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FDA View: Technical Rejection Criteria for Study Data

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ABSTRACT

Study Data Standards listed in the FDA Data Standards Catalog are required for clinical and nonclinical studies that started after December 17, 2016 (for ANDA, NDA and BLA) or December 17, 2017 (for Commercial IND). Through the technical rejection process, FDA can reject an application because of its technical deficiencies, based on the severity of the eCTD validation criteria. FDA conducted an analysis on submissions that contain study data that were already received by the Agency to assess conformance rates to Technical Rejection Criteria for Study Data (TRC). Submissions received between December 18, 2016 to March 31, 2018 (December 18, 2017 to March 31, 2018 for Commercial IND submissions) showed that about 32.0% of all submissions with study data were received with critical errors (i.e. submissions with 1734 and/or 1736 errors).

Based on findings from this analysis, FDA updated TRC to provide more clarification and developed supporting tools to help Industry meet study data requirements. FDA also conducted an analysis on submissions that contain study data received in 2018 to generate additional findings to the baseline analysis. These efforts are expected to improve conformance rates over time by making it clearer and easier for Industry to meet FDA's study data requirements.

INTRODUCTION

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 application type. FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014. For NDA, BLA, ANDA studies that started after December 17th, 2016 and for Commercial IND studies started after December 17th, 2017, sponsors must conform to standards in the FDA Data Standards Catalog. "Technical Rejection Criteria for Study Data" specified two technical rejection criteria designated as high severity, Errors 1734 and 1736. Error 1734 indicates that a Trial Summary (TS) dataset is not present for each study in required module 4 and module 5 sections. Error 1736 indicates that a DM dataset and/or define.xml were not submitted in required module 4 sections, or a DM dataset, ADSL dataset, and/or define.xml were not submitted in required module 5 sections. FDA also issued "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry" in which section III specifically calls out the requirement to submit a study tagging file anytime study data is submitted with an application. The TRC clarifications highlight study file tag requirements, as specificed in the forementioned guidance.

COMFORMANCE STATISTICS AND TREND OF FAILURE RATES

FDA conducted a baseline analysis on submissions that contained study data and found that about 32.0% of submissions with study data were received with critical errors (i.e. submissions with 1734 and/or 1736 errors). The analysis included NDA, ANDA, and BLA submissions received by CDER between December 18, 2016 to March 31, 2018 and Commercial IND submissions received between December 18, 2017 to March 31, 2018.

Failure Rate	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	1,126	1,446	473	176	3,221
Total Number Submissions with Critical Errors (Error 1734 and/or 1736)	302	551	138	41	1,032
Error 1734	290	506	137	35	968
Error 1736 *(validation not performed if a study has Error 1734)*	14	63	1	6	84
Failure Rate *(% among submissions with Study Data)*	**26.8%**	**38.1%**	**29.2%**	**23.3%**	**32.0%**

Notes: (1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments (2) Analysis includes NDA, BLA, and ANDA submissions received by CDER between 12/18/2016 and 3/31/2018, and commercial IND submissions received by CDER between 12/18/2017 and 3/31/2018 (3) Validation of error 1736 of a study is not performed if a study has Error 1734 (4) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate

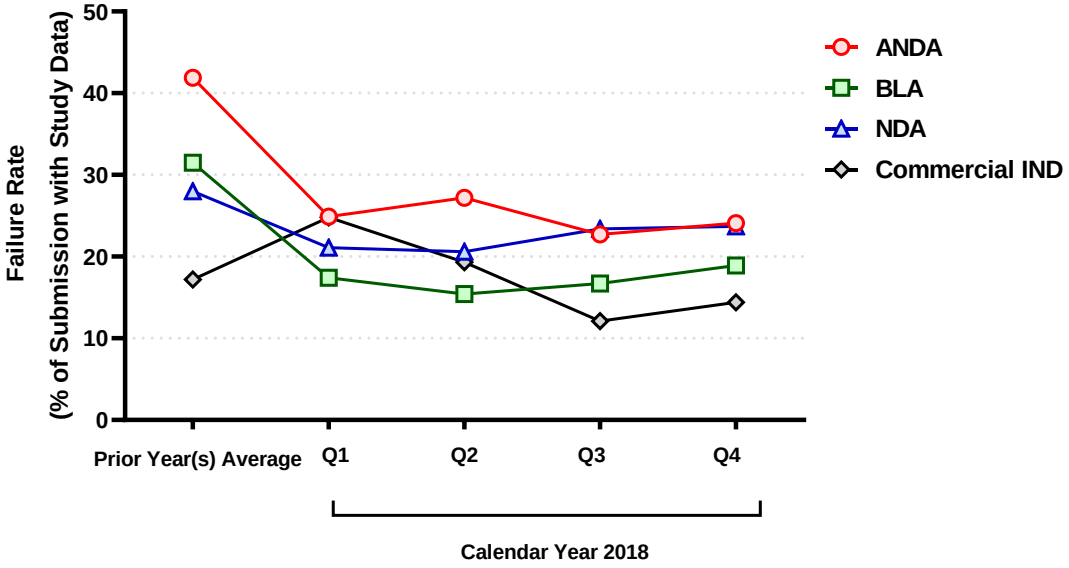
FDA has conducted a similar analysis for submissions received in 2018 to generate additional findings. The analysis includes all submissions that contained study data (NDA, ANDA, BLA, and Commercial IND) received by CDER

