Technical Rejection Criteria for Study Data

Study data standards are required in clinical and nonclinical studies that start after December 17, 2016.[1] Technical rejection criteria are being added to the existing electronic common technical document (eCTD) validation criteria to enforce the deadlines below.[2] The Food and Drug Administration (FDA or Agency) will give the industry 90 days' notice on the eCTD web page[3] prior to the criteria in this document becoming effective.

FDA will not accept an electronic submission that does not have study data in compliance with the required standards specified in the FDA Data Standards Catalog.[4]

The standards apply to the following types of submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER):

- New drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and all subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect

- Commercial investigational new drug applications (INDs) (for products that are intended to be distributed commercially)

Deadlines: Sponsors whose studies started after **December 17, 2016,** must use the data standards listed in the FDA Data Standards Catalog for NDAs, BLAs and ANDAs. For Commercial INDs, the requirement applies to studies started after **December 17, 2017**.

FDA is implementing an approach to determine compliance with the requirement to submit electronic standardized study data. The technical rejection criteria are automated validations by the Center (CDER or CBER) inbound processing system using the FDA Specifications for eCTD Validation Criteria as described below.

This document focuses on the criteria used for the automated validation process. In order for the FDA automated eCTD validation process to determine the study start date (SSD) for the submitted study, FDA relies on the SSD value provided in the Trial Summary dataset (ts.xpt) that is referenced in the Study Tagging File (STF). This validation confirms the submission of a valid STF (see validation code 1789) and a Trial Summary (TS) domain (see validation code 1734). For a study that contains a study report with file tags "pre-clinical-study-report," "legacy-clinical-study-report," or "study-report-body," and/or an xpt formatted dataset, the expectation for content in the TS domain (simplified or full)[5] depends on whether the study is submitted in compliance with a Clinical Data Interchange Standards Consortium (CDISC) standard. FDA's Study Data Technical Conformance Guide provides the appropriate content

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[1] This requirement is discussed in the guidance for industry *Providing Regulatory Submissions in Electronic Format—Standardized Study Data*, available on the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm, and on the FDA Study Data Standards Resources web page at https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page.

[2] See pp. 5-8.

[3] Available on the eCTD web page at https://www.fda.gov/ectd.

[4] Available on the FDA Study Data Standards Resources web page.

[5] Please refer to Appendix 2 of this document for more information on the simplified TS file and the Study Data Technical Conformance Guide on the FDA Study Data Standards Resources web page for more information on the full TS file.

and an example of the TS domains for each case. The expectation is that when the SSD is after the established required deadlines, the study data must comply with the standards in the FDA Data Standards Catalog. The validation will then identify that the required dataset files (see validation code 1736) are under the correct file tag within the STF (see validation code 1735). If there are no high validation errors within the eCTD submission, the submission will continue to be processed.

I M P O R T A N T

If a file is referenced within a study section in Module 4 or 5, a STF and ts.xpt must be present to identify the study ID and SSD to which the file belongs. The ts.xpt and STF need to contain matching study ID values.

If a clinical or nonclinical study, submitted to CDER or CBER, started after December 17, 2016, for NDAs, BLAs, and ANDAs (or December 17, 2017, for Commercial INDs),[6] the files must comply with CDISC standards as specified in the guidance *Providing Regulatory Submissions in Electronic Format—Standardized Study Data*.

If a clinical study, submitted to CDER or CBER, started on or prior to December 17, 2016, for NDAs, BLAs, and ANDAs,[7] and the study contains an xpt dataset (other than the ts.xpt), a simplified ts.xpt (see Appendix 2) file should be submitted.[8]

If a nonclinical study, submitted to CDER, started on or prior to December 17, 2016, for NDAs, BLAs, and ANDAs (or December 17, 2017, for Commercial INDs), [9] whether or not the study contains an xpt dataset (other than the ts.xpt), a simplified ts.xpt (see Appendix 2) file should be submitted.[10]

Study data validation **WILL APPLY** to the following eCTD sections:

- 4.2 Study Reports (CDER Only)
- 5.3 Clinical Study Reports and Related Information

