FDA View:
Technical Rejection Criteria for Study Data

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Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

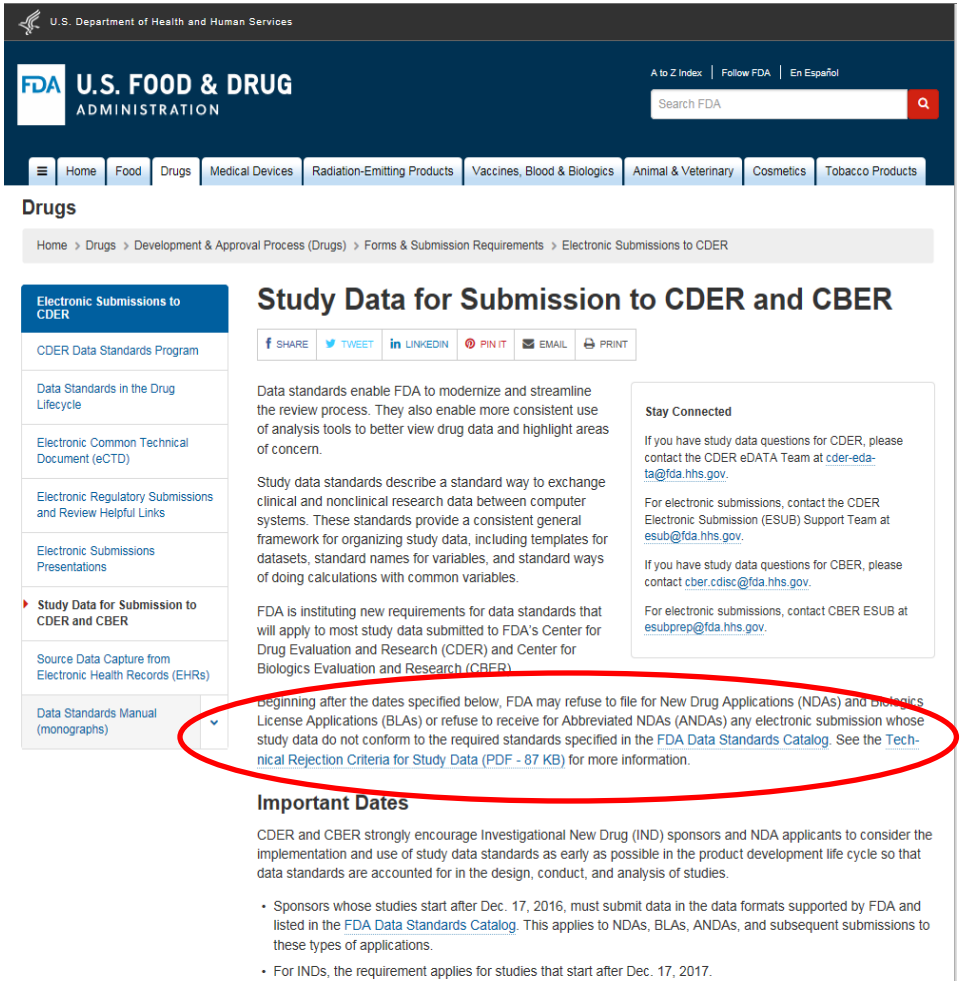
FDA Guidance and Data Standards Catalog

- **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.**
- **FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014.**
- **Sponsors must conform to standards in the FDA Data Standards Catalog:**
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017

Technical Rejection Criteria for Study Data

- FDA published "Technical Rejection Criteria for Study Data" which specified 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.



eCTD Study Data Validation Criteria and Severity Levels

High

1736: Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data;

DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data

High

1734: Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3

Medium

1735: Correct STF file-tags must be used for all standardized datasets in section 4.2 and 5.3

- Data-tabulations-dataset-sdtm
- Data-tabulations-dataset-send
- Analysis-dataset-adam

Medium

1737: For each study in eCTD section 4.2 and section 5.3, no more than one dataset of the same name should be submitted as new.

