PHUSE US Connect 2020

Paper SA04

FDA View: FDA Study Data Guidance Update

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ABSTRACT

Study Data Standards listed in the Food and Drug Administration (FDA) Data Standards Catalog are required for clinical and non-clinical studies that started after December 17, 2016 for Abbreviated New Drug Application (ANDA), New Drug Application (NDA) and Biologics License Application (BLA) or December 17, 2017 for Commercial Investigational New Drug (IND). Through the technical rejection process, FDA can reject an application because of its technical deficiencies, based on the severity of the Electronic common technical document (eCTD) validation criteria which are specified in the "Technical Rejection Criteria for Study Data" (TRC). FDA conducts quarterly analyses on submissions containing study data received by the Agency to assess conformance rates to TRC.

Based on findings from recent analyses and feedback provided by industry, FDA made three important clarifications to the TRC in October 2019. One, FDA clarified requirements for non-clinical studies that require Standard for Exchange of Nonclinical Data (SEND) datasets, two, FDA included SPREFID as a valid source for study id in ts.xpt files, and three, FDA updated guidance for Simplified Trial Summary Files (Simplified ts.xpt).

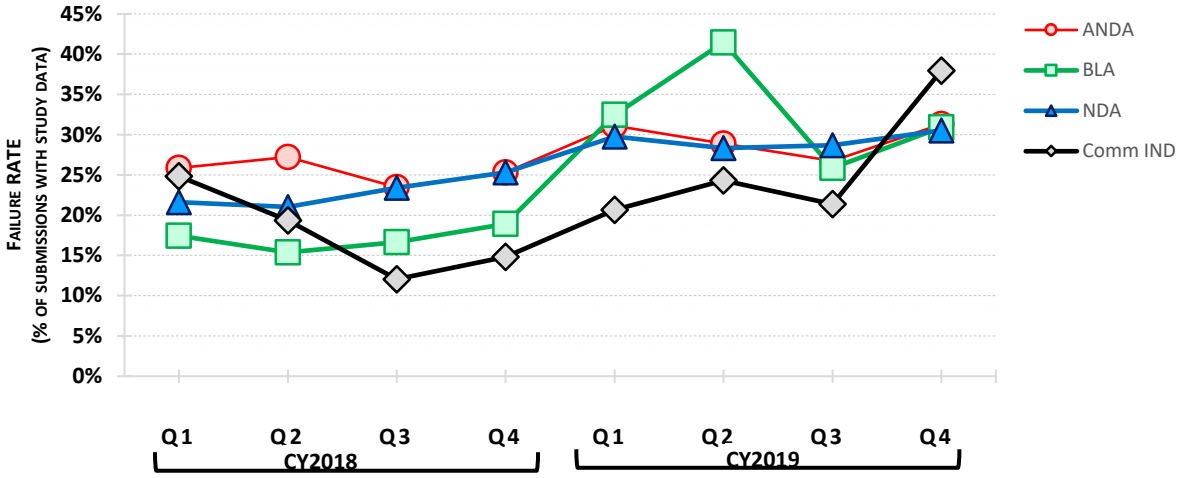
INTRODUCTION

Per Federal Food, Drug, and Cosmetic Act (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" specifies four technical rejection criteria designated as high severity, Errors 1734, 1735, 1736 and 1789. Error 1734 indicates that a Trial Summary (TS) dataset must be present for each study in required module 4 and module 5 sections. Error 1735 states that the correct study tagging file (STF) file tags must be used for all standardized datasets and corresponding define.xml files in the required module 4 and module 5 sections. Error 1736 indicates that a Demographic dataset (DM) dataset and/or define.xml must be submitted in required module 4 sections, or a DM dataset, Subject Level Analysis Dataset (ADSL) dataset, and/or define.xml must be submitted in required module 5 sections. Error 1789 states that a file submitted in a study section of a submission must be referenced in a STF. 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 STF anytime study data is submitted with an application.

COMFORMANCE STATISTICS AND TREND OF FAILURE RATES (CY2018 AND CY2019)

FDA conducts quarterly analyses on submissions containing study data received by the Agency to assess conformance rates to TRC to determine changes over time and identify potential impacts to conformance rates from FDA's policy clarifications and industry outreach activities. The analyses presented in this paper focus on TRC validation rules 1734 and 1736. Therefore, overall failure rates include submissions with study data that fail either validation rule 1734 and/or validation rule 1736 and exclude any validation rule 1735 failures. If a submission fails validation rule 1789, it cannot be validated for 1734, 1735, or 1736 because one of the studies in the submission lacks the information required to begin validation, i.e. essential information from the stf.xml.

Between Calendar Year (CY) 2018 and CY2019 overall conformance rates for all application types have trended relatively flat, excluding the fourth quarter of CY2019 Q4. As shown in the chart below, quarterly failure rates experience noticeable increases and/or decreases, but average trend lines across the time period are relatively flat. The noticeable increase in failure rates in CY2019 Q4 may be partially driven by clarifications made to the TRC in October 2019. CY2019 Q4 conformance rates were generated according to the updated criteria, explained in detail in subsequent sections.