Study data validation **WILL NOT APPLY** to the following eCTD sections:[11]

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3.3 Genotoxicity
- 4.2.3.5 Reproductive and Developmental Toxicity
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies
- 5.3.1.3 In Vitro – in Vivo correlation Study reports and related information
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
- 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
- 5.3.3.5 Population PK study reports and related information[12]
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.3.5.4 Other Study Reports and Related Information
- 5.3.6 Reports of Postmarketing Experience

[6] See footnote 1.
[7] Id.
[8] The study ID and the SSD are used to determine the start date for the study. For more information, see the Study Data Technical Conformance Guide.
[9] See footnote 1.
[10] See footnote 7.
[11] This list only applies to eCTD validation 1734, 1735, 1736, and 1737.
[12] PK/PD modeling and simulation study reports can be placed under this section, under Module 5.3.3.5.

Table 1: eCTD Technical Rejection Criteria for Study Data Expectations[13]

Study Start Date	Application Type	Data Type	Modules and Submodules	Expectation by CDER	Expectation by CBER
Prior to or on 17-Dec-16	NDA, BLA, ANDA	Non - Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
Prior to or on 17-Dec-16	NDA, BLA, ANDA	Clinical	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	Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)
Prior to or on 17-Dec-17	Commercial INDs	Non - Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
Prior to or on 17-Dec-17	Commercial INDs	Clinical	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	Rejection criteria will not be applied	Rejection criteria will not be applied
After 17-Dec-16	NDA, BLA, ANDA	Non - Clinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
After 17-Dec-16	NDA, BLA, ANDA	Clinical	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	Rejection criteria will be applied; submit a full TS	Rejection criteria will be applied; submit a full TS
After 17-	Commercial	Non -	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection	Rejection

[13] This table only applies to eCTD validation 1734, 1735, and 1736. An STF must be provided for all applications and data types for both CDER and CBER (eCTD validation 1789).

Study Start Date	Application Type	Data Type	Modules and Submodules	Expectation by CDER	Expectation by CBER
Dec-17	INDs	Clinical		criteria will be applied; submit a full TS	criteria will not be applied
After 17-Dec-17	Commercial INDs	Clinical	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,	Rejection criteria will not be applied	Rejection criteria will not be applied

Table 2: Validation 1734

Number:	1734
Group:	General
Description:	A dataset named ts.xpt with information on SSD must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD
Problem:	You have not submitted a dataset named ts.xpt with information on SSD for each study in Module 4, section 4.2, or in Module 5, section 5.3
Corrective Action:	Resubmit, including a dataset named ts.xpt with information on SSD for each study in Module 4, section 4.2, and Module 5, section 5.3
Guidance Source:	*Providing Regulatory Submissions in Electronic Format—Standardized Study Data; Study Data Technical Conformance Guide*

Table 3: Validation 1735

Number:	1735
Group:	STF
Description:	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in 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
Severity Description:	High[14]
US DTD Version	2.01 and 3.3
Effective Date:	TBD
Problem:	You have submitted XPT files or define.xml files without correct file tag. Valid file tags for XPT files are: data-tabulation-dataset-sdtm data-tabulation-dataset-send analysis-dataset-adam Valid file tags for corresponding define.xml files are: data-tabulation-data-definition analysis-data-definition
Corrective Action:	Resubmit using one of the valid file tags for all submitted datasets
Guidance Source:	*Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification; Providing Regulatory Submissions in Electronic Format—Standardized Study Data; Study Data Technical Conformance Guide*

[14] Having a dataset with its corresponding define.xml file tagged properly allows the study datasets to be identified or distinguished in case the tabulation and analysis datasets of the same study are submitted in the same location. The files need to be tagged correctly for validation to confirm necessary files are provided (see validation 1736).