Study Data Conformance Analysis

- **Study Data was assessed regardless of Study Start Date for:**
  - 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
  - No duplicates
- **Conformance was checked against the two high-level errors as described in the Technical Rejection Criteria for Study Data**
  - 1734 – TS Dataset must be present
  - 1736 – DM Dataset, ADSL Dataset and define.xml must be present
- **Warnings 1735 and 1737 are used to assist the 1736 validation**
  - 1735 – Correct STF file must be used
  - 1737 – Only one dataset should be submitted as New

Overall Conformance Statistics

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

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

Note:

- One drug application could contain multiple submissions throughout its review life-cycle, 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 contains multiple studies can report both Errors 1734 and 1736

Common Technical Rejection Criteria Validation Error

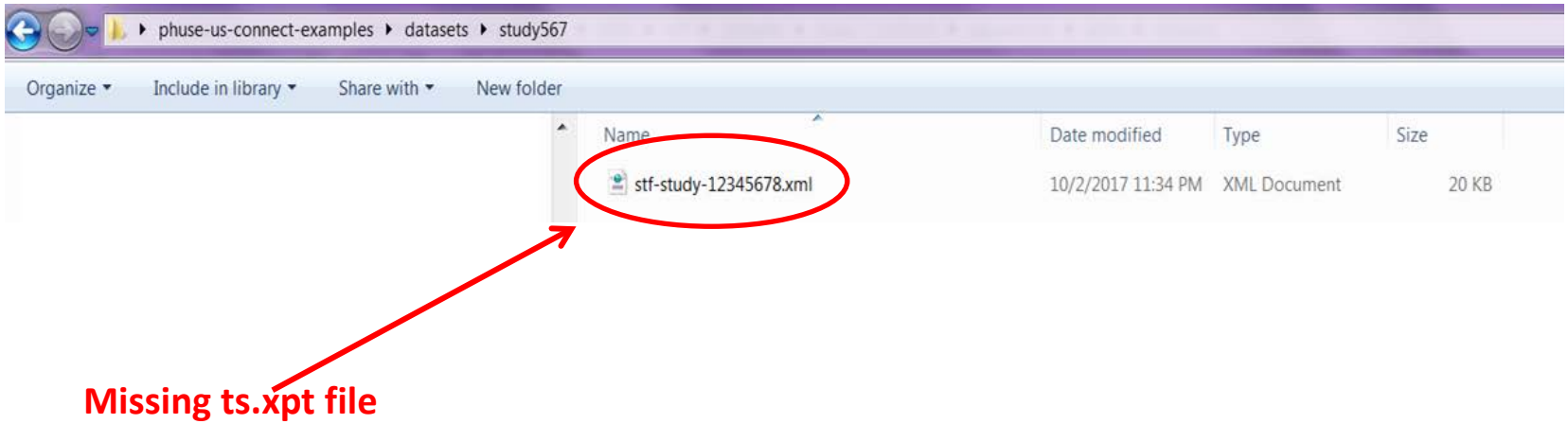
- **Top Errors for Error 1734 (968):**
  - Missing ts.xpt file for a study (753)
  - No Study Start Date (231)
  - Invalid Study Start Date. Study Start Date must be in the format of (yyyy-mm-dd) (75)
  - Study files in index.xml are not correctly linked to contents in study tag files (4)

- **Top Errors for Error 1736 (84):**
  - Missing adsl.xpt or corresponding define.xml for a study (52)
  - Study Definition File define.xml with file tag name related to analysis does not exist for a study (38)
  - Missing define.xml for a study (36)
  - Missing dm.xpt or corresponding define.xml for a study (23)

Note: Number in parentheses indicates the occurrence of the error type.

