

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.

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Electronic Submissions to CDER

- CDER Data Standards Program
- Data Standards in the Drug Lifecycle
- Electronic Common Technical Document (eCTD)
- Electronic Regulatory Submissions and Review Helpful Links
- Electronic Submissions Presentations
- Study Data for Submission to CDER and CBER**
- Source Data Capture from Electronic Health Records (EHRs)
- Data Standards Manual (monographs)

Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the [FDA Data Standards Catalog](#). See the [Technical Rejection Criteria for Study Data](#) (PDF - 87 KB) for more information.

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cdet-edata@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact cbet.cdsc@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

Important Dates

CDER and CBER strongly encourage Investigational New Drug (IND) sponsors and NDA applicants to consider the implementation and use of study data standards as early as possible in the product development life cycle so that data standards are accounted for in the design, conduct, and analysis of studies.

- Sponsors whose studies start after Dec. 17, 2016, must submit data in the data formats supported by FDA and listed in the [FDA Data Standards Catalog](#). This applies to NDAs, BLAs, ANDAs, and subsequent submissions to these types of applications.
- For INDs, the requirement applies for studies that start after Dec. 17, 2017.

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

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)

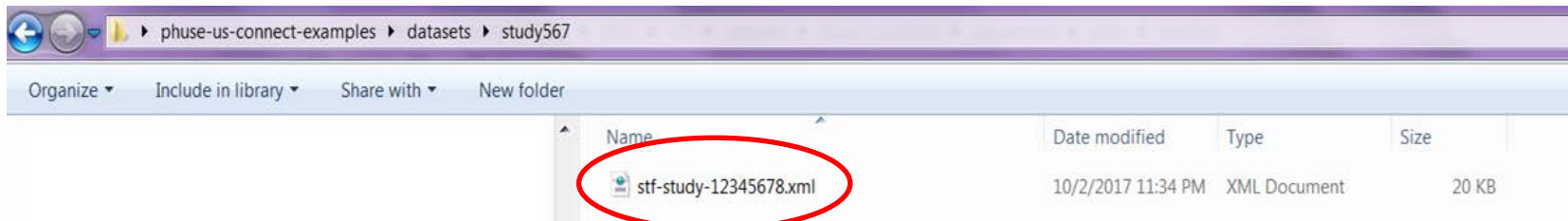
❖ Top Errors for Error 1736 (84):