between 1/1/2018 to 12/31/2018. Results show that about 21.6% of all submissions were received with critical errors in 2018. Compared to the baseline analysis, failure rates decreased for all application types in 2018.

Failure Rate	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	877	1078	291	649	2895
Total Number Submissions with Critical Errors (Error 1734 and/or 1736)	195	266	50	113	624
Error 1734	185	186	48	96	515
Error 1736 *(validation not performed if a study has Error 1734)*	16	88	2	18	124
Failure Rate *(% among submissions with Study Data)*	**22.2%**	**24.7%**	**17.2%**	**17.4%**	**21.6%**

Notes: (1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments (2) Analysis includes NDA, BLA, and ANDA submissions received by CDER between 12/18/2016 and 3/31/2018, and commercial IND submissions received by CDER between 12/18/2017 and 3/31/2018 (3) Validation of error 1736 of a study is not performed if a study has Error 1734 (4) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate (5) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

FDA compared quarterly failure rates for each application type received in 2018 to the baseline analysis. The average conformance failure rates are improved in 2018 compared with previous years, but the average among different quarters fluctuated.



Notes: (1) Prior year(s) average uses data from the baseline analysis, but excludes any submissions received in 2018 (2) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

CLARIFYING THE TECHNICAL REJECTION CRITERIA: ERRORS 1789, 1735, AND 1734

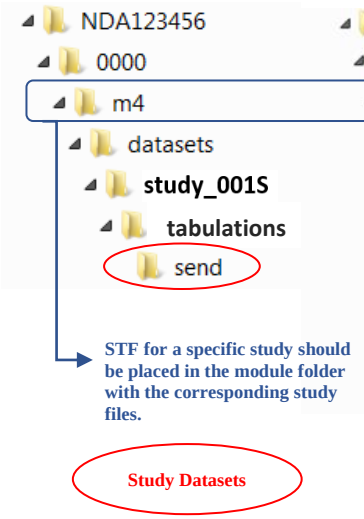
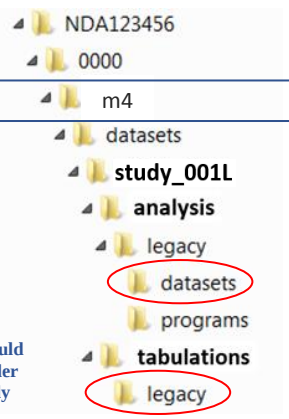
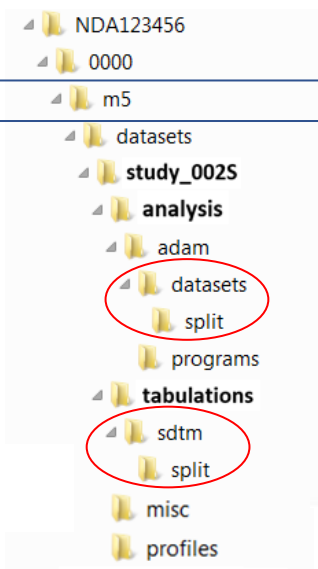
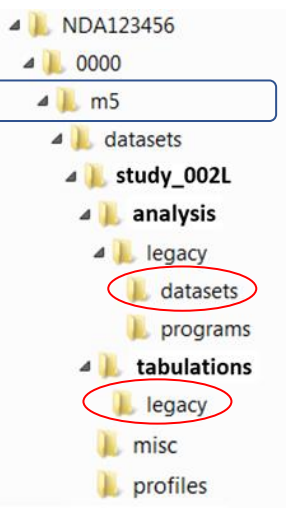
Based on the findings from these analyses, FDA has identified the need to provide additional clarifications on TRC to help Industry meet study data requirements and continue to improve the conformance trend over time. FDA has made three primary clarifications to the TRC: the inclusion of Error 1789, the inclusion of Error 1735, and additional details on Error 1734.