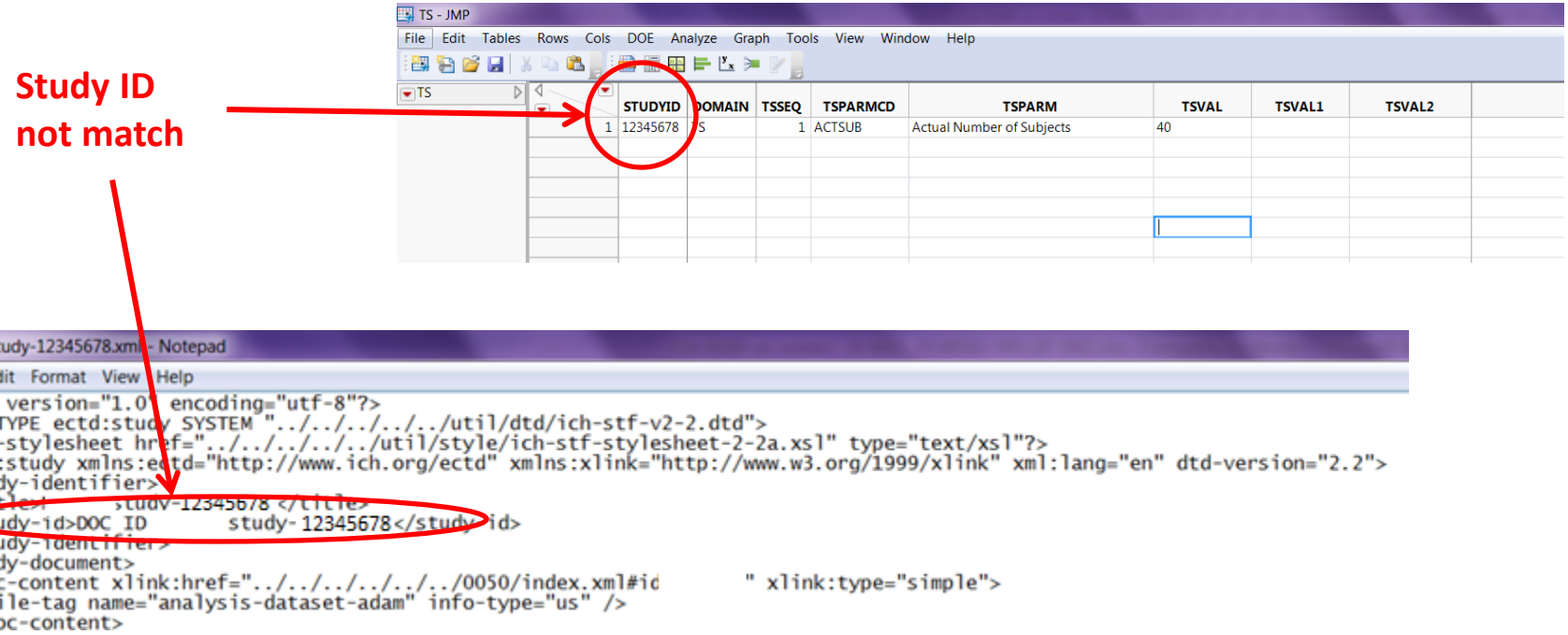
Rule 1734 Top Error Examples – Cont.

- **Missing ts.xpt file for a study (753): The validation tool cannot find the study start date to determine if the Technical Rejection Criteria is met or not.**
  - The ts.xpt file is missing in the current/previous submissions for a study