Notes (1) CY2018 & CY2019 (Q1-Q3) analysis was conducted according to the TRC (Revised Jan. 2019) (2) CY2019 (Q4) analysis was conducted according to the TRC (Revised Oct. 2019) (3) Analyses include NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 and 12/31/2019 (4) Validation of error 1736 is not performed if a study has Error 1734

CY2019 Q1-Q3 conformance rates were generated according to similar criteria as CY2018 data based on the TRC (Revised Jan. 2019). The results for all three quarters are summarized in Table 1. Approximately 27% of all submissions with study data were received with critical errors (i.e. submissions with 1734 and/or 1736 errors). ANDA submissions with study data exhibit the highest failure rates across application types at approximately 32% of all submissions with study data. Commercial IND submissions with study data exhibit the lowest failure rates at approximately 22% of all submissions with study data.

Table 1 CY2019 Q1, Q2 and Q3 TRC Failure Result Across all Application Type

Failure Rate	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	623	203	679	700	2205
Total Number of Submissions with Study Data in TRC Applicable Sections	582	161	533	645	1921
Total Number Submissions with Critical Errors (Error 1734 and/or 1736)	181	64	197	156	598
Error 1734	135	59	195	135	524
Error 1736 *(validation not performed if a study has Error 1734)*	46	5	2	21	74
Failure Rate *(% among submissions with Study Data)*	29.05%	31.53%	29.01%	22.29%	27.12%
Failure Rate (% among submissions with Study Data in TRC Applicable section)	31.10%	39.75%	36.96%	24.19%	31.13%

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, ANDA and commercial IND submissions received by CDER between 01/01/2019 and 9/30/2019 (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)

One of the three important clarifications to the TRC in October 2019 is that non-clinical studies in eCTD module 4 section 4.2.3.1, 4.2.3.2, or 4.2.3.4—which should be in compliance with SEND regulations—require a TS file (ts.xpt) if a non-clinical study report is submitted with a file tag of 'pre-clinical-study-report', 'legacy-clinical-study-report' and 'study-report-body' file tags. However, certain non-clinical studies are exempt from TRC requirements (see Study Data Technical Conformance Guide Section 8.2.2 for details). These include non-clinical studies that do not require SEND data in a submission and non-clinical studies for which study initiation dates are not relevant. In such cases, a Simplified ts.xpt must submitted with a (Null Flavor Variable)TSVALNF value of "NA".

The conformance rate analyses conducted for the last quarter of 2019 (between October 1, 2019 and December 31, 2019) was generated according to the updated TRC (Revised Oct. 2019) which include the TRC clarifications. Approximately 35% of all submissions with study data were received with critical errors (i.e. submissions with 1734 and/or 1736 errors). Compared to the first three quarters of 2019 (between January 1, 2019 and September 30,

2019) this amounts to approximately an 8% failure rate increase. For Commercial IND submissions with study data, the failure rate increased from 22% to 38%, an increase of 16%.

Table 2- CY2019 Q4 TRC Failure Result Across all Application Type

Failure Rate	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data and/or Study Report	230	110	262	827	1429
Total Number of Submissions with Study Data and/or Study Report in TRC Applicable Sections	213	80	192	480	965
Total Number Submissions with Critical Errors (Error 1734 and/or 1736)	72	34	80	314	500
Error 1734	55	27	73	293	448
Error 1736 (validation not performed if a study has Error 1734)	17	7	7	21	52
Failure Rate (% among submissions with Study Data and/or Study Report)	31.30%	30.91%	30.53%	37.97%	34.99%
Failure Rate (% among submissions with Study Data and/or Study Report in TRC Applicable section)	33.80%	42.50%	41.67%	65.42%	51.81%

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, ANDA and commercial IND submissions received by CDER between 09/30/2019 and 12/31/2019 (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) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in eCTD module 4 (6) M5 Definition of Study Data - .xpt files present in eCTD module 5 (7) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

The increase in failure rates is primarily driven by additional non-clinical studies subjected to TRC which contain a study report with a file tag of 'pre-clinical-study-report', 'legacy-clinical-study-report' and/or 'study-report-body,' but not a TS file (ts.xpt). This scenario leads to a failure of validation rule 1734. The third TRC clarification—updated guidance for Simplified TS Files (Simplified ts.xpt)—is intended to help sponsors address this by submitting a Simplified ts.xpt file with the submission and avoid failing validation rule 1734.

CLARIFYING THE TECHNICAL REJECTION CRITERIA: USE OF SIMPLIFIED TS AND SPREFID

FDA included additional detail in the TRC (Revised Oct. 2019) by clarifying the expectation of a Simplified TS file (Simplified ts.xpt), particularly for non-clinical studies submitted in eCTD module 4. A Simplified ts.xpt for a non-clinical or clinical study should have four variables, STUDYID, TSPARMCD, TSVAL, and TSVALNF.