The inclusion of Errors 1789 and 1735 are intended to improve conformance to 1734 and 1736 by enabling FDA to associate study files with the proper clinical and nonclinical studies. Error 1789 states that a file has been submitted in a study section of a submission without providing a study tagging file (STF). Error 1735 states that the correct STF file tags were not used for all standardized datasets and corresponding define.xml files in the required module 4 and module 5 sections.

Because each submission typically contains many studies, an STF file is necessary to process study files into their corresponding studies. Accepting a submission where CDER cannot process the study tagging file will result in the reviewer seeing a list of files for which they do not know the study they belong to. STF files include information on associated study files that require correct file tags to be used. File tags, as specified in *ICH M2 EWG: The eCTD*

Backbone File Specification for Study Tagging Files, are used to identify all the files associated with a study. If a study data file (e.g. define.xml) is not properly tagged in the STF file, it cannot be identified and located, resulting in Error 1736 being reported. Therefore, the revised TRC includes updated validation rules 1735 and 1789, requiring a submission with study files to include STF file with correct file tag.

STF files and their associated datasets should be organized into a specific file directory structure and a specific headings and hierarchy structure. According to *ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files*, STF files should be placed in the module folder with the corresponding study files and a leaf element for the STF should be placed in the index.xml file based on the appropriate Module 4 or 5 eCTD Table of Contents element for that sequence. The STF file for a specific study should be placed in the module folder with the corresponding study files. The specific folder in which study datasets should be placed depends on the module, whether the dataset is in standardized or legacy format, and whether the dataset is tabulation or analysis. Study datasets should be organized by study, in a sub-folder named "datasets" within the appropriate module folder. Appendix E of the *Study Data Technical Conformance Guide* provides example folder structures for study data.

Module 4		Module 5	
Standardized Data	**Legacy Data**	**Standardized Data**	**Legacy Data**
			

FDA has also provided additional details on Error 1734 to clarify how the study start date is used to determine study data requirements. Error 1734 states that a dataset named ts.xpt with information on study start date must be present for each study in the required module 4 and module 5 sections. 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) depends on whether the study is submitted in compliance to a CDISC standard. When the study start date is after the established required deadlines, a full ts.xpt file should be submitted with study data in compliance to a CDISC standard and the FDA's Technical Conformance Guide. When the study start date is before the established required deadlines, a simplified ts.xpt file should be submitted.

A simplified ts.xpt for a nonclinical or clinical study should have four variables (STUDYID, TSPARMCD, TSVAL, and TSVALNF) in one row of information. The variable TSVALNF should be used in cases where a submitted study does not have a study start date (TSVAL), as specified in the ISO 21090 Standard. The revised TRC (Revised Jan. 2019) provides examples of ts.xpt datasets.

STUDYID	TSPARMCD	TSVAL	TSVALNF
• Study ID in STF file	• SSTDTC for a clinical study • STSTDTC for a nonclinical study	• Study start date in yyyy-mm-dd format • Left blank when study start date is not available	• Left blank when study start date is provided in TSVAL • Exception code as specified in the ISO 21090 Standard when study start date is not available