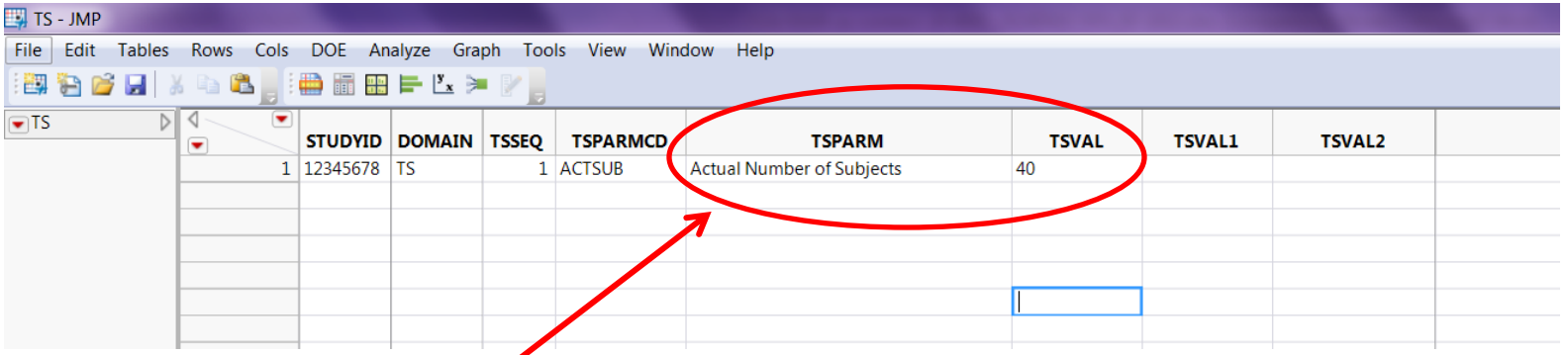
Rule 1734 Top Error Examples

- **Missing ts.xpt file for a study (753): The validation tool cannot find the study start date to determine if the Technical Rejection Criteria is met or not.**
  - ❑ The Study ID tag in the STF file does not match the study id in ts.xpt file



Rule 1734 Top Error Examples – Cont.

- **No Study Start Date records for study id in ts.xpt (231)**

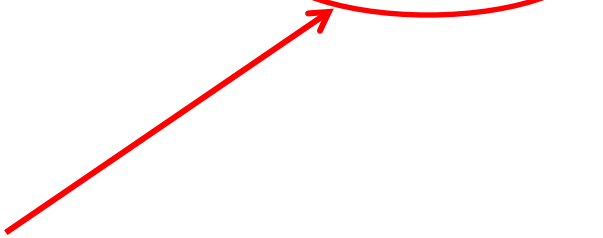


No study start date in ts.xpt

Rule 1734 Top Error Examples – Cont.

- **Invalid Study Start Date: Study Start Date must be in the format of (yyyy-mm-dd) (75)**

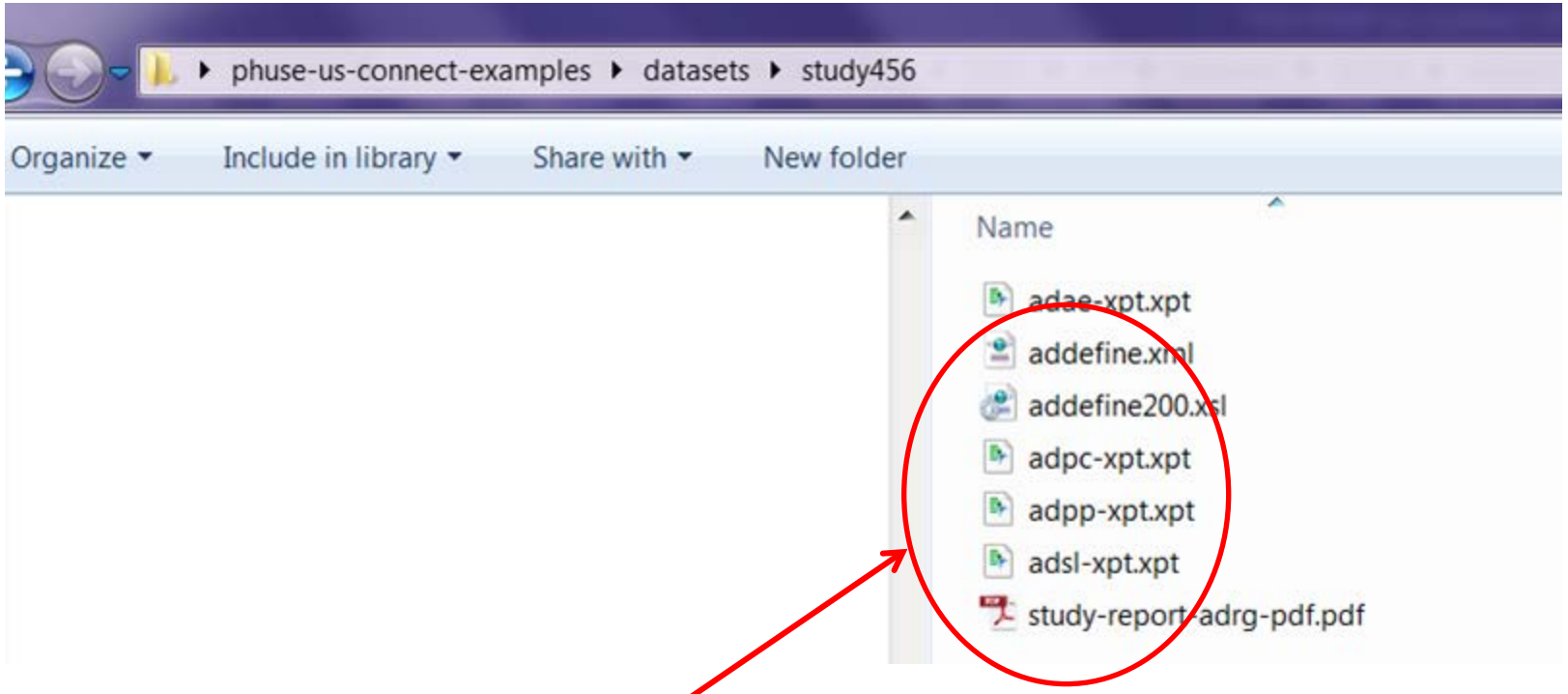
DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL
TS	1	SSTDTC	Study Start Date	42622