For clinical studies without a study start date, a Simplified TS file can be submitted with the with a value of "NA" in the TSVALNF variable. For non-clinical studies, when the study does not require SEND formatted dataset to be submitted or for studies where an initiation date is not applicable, the variable TSVALNF with a value of "NA" should be used. Please refer SDTCG section 8.2.2 for more detail. The revised TRC (Oct. 2019) provides examples of Simplified ts.xpt datasets, shown below.

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC		Use the value 'NA'

A revised requirements table is also included to help sponsors determine FDA's study data requirements for eCTD validation rules 1734, 1735, and 1736. The revisions are highlighted in the table below. FDA requires that if a clinical or non-clinical study, submitted to (Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (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 non-clinical 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 the study contains a study report with the proper file tags and/or an xpt dataset (other than the ts.xpt), a Simplified ts.xpt file should be submitted.

Study Start Date	Application Type	Data Type	Modules and Submodules	Expectation by Center[1]	
				CDER	CBER
Prior to or on 17-Dec-16	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		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)	
Prior to or on 17-Dec-17	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		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	
After 17-Dec-16	NDA, BLA, ANDA	Nonclinical	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
		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	
After 17-Dec-17	Commercial INDs	Nonclinical	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
		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	

Also added to October 2019 TRC revision, an alternate way for sponsors to provide a matching study id in the SPREFID parameter. This was based on feedback received from industry regarding cases where the study id match criteria between STF and TS file cannot be fulfilled, for example when a study is bought by new company and the study id is already established. After further evaluation FDA included the alternate study id match parameter "SPREFID" in ts.xpt file.

SUPPORTING TOOLS FOR INDUSTRY

In addition to providing clarifications on the TRC, FDA updated the Self-Check Worksheet for Study Data Preparation (Nov. 2019) to help sponsors evaluate their planned submissions of new study data. This worksheet provides clarification on how FDA validates submissions against TRC. The Self-Check Worksheet includes each TRC validation step to check for Errors 1789, 1734, 1735, and 1736. 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 updated Self-Check Worksheet Instructions(Nov.

[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).

2019) document was developed to provide additional details on each validation step and explain how sponsors can correct issues that cause TRC errors. The latest version of the Self-Check Worksheet and Instructions (Nov. 2019) reflects all updated made in the TRC (Oct. 2019). Some of the important updates were (1) the inclusion of the new section for Simplified TS and (2) the inclusion of SPREFID as an alternate study id match criterion for TRC validation rule 1734. FDA also recognized that many small business and especially non-clinical researchers find it difficult to generate Simplified TS file. FDA addressed this need and published a document called “Simplified ts.xpt Creation Guide” to generate a Simplified ts.xpt. This guide allows sponsors/applicants to generate a Simplified ts.xpt file using popular and free open source programming language tools such as “R” and “Python”. This guide has step by step textual instructions and graphical representations on how to install software’s, packages and scripts to create Simplified TS file with limited software experience. Additionally, the PHUSE Consortium developed an online utility to generate a Simplified ts.xpt file available to industry.

CONCLUSION

Reviewing study data in a timely manner is critical for FDA's review process. Currently, FDA has not rejected any submission that contains errors as reflected in these analyses. When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions. FDA plans to use the 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. Based on findings from the 2019 TRC conformance analyses of submissions with study data, FDA identified that missing ts.xpt (Simplified or full) especially for non-clinical studies is one of the leading causes of increased failure rates. To avoid rejection of submission in future, sponsors can ensure that these technical deficiencies are addressed. Moreover, FDA has developed the Self-Check Worksheet for Study Data Preparation and a guide to create a Simplified ts.xpt file as helpful resources to help Industry meet study data requirements. FDA intends that these efforts will improve conformance rates over time.

REFERENCES

“Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-standardized-study-data

“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/providing-regulatory-submissions-electronic-format-submissions-under-section-745aa-federal-food-drug

“Technical Rejection Criteria for Study Data”
https://www.fda.gov/media/100743/download

“Study Data Technical Conformance Guide”
https://www.fda.gov/media/131872/download

“FDA Data Standards Catalog”
https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

“Technical Rejection Criteria Self-Check Worksheet”
https://www.fda.gov/media/123098/download

“Technical Rejection Criteria Self-Check Worksheet Instructions”
https://www.fda.gov/media/123099/download

Simplified ts.xpt Creation Guide
https://www.fda.gov/media/132457/download

ACKNOWLEDGMENTS

The authors would like to thank Heather Crandall, Nitin Guptan, Ryan Olivett, Jiang Xu, Jonathan Resnick, Lisa Lin, Gang Wang, and other FDA staff for their time and effort in helping collect and analyze data and information as presented in this paper.

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/industry/study-data-standards-resources/study-data-submission-cder-and-cber

For the full list of study data standards, see the FDA "Study Data Standards Resources" page at: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

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