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A regulatory journey from PDUFA, FDASIA, and Guidances for standardized study data

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Agenda

• PDUFA and 745A
• Data Standards Requirements
• Study Data Technical Rejection Criteria
• Tools to Help Industry
A Brief History

PDUFA and 745A
Looking back to 2012...

**Problem to be Addressed**

- The extreme variability and unpredictability of the format and content of submitted application data present a major obstacle to timely, consistent, and efficient review within current PDUFA timeframes.

- Lack of standardized clinical data:
  - Limits ability to address in-depth questions and late-emerging issues in a timely manner.
  - Impedes timely safety analysis to inform REMS decisions.
  - Limits ability to transition to more standardized and quantitative approaches to benefit-risk assessment.

FDASIA/PDUFA V

- **PDUFA V goals** include a section “Improving the efficiency of human drug review through required electronic submissions and standardization of electronic drug application data”

- “Section 1136 of FDASIA amended the FD&C Act by adding section 745A, which addresses electronic submissions. ... Section 745A(a)(1) of the FD&C Act describes the general scope of section 745A(a) and provides that submissions under NDAs, ANDAs, BLAs, and INDs must be in electronic format specified in FDA guidance...”  
  Provided Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, Section II
Timeline of PDUFA & Guidances

- July 9, 2012 – FDASIA signed
- Oct 1, 2012 – PDUFA V begins
- December 16, 2014 – Study Data Guidance published
- May 5, 2015 – eCTD Guidance published
- December 2014 - Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act Guidance published
745A(a) Guidances

• FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry” in December 2014 (updated in June 2021)
  – Sponsors must conform to standards in the FDA Data Standards Catalog:
    • NDA, certain BLA, ANDA studies that started after December 17th, 2016
    • Commercial IND studies started after December 17th, 2017

  – Sponsors must submit in eCTD format:
    • NDA, certain BLA, ANDA applications starting May 5th, 2017
    • Commercial IND and certain MFs applications starting May 5th, 2018
Timeline of PDUFA & Guidances

- **2011**
  - July 9, 2012 – FDASIA signed
  - October 1, 2012 – PDUFA V begins
  - December 16, 2014 – Study Data Guidance published

- **2014**
  - July 9, 2012 – FDASIA signed
  - December 16, 2014 – Study Data Guidance published

- **2015**
  - May 5, 2015 – eCTD Guidance published

- **2017**
  - August 2017 – FDARA signed
  - October 1, 2017 – PDUFA VI begins

- **2017**
  - December 2014 - Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act Guidance published

- **2021**
FDARA/PDUFA VI

- **PDUFA VI goals** include a section “Enhance transparency and accountability of FDA electronic submission and data standards activities”

- **Deliverables** include:
  - Public Meetings for Electronic Submissions and Data Standards
  - CBER-CDER Data Standards Program Action Plan
  - FDA Data Standards Catalog
  - Joint Quarterly Meetings to Enhance Transparency and Accountability of FDA Electronic Submission and Data Standards Activities
How does it all connect?

Data Standards Requirements
Timeline of data standards

- December 16, 2016 – study data standards requirement for NDAs, ANDAs, certain BLAs
- December 16, 2017 – study data standards requirement for commercial INDs
- May 5, 2017 – eCTD format requirement for NDAs, ANDAs, certain BLAs
- May 5, 2018 – eCTD format requirement for commercial INDs and certain MFs
eCTD Submission Metrics 2003 - 2020

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
FDA uses Lorenz docuBridge to support the review of eCTD formatted submissions.
# FDA Data Standards Catalog v7.2 (07-01-2021) - Supported and Required Standards

*For full description of column headings, see Instr.& Column Descriptions tab*

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<tr>
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<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Standards Development Organization (SDO)</th>
<th>Supported Version</th>
<th>Supported Implementation Guide Version</th>
<th>FDA Center(s)</th>
<th>Date Support Begins (MM/DD/YYYY)</th>
<th>Date Support Ends (MM/DD/YYYY)</th>
<th>Date Requirement Begins (MM/DD/YYYY)</th>
<th>Date Requirement Ends (MM/DD/YYYY)</th>
<th>Statutory, Regulatory, or Guidance Authority</th>
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<td>CDISC.org - ADaM</td>
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<td>Standardized Study Data</td>
<td>CDISC.org - SEND</td>
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</table>
Review of Study Data

FDA also utilizes multiple tools and systems to support analysis of standardized study data:

An unstandardized study cannot display with the same detailed information as a standardized study.
Review of Study Data

FDA also utilizes multiple tools and systems to support analysis of standardized study data:
Timeline of data standards

- December 16, 2016 – study data standards requirement for NDAs, ANDAs, certain BLAs
- December 16, 2017 – study data standards requirement for commercial INDs
- March 15, 2021 –
  - CBER begins support for SEND v1.5
  - CDER & CBER begin support for SDTM v1.7 and Define v2.1
- September 15, 2021 –
  - eCTD validation error codes 1734, 1735, 1736, and 1789 become effective
- May 5, 2017 – eCTD format requirement for NDAs, ANDAs, certain BLAs
- May 5, 2018 – eCTD format requirement for commercial INDs and certain MFs
How are we checking the Study Data Guidance requirements?

Validation, as listed in the Specification for eCTD Validation Criteria, occurs during this step (including 1734, 1735, and 1736).
Are You Ready?

Study Data Technical Rejection Criteria
Overview of TRC Errors

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

<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>
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<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>
<tr>
<td>1736</td>
<td>For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections*&lt;br&gt;For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections*&lt;br&gt;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*</td>
<td>High</td>
<td>Sept. 15, 2021</td>
</tr>
<tr>
<td>1789</td>
<td>A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports</td>
<td>High</td>
<td></td>
</tr>
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* 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
Relationship between the Technical Rejection Criteria for Study Data and the Specification for eCTD Validation Criteria

The Specification for eCTD Validation Criteria contains a total of 161 validations

46 are High severity, meaning failure of that validation leads to rejection

The Technical Rejection Criteria for Study Data provides additional detail on 4 of these validations (1734, 1735, 1736, 1789) to help industry understand under what conditions submission of study files will trigger them and criteria to pass
TRC Warning Notices (March 15 – August 15, 2021)

• 1734 is the most common failure reason, especially for Commercial IND submissions

• 1789 is the second largest failure reason and is particularly high for Commercial IND submissions

Note: Warnings generated by CDER between March 15th and August 15th, 2021
Validation Rule 1734

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

Submissions CY2021 (March 15 – August 15, 2021)

- 34% of submissions with Study Data in sdTRC applicable sections
- 83% of Study Errors: Missing TS File

1734 Error Reasons**

- Study ID Mismatch
- No Study Start Date (SSD)
- Invalid Study Start Date (SSD)
- Missing TS File

* 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

**1388 Studies in 528 Submissions with Error 1734 between March 15, 2021 and August 15, 2021
Validation Rule 1789

A file has been submitted in a study section without providing an STF file (STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports).

☑ All study files are included in a Study Tagging File (STF)

1789 errors are the second largest source of sdTRC failures*

Submission Types for 1789 Errors*

- 56% Commercial IND
- 54% Commercial IND

*117 1789 failures out of 751 total warning notices March 15 – August 15, 2021
Validation Rule 1735

The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*

- Standardized dataset domains (e.g., adsl.xpt, dm.xpt) are tagged as:
  - “data-tabulation-dataset-sdtm” for SDTM
  - “analysis-dataset-adam” for ADaM
  - “data-tabulation-dataset-send” for SEND

- Define.xml files are tagged as:
  - “data-tabulation-data-definition” for SDTM & SEND
  - “analysis-data-definition” for ADaM

ANDA submissions have the highest number of 1735 errors*

Submission Types for 1735 Errors*

- ANDA: 53%
- BLA: 4%
- NDA: 5%
- IND: 38%

*110 1735-only failures out of 751 total warning notices March 15 – August 15, 2021
Tools to Help Industry
The Self-Check Worksheet

- Designed to walk sponsors through each step of sdTRC validation process
- Dynamically guides sponsors through study data requirements based on study information entered
- Helps sponsors prepare study data to submit to the FDA for the first time

**Demonstration Videos & Other Supporting Material**

**Technical Rejection Criteria Self-Check Worksheet**

**Self-Check Worksheet Instructions**
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/)
References

- **Study Data Standards Resources** [https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources]
  - Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry [June 2021]
  - Study Data Technical Conformance Guide [August 2021]
  - FDA Data Standards Catalog [March 2021]

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

  - eCTD Submission Standards [August 2021]
  - Specifications for eCTD Validation Criteria [August 2021]

- **Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry** [https://www.fda.gov/regulatory-information/search-fda-guidance-documents]

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