Submitting Data to CDER: Requirements for your Application

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FDA Disclaimer

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Agenda

- Electronic Submissions to CDER
- eCTD Requirements
- Study Data Requirements
- Addressing the Most Common Error Reason
Requirements for Electronic Submissions

- Electronic submissions to CDER must conform to standards in the FDA Data Standard Catalog

- Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that submissions under section 505(b), (i), or (j) of the FD&C Act and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act) be submitted in electronic format.

- Submissions to NDA, BLA, ANDA, Commercial IND and Master Files* must be in eCTD format.

*excluding Non-Commercial IND and DMF Type III
Electronic Submissions to CDER

Electronic submissions can be submitted to CDER in one of two ways:

- **Electronic Submission Gateway (ESG)**
  - eCTD submission to NDA, BLA, ANDA, IND, DMF applications
  - Non-eCTD submission to Research IND applications
  - Non-eCTD submission to applications granted eCTD Waiver

- **CDER NextGen**
  - Non-eCTD submission to Research IND applications
  - Non-eCTD submission to applications granted eCTD Waiver
  - Non-eCTD submission of EUA or Pre-submission Correspondence

**eCTD is the standard format for submitting applications, amendments, supplements, and reports to CDER**
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
Study Data Requirements

- **Study Data Guidance** specifies that study data submitted to CDER must be in standardized format:
  - For NDAs, BLAs, ANDAs, studies that started after Dec. 17th, 2016
  - For Commercial INDs, studies that started after Dec. 17th, 2017

- Clinical Data Interchange Standards Consortium (CDISC) study data standards:
  - Study Data Tabulation Model (SDTM) for clinical trial tabulations data
  - Standard Exchange for Nonclinical Data (SEND) for non-clinical trial tabulations data
  - Analysis Data Model (ADaM) for clinical trial analysis data

- Study datasets should be provided in .xpt format
eCTD Placement of Study Data Files

- Most study data files should be submitted in eCTD Module 4 (non-clinical) and Module 5 (clinical).
- The proper placement of the datasets should follow the Comprehensive Table of Headings and Hierarchy.

The eCTD File Format Types Specifications provides accepted file types and proper eCTD locations for those file types. Examples include:

<table>
<thead>
<tr>
<th>File Type</th>
<th>File Format</th>
<th>Format Name</th>
<th>Accepted eCTD location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modeling and Simulation</td>
<td>.rmd</td>
<td>R Markdown file</td>
<td>M5</td>
</tr>
<tr>
<td>Modeling and Simulation Reporting</td>
<td>.r</td>
<td>R Script file</td>
<td>M3 – M5</td>
</tr>
</tbody>
</table>

The CTD File Format Types Specifications provides accepted file types and proper eCTD locations for those file types. Examples include:

Module 4 - Non-clinical studies and components such as reports, datasets, protocols, etc.
Example:

- 4.2.3 Toxicology
  - 4.2.3.1 Single dose toxicity
  - 4.2.3.2 Repeat dose toxicity

Module 5 - Clinical studies and components such as reports, datasets, protocols, etc.
Example:

- 5.3.1 Biopharmaceutic Studies
  - 5.3.1.1 Bioavailability (BA) Study reports
  - 5.3.1.2 Comparative BA and bioequivalence (BE) Study reports
eCTD & Study Data Resources

- **eCTD Technical Conformance Guide** (eCTD TCG) provides technical recommendations for submitting files in eCTD

- **Technical Rejection Criteria for Study Data** (TRC) provides the conditions under which FDA will not accept submissions with study data

- **Study Data Technical Conformance Guide** (SD TCG) provides technical recommendations for submitting study data according to CDISC standards
  - Planning and Providing Standardized Study Data
  - Exchange Format: Electronic Submissions
  - Study Data Submission Format: Clinical and Nonclinical
  - Therapeutic Area Standards
  - Terminology
  - Electronic Submission Format
  - Study Data Validation and Traceability
Overview of Technical Rejection Criteria

The TRC are eCTD validation criteria to determine compliance with requirements for submitting standardized study data in required sections in Modules 4 and 5, including:

- 4.2.3.1, 4.2.3.2, 4.2.3.4
- 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)</th>
<th>Severity Level</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>A dataset named ts.xpt with information on study start date must be present for each study in required sections</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>1735</td>
<td>The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
| 1736  | For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections  
For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections  
For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in Module 5 required sections | High           | Sept. 15, 2021 |