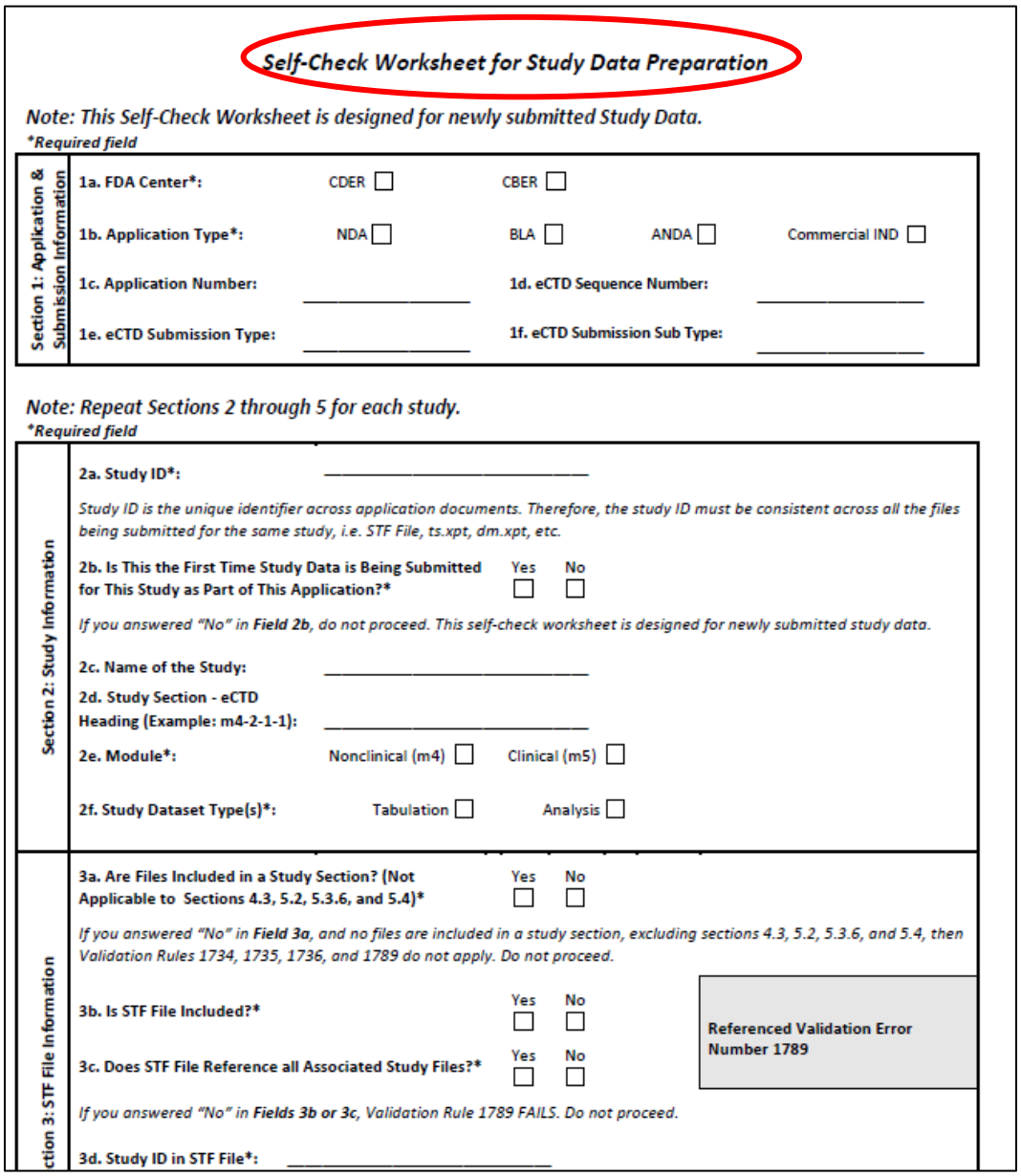
A requirements table is included in the TRC to help sponsors determine FDA's study data requirements for eCTD Validation 1734 and also eCTD Validations 1735 and 1736. FDA requires that if a clinical or nonclinical study, submitted to CDER or CBER, started after December 17, 2016 for NDAs, BLAs, and ANDAs (or December 17, 2017 for Commercial INDs), the files must comply with CDISC standards as specified in the Study Data Guidance. If a clinical study, submitted to CDER or CBER, started on or prior to December 17, 2016 for NDAs, BLAs, and ANDAs and the study contains an xpt dataset (other than the ts.xpt), a simplified ts.xpt file should be submitted. 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), whether or not the study contains an xpt dataset (other than the ts.xpt), a simplified ts.xpt file should be submitted.