Table 4: Validation 1736

Number:	1736
Group:	General
Description:	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted 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 For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must be submitted in 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
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD
Problem:	You have not submitted SEND DM and corresponding define.xml for each study in Module 4, section 4.2. You have not submitted SDTM DM and corresponding define.xml for each study in Module 5, section 5.3. You have not submitted ADSL, and corresponding define.xml for each study in Module 5, section 5.3.
Corrective Action:	Resubmit the submission with the SEND DM and corresponding define.xml for each study in Module 4, section 4.2 Resubmit including SDTM DM and corresponding define.xml for each study in Module 5, section 5.3 Resubmit including ADSL and corresponding define.xml for each study in Module 5, section 5.3
Guidance Source:	*Providing Regulatory Submissions in Electronic Format—Standardized Study Data; Study Data Technical Conformance Guide*

Table 5: Validation 1789

Number:	1789
Group:	STF
Description:	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
Severity Description:	High[15]
US DTD Version	2.01 and 3.3
Effective Date:	TBD
Problem:	All files in a study section must be referenced by an STF file
Corrective Action:	In a new submission include an STF and use the "Replace" operator to replace previously submitted documents which were not referenced in an STF
Guidance Source:	*Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification*; the eCTD Backbone File Specification for Study Tagging Files V2.6.1

[15] See *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification*, Section J: "Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2. When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files* (see section III.D). Datasets must be referenced in an STF using the appropriate STF file-tag describing the document's contents."

APPENDIX 1: EXAMPLES OF VALIDATION FINDINGS IN STUDY DATA

The following examples illustrate how FDA will validate study data received in electronic format:

1. A study prior to December 17, 2016, for NDAs, BLAs, and ANDAs (or December 17, 2017, for Commercial INDs), is submitted to FDA and the study files are referenced in a STF, a ts.xpt dataset is not included in the study. The SSD cannot be determined, the study fails validation 1734.
2. A study in standardized format is submitted to FDA and the study files are referenced in a STF, a ts.xpt dataset is included in the study. The study ID in the ts.xpt dataset matches the study ID in the STF. The SSD in the ts.xpt is in SDTM or SEND format and the study begins after the specified validation start date. The study passes validation 1734.
3. A study has already been submitted that includes a valid ts.xpt. New or updated study data files are being submitted to the study, the ts.xpt content information has not been changed, and no ts.xpt was included in the submission. The study will pass validation 1734.
4. A study in standardized format is submitted to FDA and the study files are referenced in a STF. The XPT files submitted in the study are appropriately file-tagged in the STF using the four file tags referenced in validation code 1735. The study passes validation 1735.
5. A study in standardized format is submitted to FDA and the study files are referenced in a STF. The SEND study in Module 4 contains a define.xml file and a DM.xpt file and they are appropriately file tagged. The study passes validation 1736.
6. A study in standardized format is submitted to FDA and the study files are referenced in a STF). The SDTM study in Module 5 contains a define.xml file and a DM.xpt file and they are appropriately file tagged. The study passes validation 1736.
7. A study in standardized format is submitted to FDA and the study files are referenced in a STF. The ADaM study in Module 5 contains a define.xml file and a ADSL.xpt file and they are appropriately file tagged. The study passes validation 1736.
8. If a study does not have a SSD that is submitted to FDA and the study files are referenced in a STF. The submitted simplified ts.xpt file listed TSVAL as NULL and TSVALNF as "NA." The study passes validation 1734.

APPENDIX 2: EXAMPLES OF TS.XPT DATASETS

Examples of simplified ts.xpt datasets for a clinical study:

Sponsors should submit a dataset named 'ts.xpt' with four variables (STUDYID, TSPARMCD, TSVAL, and TSVALNF) and one row of information. Example datasets are shown below. Additional details can be found in the Study Data Technical Conformance Guide.

For a study with a valid SSD:

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	SSTDTC	yyyy-mm-dd	

For a study without a valid SSD:

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	SSTDTC		As specified in the ISO 21090 Standard

Examples of simplified ts.xpt datasets for a nonclinical study:

Sponsors should submit a dataset named 'ts.xpt' with four variables (STUDYID, TSPARMCD, TSVAL, and TSVALNF) and one row of information. Example datasets are shown below. Additional details can be found in the Study Data Technical Conformance Guide.

For a study with a valid SSD:

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC	yyyy-mm-dd	

For a study without a valid SSD:

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC		As specified in the ISO 21090 Standard