- Between September 15th and October 15th, 2021, 65% of TRC related rejections were caused by 1734 errors
Addressing the Most Common Error Reason
Causes of 1734 Errors

A dataset named ts.xpt with information on study start date must be present for each study in required sections*

- Trial Summary Dataset (ts.xpt) is present
- Study ID (or SPREFID) matches STF Study ID
- Study start date is provided (or TSVALNF = NA)
- Study start date is in a valid format

CDER Submissions: September 15th – October 15th 2021

15% of submissions with study data in TRC applicable sections

1734 Error Reasons**

- Missing TS File: 58%
- Study ID Mistmatch: 38%
- No Study Start Date: 3%
- Invalid Study Start Date: 1%
- Missing ts.xpt: 1%**

102 Studies in 45 Submissions with Error 1734 (September 15th – October 15th, 2021)

* Module 4 sections: 4.2.3.1, 4.2.3.2, 4.2.3.4
Module 5 sections: 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

**102 Studies in 45 Submissions with Error 1734 (September 15th – October 15th, 2021)
The Simplified ts.xpt Creation Guide

- Helps industry create simplified TS files using free and open-source software, R and Python
- Provides step by step instructions to install the necessary software
- Users can copy and paste code samples from the guide into R or Python
- Available on FDA’s web page, Study Data for Submission to CDER and CBER
- Demonstration video also available at Study Data for Submission to CDER and CBER
- Additionally, a publicly available tool was developed by PHUSE: Simplified ts.xpt File Generator (https://geotiger.shinyapps.io/07_genTS/)
Option 1: Use the Simplified ts.xpt Creation Guide

1. Copy and paste code from the Guide into R Editor to create a script

Table 2: Code for Creating ts.xpt Using R: Option B - Using the SASExport Package

<table>
<thead>
<tr>
<th>R Package</th>
<th>Clinical Study</th>
<th>Non-clinical Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#Load package</td>
<td></td>
<td></td>
</tr>
<tr>
<td>library(SASExport)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#Create data file</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abc&lt;-data.frame(STUDYID=&quot;XYZ123&quot;, TSPARMCD=&quot;SSTTDC&quot;, TSVAL=&quot;string(Date(&quot;YYYY-MM-DD&quot;), &quot;%Y-%m-%d&quot;), TSVALNF=&quot;NA&quot;, stringsAsFactors = FALSE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#Add labels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>label&lt;-'Trial Summary'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abcSTUDYID&lt;-&quot;Study Identifier&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abcSTSPARMCD&lt;-&quot;Trial Summary Parameter Short Name&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abcTSVALNF&lt;-&quot;Parameter Null Value&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Write data into spt format</td>
<td>Write data into spt format</td>
</tr>
<tr>
<td>abc&lt;-write.xpt(abc, file=&quot;C:/Simplest TS File/xpt.xpt&quot;)</td>
<td>abc&lt;-write.xpt(abc, file=&quot;C:/Simplest TS File/xpt.xpt&quot;)</td>
<td></td>
</tr>
</tbody>
</table>

2. Edit the Study ID

R Application

3. Edit the Study Start Date and TSVALNF Value

4. Edit where to save the file

www.fda.gov
Option 2: Use the PHUSE Utility

Example using the online PHUSE Utility to generate a Simplified TS File:

1. Enter the Study ID
2. Select the TSPARMCD Code
3. Enter the Study Start Date or TSVALNF Value
4. Download the file
References

❖ Study Data Standards Resources
  • Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [Jun 2021]
  • Study Data Technical Conformance Guide [Sep 2021]
  • FDA Data Standards Catalog [Sep 2021]
  • Link: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

❖ Study Data for Submission to CDER and CBER
  • Technical Rejection Criteria For Study Data [August 2021]
  • Technical Rejection Criteria Self-Check Worksheet
  • Technical Rejection Criteria Self-Check Worksheet Instructions
  • Link: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

❖ Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry
  • Link: Providing Regulatory Submissions in Electronic Format
Questions

For Questions Please Contact:

- Study Data Questions: edata@fda.hhs.gov
- eCTD Questions: esub@fda.hhs.gov
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