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Center for Drug Evaluation and Research

Update on eCTD Submissions

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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)

Module 5 Clinical Study Reports

- 5.2 *Tabular listing of all clinical studies*
- 5.3 *Clinical study reports and related information*
- ...
- Pharmacogenomics*
- Pharmacokinetics*
- Quality of life*
- Hepatic Impairment Study* (TBD)
- Renal Impairment Study* (TBD)
- Drug-drug Interaction Study* (TBD)
- Mass Balance Study* (TBD)
- Population PK Report* (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

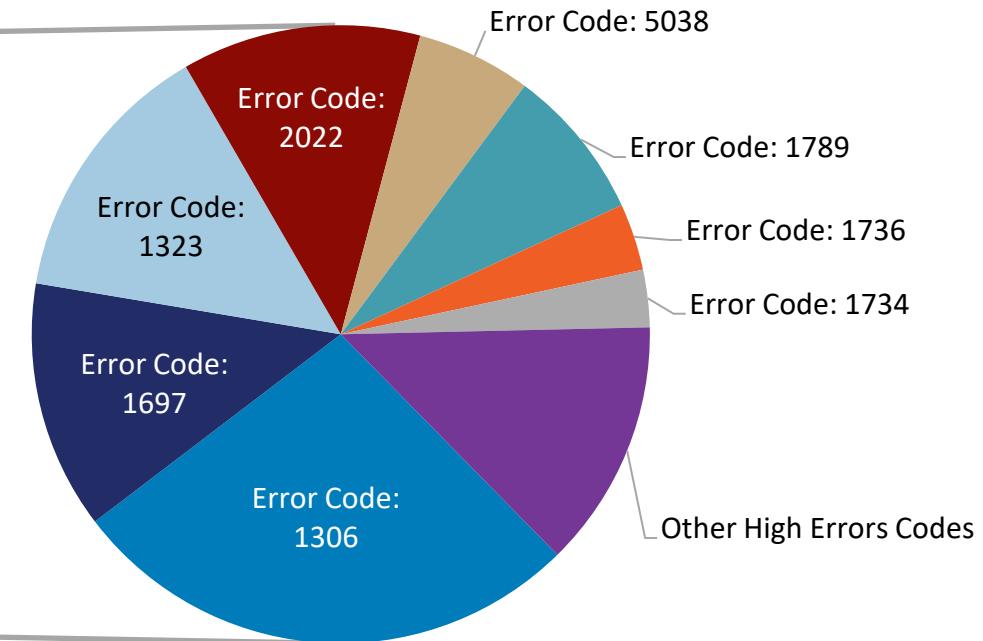
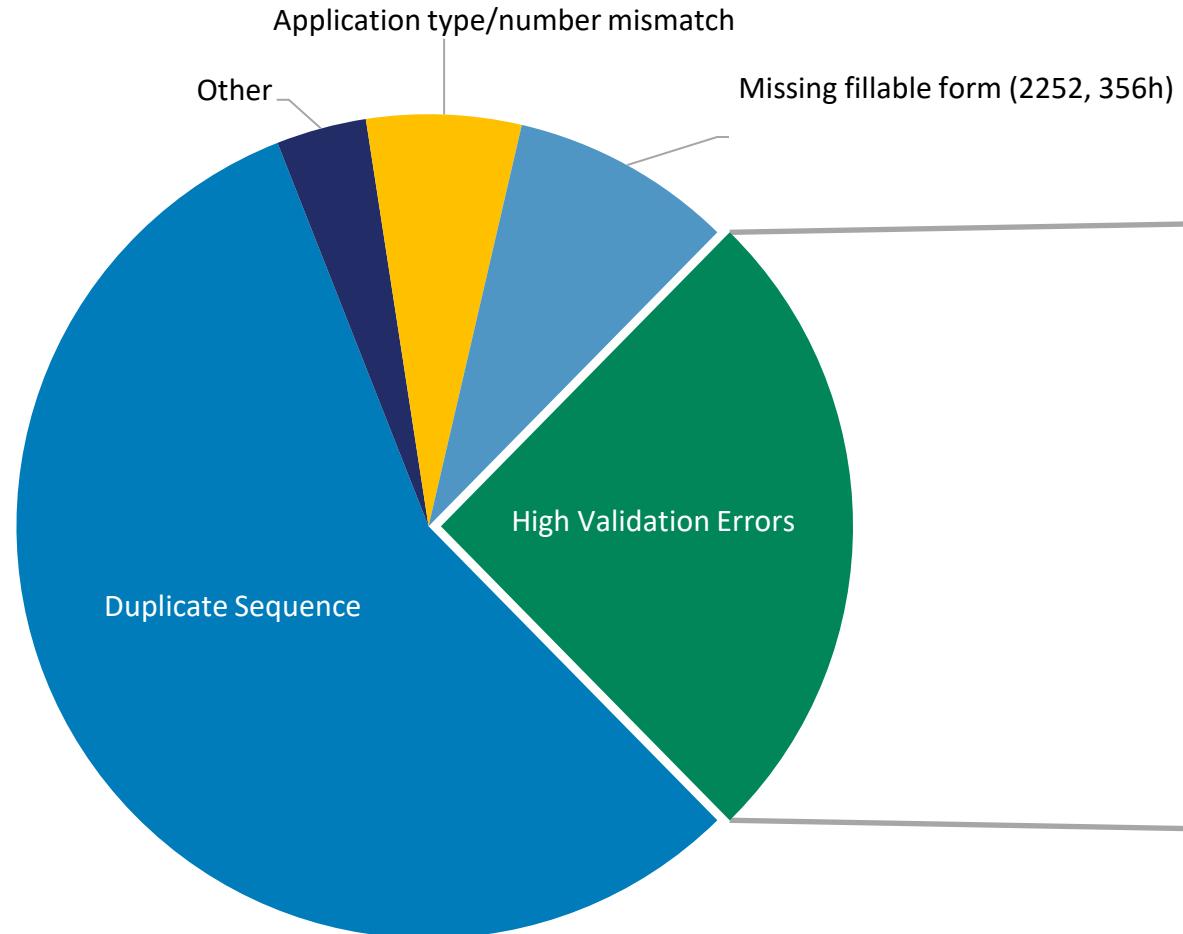
Top Reasons for ANDA eCTD Rejection