Incorrect Study Start Date format

Rule 1736 Top Error Examples

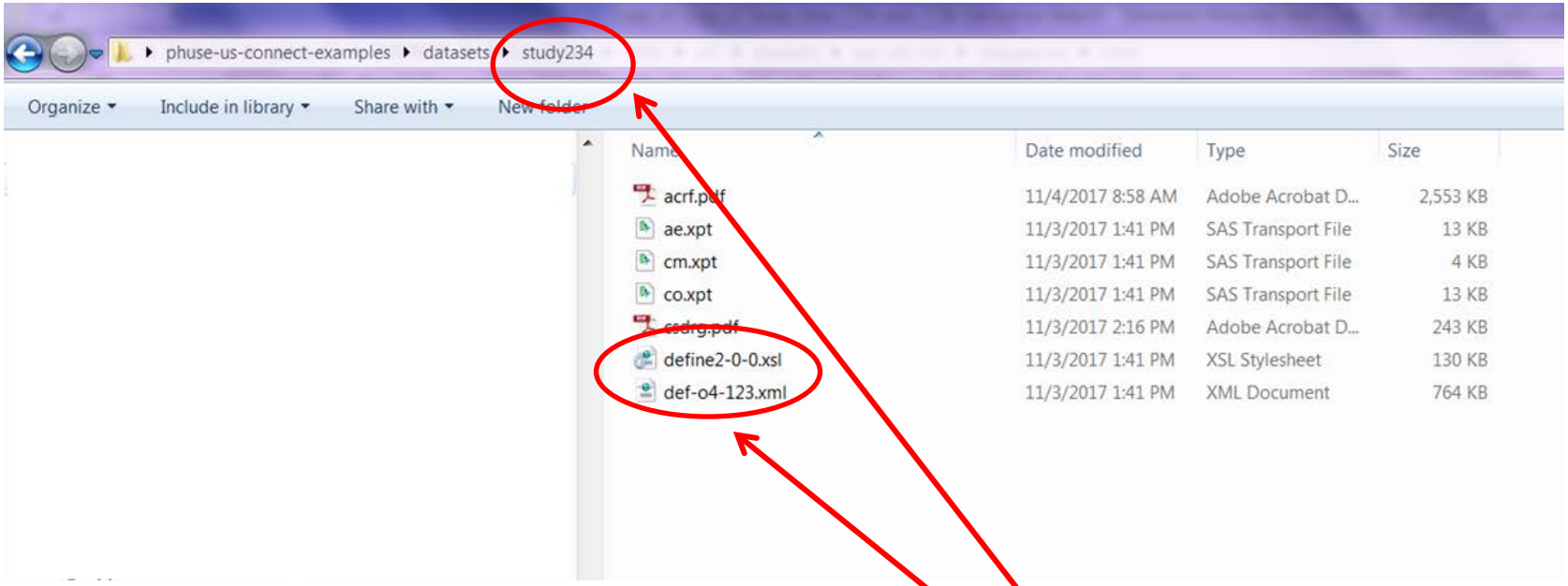
- **Missing adsl.xpt or define.xml for a study (52)**



The file adsl-xpt.xpt is in the submission, but not named as adsl.xpt

Rule 1736 Top Error Examples – Cont.