- ☐ 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



Missing ts.xpt file

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

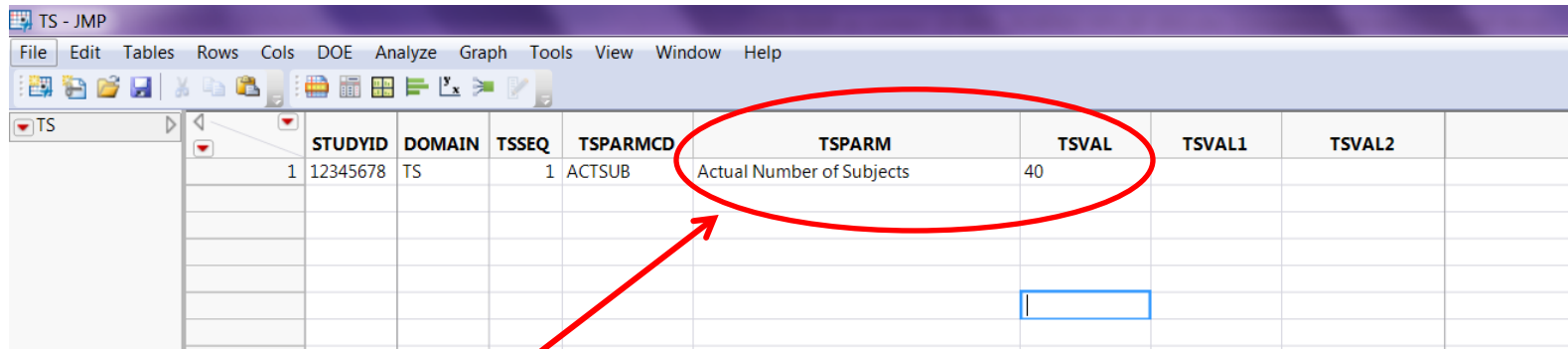
Study ID
not match

STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL	TSVAL1	TSVAL2
1 12345678	S	1	ACTSUB	Actual Number of Subjects	40		

```
<?xml version="1.0" encoding="utf-8"?>
<!DOCTYPE ectd:study SYSTEM "../../../../../util/dtd/ich-stf-v2-2.dtd">
<?xml-stylesheet href="../../../../../util/style/ich-stf-stylesheet-2-2a.xsl" type="text/xsl"?>
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xmlns:xlink="http://www.w3.org/1999/xlink" xml:lang="en" dtd-version="2.2">
  <study-identifier>
    <title> study-12345678 </title>
    <study-id>DOC ID study- 12345678</study-id>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="../../../../../0050/index.xml#id " xlink:type="simple">
      <file-tag name="analysis-dataset-adam" info-type="us" />
    </doc-content>
  </study-document>
</ectd:study>
```

Rule 1734 Top Error Examples – Cont.

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



	STUDYID	DOMAIN	TSSEQ	TSPARMCD	TSPARM	TSVAL	TSVAL1	TSVAL2
1	12345678	TS	1	ACTSUB	Actual Number of Subjects	40		

No study start date
in ts.xpt

Rule 1734 Top Error Examples – Cont.

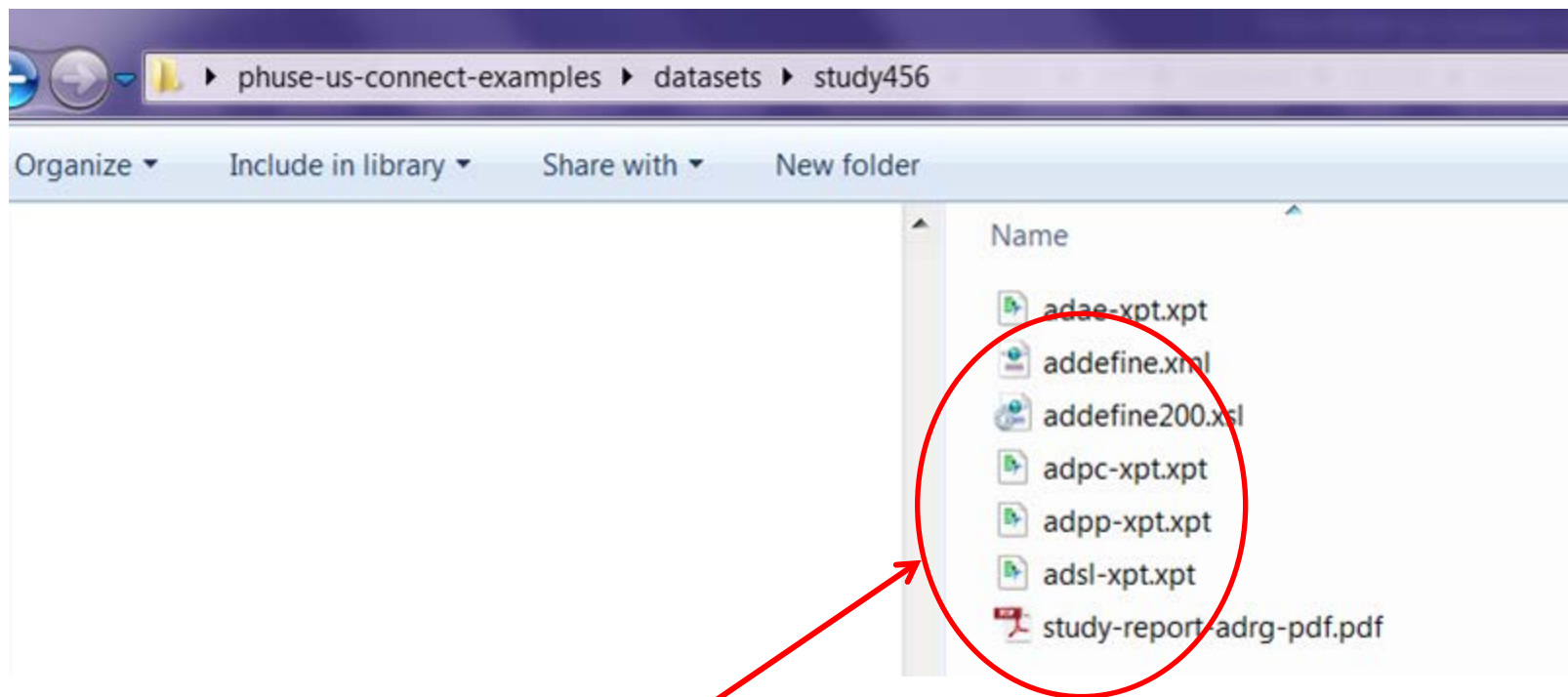
- ❖ **Invalid Study Start Date: Study Start Date must be in the format of (yyyy-mm-dd) (75)**

