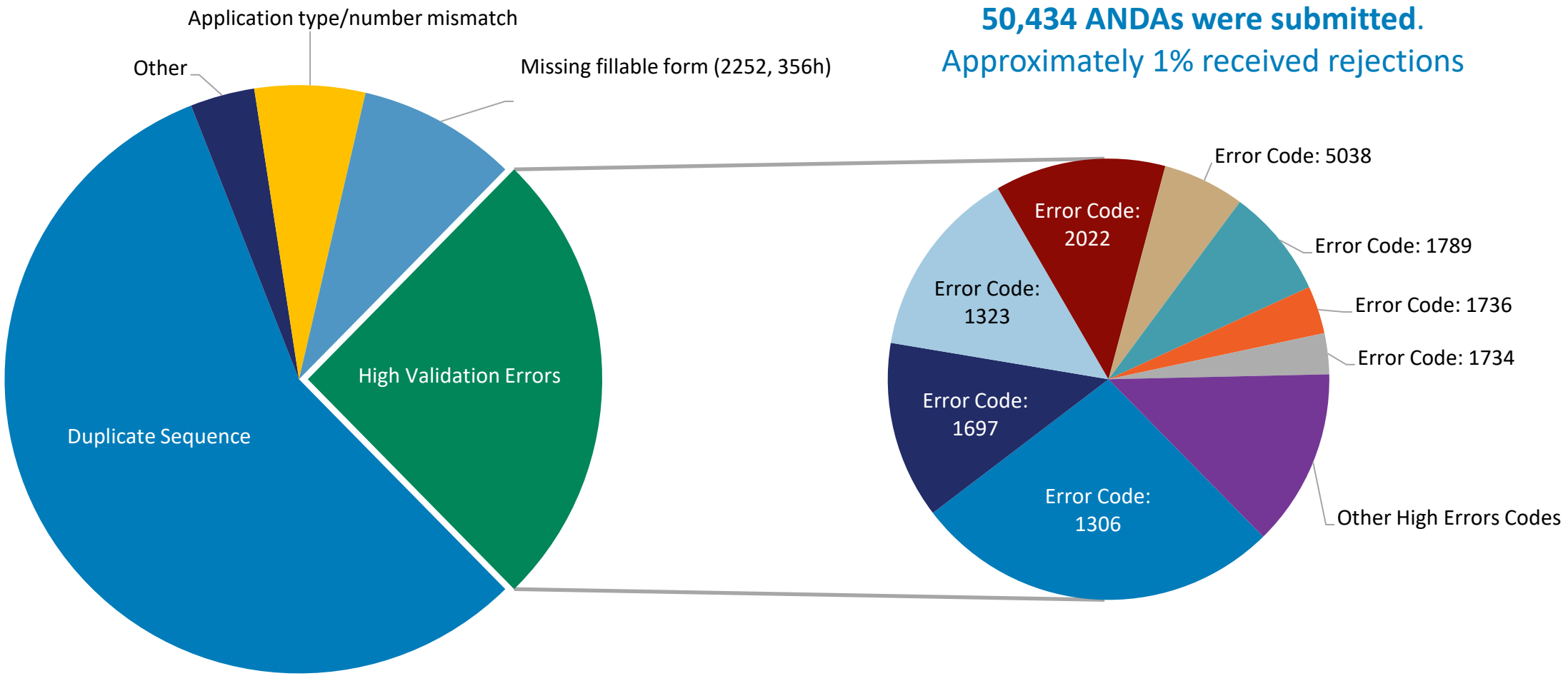
Formerly "Submit **an eCTD** or Standardized Data Sample to FDA"

- FDA now encourages all eCTD samples to be in v4.0 format
- Standardized data samples can be submitted for sample evaluation and feedback utilizing **either** v3.2.2 or v4.0 format

Common Errors for ANDAs

Top Reasons for ANDA eCTD Rejection

From January 1, 2024 through September 30, 2024
50,434 ANDAs were submitted.
Approximately 1% received rejections



Duplicate Sequence Numbers

- From January 1 through September 30, 2024, **472 ANDA applications were rejected** for duplicate sequence numbers
  - All sequence numbers, including sequence numbers for child applications in a grouped submission must be unique

- Sequence numbers for a given application **must** be unique
  - The sequence-number element is used to uniquely identify each individual submission to an application. It must be a unique number with a maximum of four (4)-numeric digits – The eCTD Backbone Files Specification for Module 1