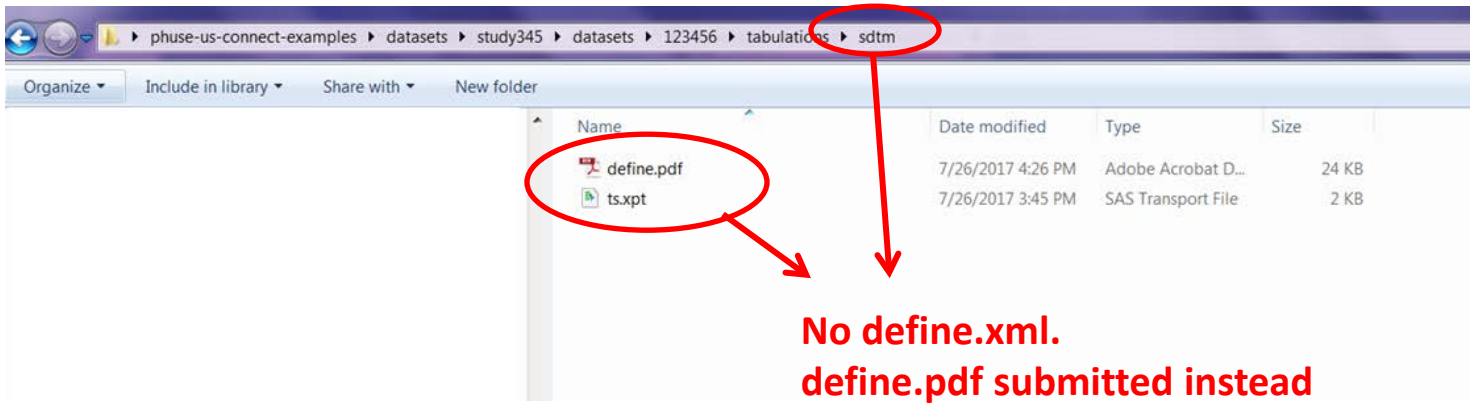
- **Missing define.xml for a study (36)**



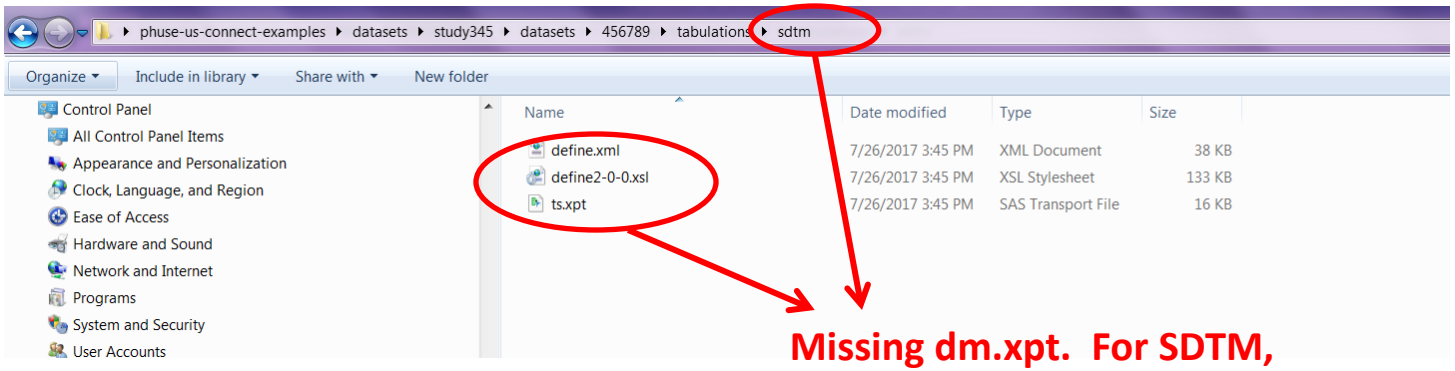
Missing define.xml for a study

Rule 1736 Top Error Examples – Cont.