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

**Incorrect Study
Start Date format**

Rule 1736 Top Error Examples

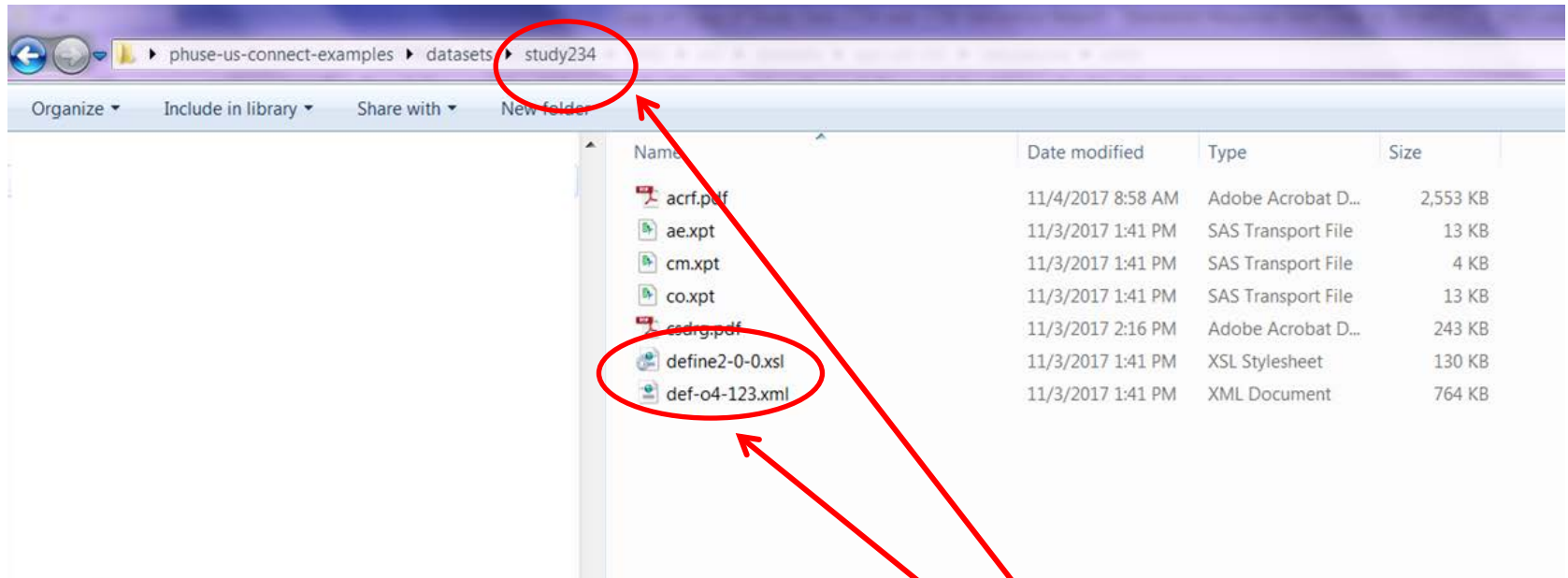
❖ Missing adsl.xpt or define.xml for a study (52)



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)