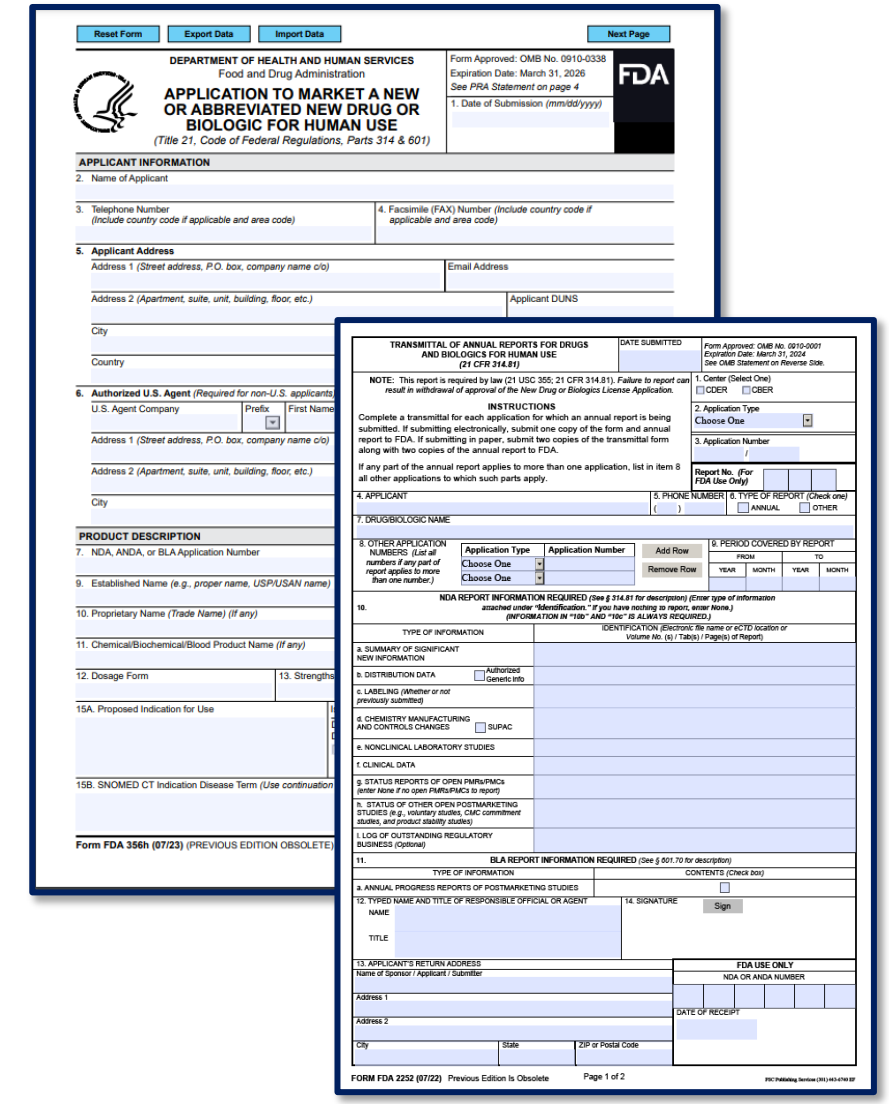
Leaf element errors

```
<m5-clinical-study-reports>
    <m5-3-clinical-study-reports>
    <m5-3-5-reports-of-efficacy-and-safety-studies indication = "pain">
        <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
            <leaf ID="a123458" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "a4529c4a257f07f8a0ec591dde854578" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                stud/pain/pain-sr1.pdf">
                <title>pain study report 1</title>
            </leaf>
        </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
    </m5-3-5-reports-of-efficacy-and-safety-studies>
    <m5-3-5-reports-of-efficacy-and-safety-studies indication = "nausea">
        <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
            <leaf ID="a123459" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "c5c39f594b2070a57bea66e58860efcf" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                stud/nausea/nausea-sr15.pdf" >
                <title>nausea study report 15</title>
            </leaf>
            <leaf ID = "a123460" operation = "new" xlink:type = "simple" checksum-type = "md5" checksum
                = "15faf198015f3599acabb7755c2d6b0c" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-
                safety-stud/nausea/5351-stud-rep-contr/xyz0015/nausea-sr15.pdf">
                    <title>nausea study report 15</title>
            </leaf>
        </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
    </m5-3-5-reports-of-efficacy-and-safety-studies>
    </m5-3-clinical-study-reports>
</m5-clinical-study-reports>
```

- From January 1 through September 30, 2024, **82 ANDA applications were rejected** for leaf element errors
  - A leaf element is “Information for an individual document is contained in the leaf element, its attributes, and its title element.” – The eCTD Backbone Files Specification for Module 1
  - Validation Code 1306 - No leaf element for file
  - Validation Code 1323 – No file for leaf element

No fillable form

- From January 1 through September 30, 2024, **81 ANDA applications were rejected** for fillable form errors
  - Annual Report submissions must have a fillable 2252 form
  - All other ANDA submissions must have a fillable 356h form



Submission type/sub-type mismatch

- From January 1 through September 30, 2024, **25 ANDA applications were rejected** for invalid submission type/sub-type designation
  - Full listing of the allowed submission type/sub-type combinations is in The eCTD Backbone Specifications for Module 1

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	

No Study Tagging File reference

- From January 1 through September 30, 2024, **16 ANDA applications were rejected** not referencing a study file in a study tagging xml

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Single dose oral toxicity study in the mouse and dog</title>
        <study-id>jm-12-345</study-id>
        <category name="species" info-type="ich">mouse</category>
        <category name="species" info-type="ich">dog</category>
        <category name="route-of-admin" info-type="ich">oral</category>
    </study-identifier>
    <study-document/>
</ectd:study>
```

- Study Tagging Files are **required for all Module 4 and Module 5 sections except** 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports

Resources

- Contact us:
  - eCTD and electronic submission questions: esub@fda.hhs.gov
  - Standardized study data questions: edata@fda.hhs.gov

- eCTD
  - Web page for latest version of eCTD guidance, specifications, and validations
  - eCTD v3.2.2 Comprehensive Table of Contents Headings and Hierarchy
  - eCTD v3.2.2 Technical Conformance Guide
  - The eCTD Backbone Files Specification for Module 1
  - Specifications for File Format Types

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