- Missing define.xml for a study (36)
- Missing dm.xpt or corresponding define.xml for a study (23)



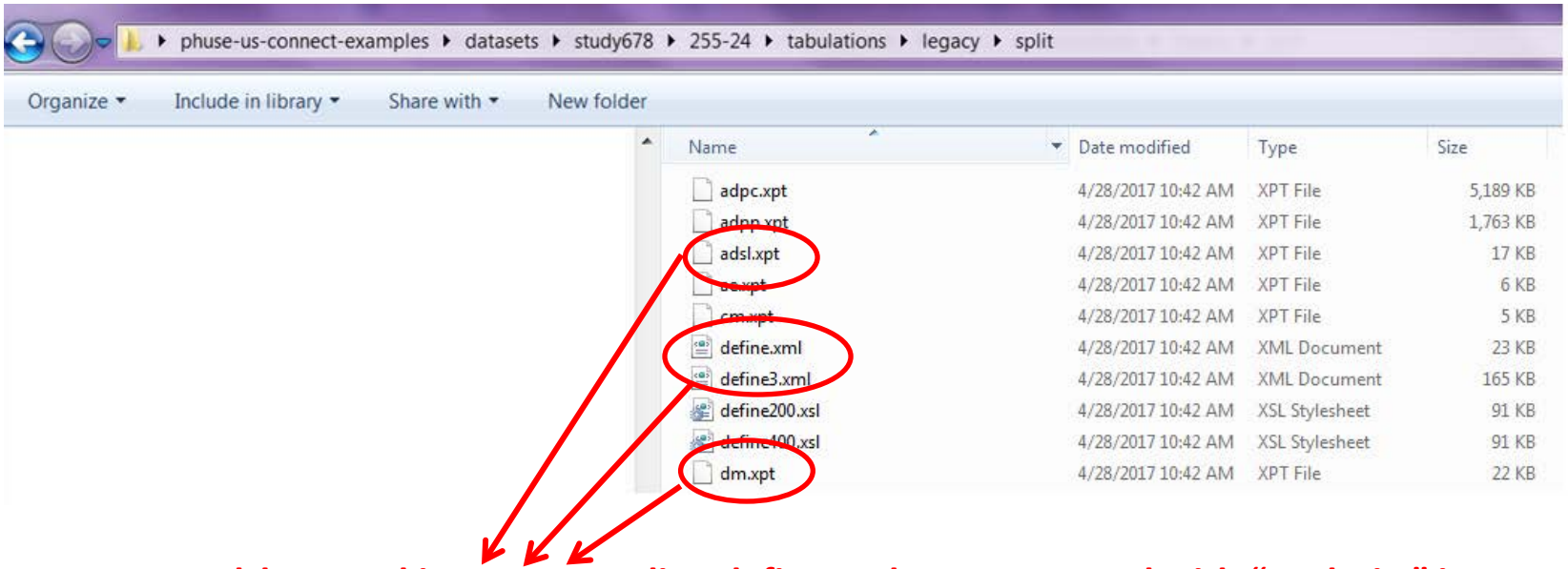
No define.xml.
define.pdf submitted instead



Missing dm.xpt. For SDTM, define.xml and dm.xpt need to exist.

Rule 1736 Top Error Examples – Cont.

- Missing adsl.xpt or corresponding define.xml for a study (52)
- Study Definition File define.xml with file tag name related to analysis does not exist for a study (38)



adsl.xpt and its corresponding define.xml are not tagged with "analysis-" in the stf file so they can not be easily identified.

Explanation: analysis data (eg. adsl.xpt) requires a define.xml file, which needs to be tagged as "analysis-", e.g. "analysis-data-definition" in the STF file

Summary

- Based on the analysis, less than 70% all submissions were received with non-critical errors. However, identified errors are not difficult to correct.
- FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog.
- FDA has not rejected any submission that contains errors as reflected in this analysis.
- FDA plans to use technical rejection criteria to identify applications that are not fulfilling this requirement.

TIP

To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.

References

- **"Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM292334.PDF

- **"Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM384686.PDF

- **"Technical Rejection Criteria For Study Data"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM523539.PDF

- **"Study Data Technical Conformance Guide"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM384744.PDF

- **"FDA Data Standards Catalog"**
  HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM

Recommended Reading:

- **For FDA instruction of Study Data submission, see the FDA "Study Data for Submission to CDER and CBER" page at:**
  HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM248635.HTM

- **For the full list of Study Data standards, see the FDA "Study Data Standards Resources" page at:**
  HTTP://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS

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