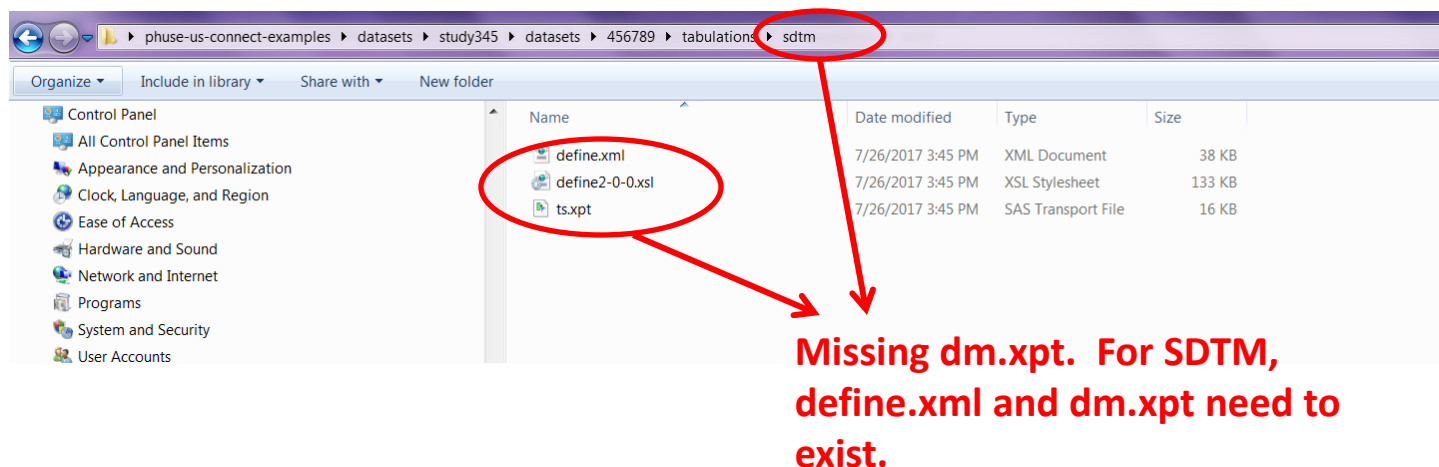
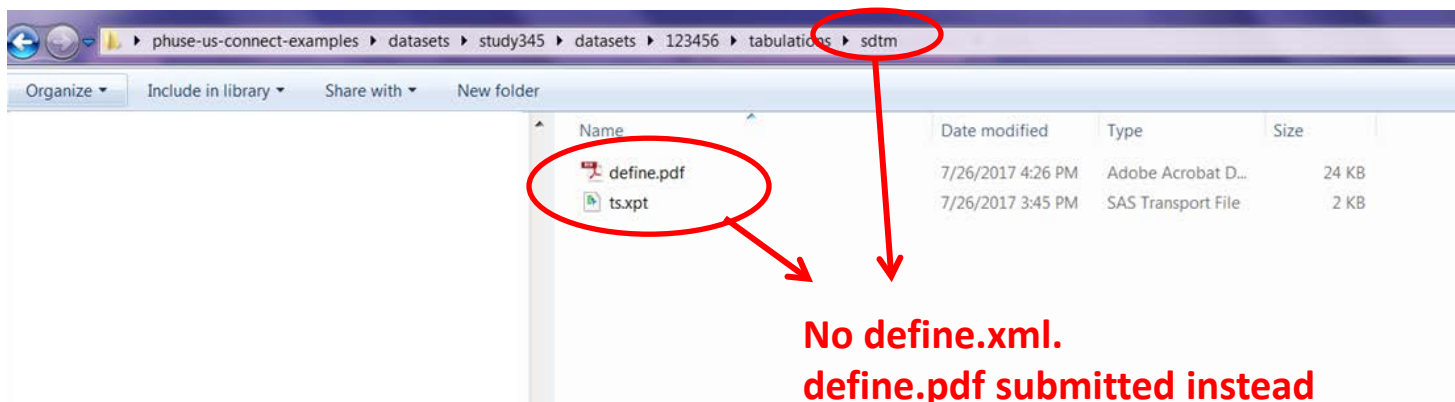


Name	Date modified	Type	Size
acrf.pdf	11/4/2017 8:58 AM	Adobe Acrobat D...	2,553 KB
ae.xpt	11/3/2017 1:41 PM	SAS Transport File	13 KB
cm.xpt	11/3/2017 1:41 PM	SAS Transport File	4 KB
co.xpt	11/3/2017 1:41 PM	SAS Transport File	13 KB
cdrg.pdf	11/3/2017 2:16 PM	Adobe Acrobat D...	243 KB
define2-0-0.xsl	11/3/2017 1:41 PM	XSL Stylesheet	130 KB
def-o4-123.xml	11/3/2017 1:41 PM	XML Document	764 KB