<table>
<tr><th rowspan="2">Study Start Date</th><th rowspan="2">Application Type</th><th rowspan="2">Data Type</th><th rowspan="2">Modules and Submodules</th><th colspan="2">Expectation by Center[1]</th></tr>
<tr><th>CDER</th><th>CBER</th></tr>
<tr><td rowspan="2">Prior to or on 17-Dec-16</td><td rowspan="2">NDA, BLA, ANDA</td><td>Nonclinical</td><td>4.2.3.1, 4.2.3.2, 4.2.3.4</td><td>Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)</td><td>Rejection criteria will not be applied</td></tr>
<tr><td>Clinical</td><td>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</td><td colspan="2">Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)</td></tr>
<tr><td rowspan="2">Prior to or on 17-Dec-17</td><td rowspan="2">Commercial INDs</td><td>Nonclinical</td><td>4.2.3.1, 4.2.3.2, 4.2.3.4</td><td>Rejection criteria will be applied; submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)</td><td>Rejection criteria will not be applied</td></tr>
<tr><td>Clinical</td><td>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</td><td colspan="2">Rejection criteria will not be applied</td></tr>
<tr><td rowspan="2">After 17-Dec-16</td><td rowspan="2">NDA, BLA, ANDA</td><td>Nonclinical</td><td>4.2.3.1, 4.2.3.2, 4.2.3.4</td><td>Rejection criteria will be applied; submit a full TS</td><td>Rejection criteria will not be applied</td></tr>
<tr><td>Clinical</td><td>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</td><td colspan="2">Rejection criteria will be applied; submit a full TS</td></tr>
<tr><td rowspan="2">After 17-Dec-17</td><td rowspan="2">Commercial INDs</td><td>Nonclinical</td><td>4.2.3.1, 4.2.3.2, 4.2.3.4</td><td>Rejection criteria will be applied; submit a full TS</td><td>Rejection criteria will not be applied</td></tr>
<tr><td>Clinical</td><td>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</td><td colspan="2">Rejection criteria will not be applied</td></tr>
</table>

SUPPORTING TOOLS FOR INDUSTRY

In addition to providing clarifications on TRC, FDA designed the Self-Check Worksheet for Study Data Preparation to help sponsors evaluate their planned submissions of new study data and provide clarification on how FDA validates submissions against TRC. The Self-Check Worksheet includes each TRC validation step to check for Errors 1734, 1735, 1736, and 1789. Each step prompts the users to answer a question or enter information about the submission and/or study. Based on users' responses, the Self-Check Worksheet dynamically guides users through each step. When a response indicates a TRC error, sponsors can interpret that as an issue to correct before submitting study data. An associated Self-Check Worksheet Instructions document was developed to provide additional details on each validation step and explain how sponsors can correct issues that cause TRC errors.

[1] This table only applies to eCTD Validation 1734, 1735, and 1736. Study Tagging File (STF) must be provided for all Application and Data Types for both CDER and CBER (eCTD Validation 1789).



Self-Check Worksheet for Study Data Preparation

Note: This Self-Check Worksheet is designed for newly submitted Study Data.

**Required field*

Section 1: Application & Submission Information

1a. FDA Center*: CDER ☐ CBER ☐

1b. Application Type*: NDA ☐ BLA ☐ ANDA ☐ Commercial IND ☐

1c. Application Number: _____ **1d. eCTD Sequence Number:** _____

1e. eCTD Submission Type: _____ **1f. eCTD Submission Sub Type:** _____

Note: Repeat Sections 2 through 5 for each study.

**Required field*

Section 2: Study Information

2a. Study ID*: _____

Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?* Yes ☐ No ☐

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

2c. Name of the Study: _____

2d. Study Section - eCTD Heading (Example: m4-2-1-1): _____

2e. Module*: Nonclinical (m4) ☐ Clinical (m5) ☐

2f. Study Dataset Type(s)*: Tabulation ☐ Analysis ☐

ction 3: STF File Information

3a. Are Files Included in a Study Section? (Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)* Yes ☐ No ☐

*If you answered "No" in **Field 3a**, and no files are included in a study section, excluding sections 4.3, 5.2, 5.3.6, and 5.4, then Validation Rules 1734, 1735, 1736, and 1789 do not apply. Do not proceed.*

3b. Is STF File Included?* Yes ☐ No ☐

3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐

Referenced Validation Error Number 1789

*If you answered "No" in **Fields 3b or 3c**, Validation Rule 1789 FAILS. Do not proceed.*

3d. Study ID in STF File*: _____

CONCLUSION

Based on findings from the baseline and 2018 analyses of submissions with study data, FDA identified the need to provide additional clarifications on TRC. FDA has included Errors 1789 and 1735 in TRC and provided additional details on Error 1734 to more effectively associate study files with the proper clinical and nonclinical studies and help determine what study data requirements to apply to particular submissions. Moreover, FDA has designed the Self-Check Worksheet for Study Data Preparation as a tool to help Industry meet study data requirements. Combined, FDA intends that these efforts will further improve conformance rates over time.

FDA has not rejected any submission that contains errors as reflected in this analysis. FDA plans to use TRC to identify applications that are not fulfilling this requirement. 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/ForIndustry/DataStandards/StudyDataStandards/UCM630740.pdf

"Study Data Technical Conformance Guide"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf

"FDA Data Standards Catalog"
https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf

"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

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RECOMMENDED READING

For the FDA Instruction of Study Data Submission, see the FDA "Study Data for Submission to CDER and CBER" page at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.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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