FDA

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/535rep-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/535rep-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/535rep-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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4
1. Date of Submission (mm/dd/yyyy)

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

APPLICANT INFORMATION
2. Name of Applicant

3. Telephone Number (Include country code if applicable and area code) 4. Facsimile (FAX) Number (Include country code if applicable and area code)

5. Applicant Address
Address 1 (Street address, P.O. box, company name c/o) Email Address
Address 2 (Apartment, suite, unit, building, floor, etc.) Applicant DUNS

City
Country

6. Authorized U.S. Agent (Required for non-U.S. applicants)
U.S. Agent Company Prefix First Name
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)

City

PRODUCT DESCRIPTION
7. NDA, ANDA, or BLA Application Number

8. OTHER APPLICATION NUMBERS (List numbers of any other application to FDA if applicable to more than one number)
Choose One Application Type Application Number Add Row Remove Row
Choose One

9. Established Name (e.g., proper name, USP/USAN name)

10. Proprietary Name (Trade Name) (if any)

11. Chemical/Biochemical/Blood Product Name (if any)

12. Dosage Form 13. Strengths

15A. Proposed Indication for Use

15B. SNOMED CT Indication Disease Term (Use continuation)

Form FDA 356h (07/23) (PREVIOUS EDITION OBSOLETE)

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS AND BIOLOGICS FOR HUMAN USE
(21 CFR 314.81)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4

NOTE: This report is required by law (21 U.S.C. 356, 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug or Biologics License Application.

INSTRUCTIONS
Complete a transmittal for each application for which an annual report is being submitted. If submitting electronically, submit one copy of the form and annual report to FDA. If submitting in paper, submit two copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 8 all other applications to which such parts apply.

4. APPLICANT 5. PHONE NUMBER 6. TYPE OF REPORT (Check one)
Report No. (For FDA Use Only) () ANNUAL OTHER

7. DRUG/BIOLOGIC NAME

9. PERIOD COVERED BY REPORT
FROM TO
YEAR MONTH YEAR MONTH

8. OTHER APPLICATION NUMBERS (List numbers of any other application to FDA if applicable to more than one number)
Choose One Application Type Application Number Add Row Remove Row
Choose One

10. PROPRIETARY NAME (Trade Name) (if any)

11. CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

12. DOSAGE FORM 13. STRENGTHS

15A. PROPOSED INDICATION FOR USE

15B. SNOMED CT INDICATION DISEASE TERM (Use continuation)

11. BLA REPORT INFORMATION REQUIRED (See § 314.81 for description) (Enter type of information attached under "Identification" if you have more than one, enter None.)
INFORMATION IN "BLA" AND "ANDA" IS ALREADY RECEIVED
TYPE OF INFORMATION
a. SUMMARY OF SIGNIFICANT NEW INFORMATION
b. DISTRIBUTION DATA
c. LABELING (Whether or not previously submitted)
d. CHEMICAL MANUFACTURING AND CONTROLS CHANGES
e. NONCLINICAL LABORATORY STUDIES
f. STATUS REPORTS OF OPEN PMR/UPMC
g. STATUS OF OTHER OPEN POSTMARKETING STUDIES (including PDUFA Commitment studies, and product stability studies)
h. LOG OF OUTSTANDING REGULATORY BUSINESS (optional)

12. BLA REPORT INFORMATION REQUIRED (See § 314.70 for description)
TYPE OF INFORMATION
a. ANNUAL PROGRESS REPORTS OF POSTMARKETING STUDIES
b. TREATMENT AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
NAME
TITLE

13. SIGNATURE
NAME
TITLE

14. SIGNATURE
NAME
TITLE

15. APPLICANT'S RETURN ADDRESS
Name of Sponsor / Applicant / Submitter
Address 1
Address 2
City State ZIP or Postal Code

FDA USE ONLY
NDA OR ANDA NUMBER
DATE OF RECEIPT

FORM FDA 2252 (07/22) Previous Edition Is Obsolete Page 1 of 2

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 <i>submission-sub-type</i> = “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 Effectuated (CBE-0), or Changes Being Effectuated 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](#)