Missing define.xml for a study

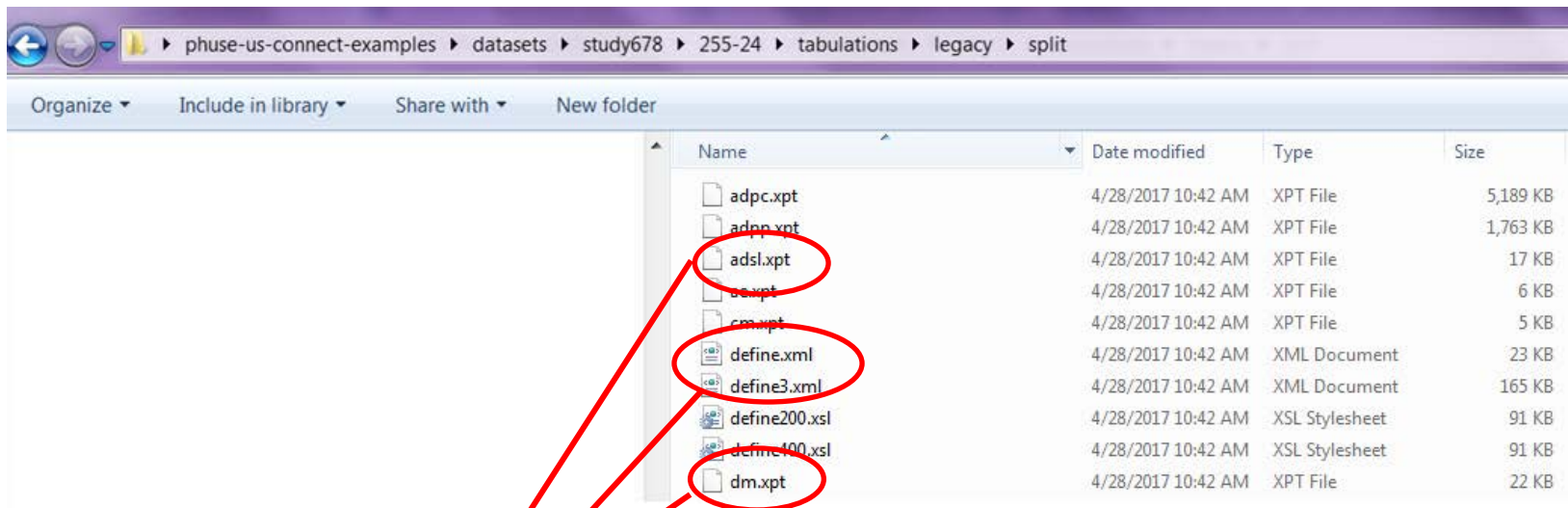
Rule 1736 Top Error Examples – Cont.

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



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)



Name	Date modified	Type	Size
adpc.xpt	4/28/2017 10:42 AM	XPT File	5,189 KB
adpp.xpt	4/28/2017 10:42 AM	XPT File	1,763 KB
adsl.xpt	4/28/2017 10:42 AM	XPT File	17 KB
ad.xpt	4/28/2017 10:42 AM	XPT File	6 KB
cm.xpt	4/28/2017 10:42 AM	XPT File	5 KB
define.xml	4/28/2017 10:42 AM	XML Document	23 KB
define3.xml	4/28/2017 10:42 AM	XML Document	165 KB
define200.xsl	4/28/2017 10:42 AM	XSL Stylesheet	91 KB
define100.xsl	4/28/2017 10:42 AM	XSL Stylesheet	91 KB
dm.xpt	4/28/2017 10:42 AM	XPT File	22 KB

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/GUIDANCECOMPLIANCEREGLATORYINFORMATION/GUIDANCES/UCM292334.PDF](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/GUIDANCECOMPLIANCEREGLATORYINFORMATION/GUIDANCES/UCM384686.PDF](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](https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm523539.pdf)
- ❖ **“Study Data Technical Conformance Guide”**
[HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM384744.PDF](https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf)
- ❖ **“FDA Data Standards Catalog”**
[HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM](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](https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/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](http://www.fda.gov/forindustry/datastandards/studydatastandards)

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*Thank
You*