PhUSE US Connect 2020

Paper SI03

# FDA View: FDA Study Data Submission Update

Heather Crandall, CDER, US FDA, Silver Spring, USA

## ABSTRACT

Study Data Standards listed in the FDA Data Standards Catalog are required for clinical and non-clinical 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 which are specified in the "Technical Rejection Criteria for Study Data." FDA conducts quarterly analyses on submissions containing study data received by the agency to assess conformance rates to Technical Rejection Criteria for Study Data (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 SEND datasets, two, FDA included SPREFID as a valid source for study id in ts.xpt files, and three, FDA updated guidance for Simplified TS Files (Simplified ts.xpt).

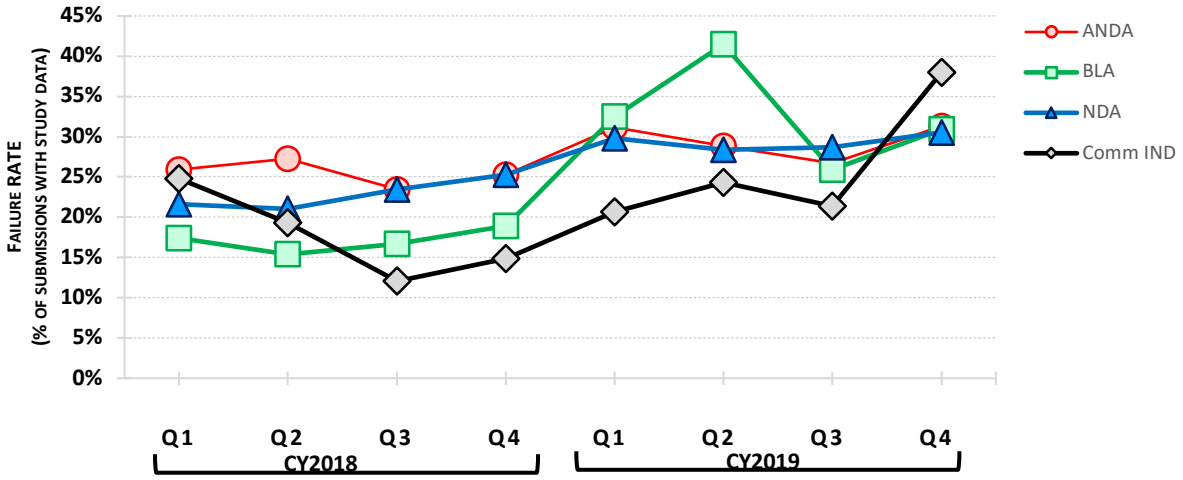
## INTRODUCTION

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" 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 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 DM dataset and/or define.xml must be submitted in required module 4 sections, or a DM 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 study tagging file (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 study tagging file anytime a 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 Technical Rejection Criteria (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 CY2018 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 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 Technical Rejection Criteria (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 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 Technical Rejection Criteria (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)

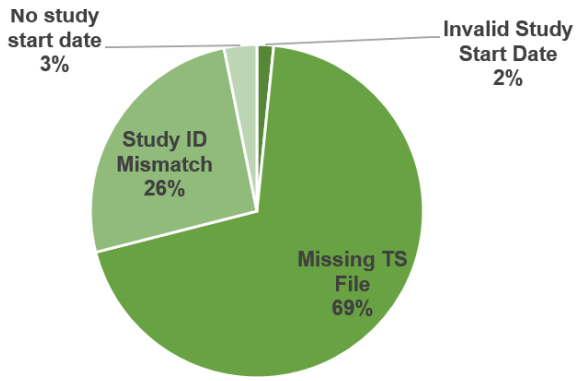
The increase in failure rates is primarily driven by additional non-clinical studies subjected to TRC which contain a study report with a file tag of 'pre-clinical-study-report', 'legacy-clinical-study-report' and/or 'study-report-body,' but not a TS file (ts.xpt). This scenario leads to a failure of 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.

## COMMON TRC ERROR REASONS

### VALIDATION RULE 1734

From the CY2019 analyses FDA observed that out of 2044 studies submitted in 1770 submissions 69% of the studies had a missing ts.xpt file. The other common error reason was "Study ID Mismatch" between STF and ts.xpt and "Invalid Study Start Date". The missing ts.xpt error is commonly observed for non-clinical studies. FDA realized that Jan 2019 TRC version did not provide enough clarification about expectation of a ts.xpt (Simplified or Full) especially for non-clinical studies and hence updated the TRC in Oct. 2019. This update gave more information on when a ts.xpt (Simplified or Full) is expected. The Oct. 2019 version also provided examples of Simplified ts.xpt and when sponsors can submit a Simplified ts.xpt with TSVALNF value as "NA". Nonclinical studies submitted in module 4 eCTD modules 4.2.3.1, 4.2.3.2, or 4.2.3.4 that includes study report with one of the following three file tags: "pre-clinical-study-report", "legacy-clinical-study-report" and "study-report-body" and/or .xpt formatted dataset must submit a TS file (Simplified or Full) according. However, there are certain non-clinical studies that are exempted from TRC for example non-clinical studies that do not require SEND Data (see Study Data Technical Conformance Guide Section 8.2.2 for details). Additionally, there may be non-clinical studies where a study initiation date is not relevant. In such cases a Simplified ts.xpt must submitted with TSVALNF as "NA" as shown below:

*Figure 1- TRC validation rule 1734 Error Reasons (2044 Studies)*




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

Below are two examples of a Simplified ts.xpt file submitted for a non-clinical study with study-id "S107" in the STF file:

| | STUDYID | TSPARMCD | TSVAL | TSVALNF |
|---|---|---|---|---|
| 1 | S107 | STSTDTC | 2014-10-26 | |

*Figure 2- Example of a Simplified TS with valid study start date*

Example of a Simplified ts.xpt file submitted for a non-clinical study with study-id "S107" in the STF file with a study start date "2014-01-26".

| | STUDYID | TSPARMCD | TSVAL | TSVALNF |
|---|---|---|---|---|
| 1 | S108 | STSTDTC | | NA |

*Figure 3- Example of a Simplified TS with valid TSVALNF value as "NA"*

Example of a Simplified ts.xpt file submitted for a non-clinical study with study-id "S107" in the STF file without a study start date or when a study is not required to submit SEND dataset.

The other reason for 1734 failure was study-id mismatch between stf.xml and ts.xpt. An alternate way for sponsors to provide a matching study id in the SPREFID parameter was also added to the Oct. 2019 TRC revision. This was based on feedback received from industry regarding cases where the study id match criteria between STF and ts.xpt 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. The addition of SPREFID will allow FDA to pass 1734 when a study id mismatch is observed between STF and ts.xpt study id. (See example of a Full ts.xpt with SPREFID below)

*Figure 4- Example of a Full TS file with SPREFID*

| | STUDYID | DOMAIN | TSSEQ | TSGRPID | TSPARMCD | TSPARM | TSVAL |
|---|---|---|---|---|---|---|---|
| 27 | pqr-456 | TS | 1 | | SPLRNAM | Test Subject Supplier | Strain X |
| 28 | pqr-456 | TS | 1 | | SPREFID | Sponsor's Study Reference ID | S107 |
| 29 | pqr-456 | TS | 1 | | SRANDOM | Study Is Randomized | FDA |
| 36 | pqr-456 | TS | 1 | | STSTDTC | Study Start Date | 2019-01-01 |
| 37 | pqr-456 | TS | 1 | 1 | TFCNTRY | Test Facility Country | USA |

TS STUDYID

Study Start Date

SPREFID

FDA also recognized that many small business and especially nonclinical 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.

**VALIDATION RULE 1735**

From the CY2019 analyses FDA observed that the most common error reason is "Incorrect file tag for define.xml" and "Missing DM and/or ADSL" file when standardized dataset are submitted. In CY2019, 787 studies subjected to validation rule 1735 out of which 85% of the studies had incorrect file tag for define.xml.

*Figure 5- TRC validation rule 1735 Error Reasons (787 Studies)*

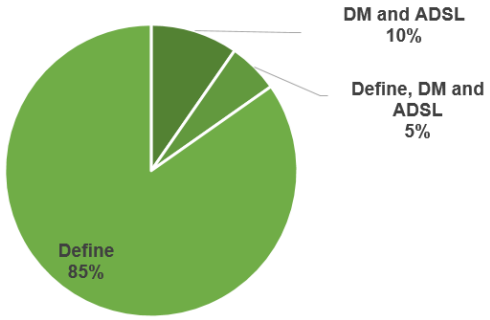
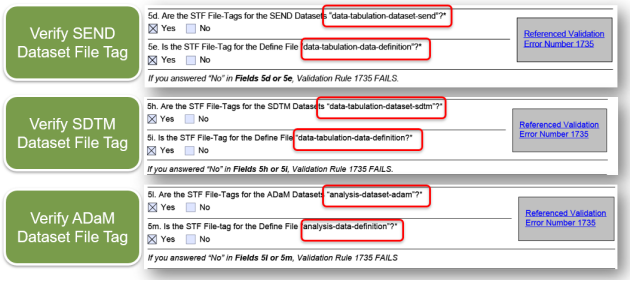


*Figure 6- Self Check Worksheet questions for 1735*




Sponsors can utilize section 5 of the revised Self-check Worksheet to make sure that for all standardized study data a DM and/or ADSL file and corresponding Define file is submitted

**VALIDATION RULE 1736**

Form the CY2019 analyses, out of 141 submissions subjected to TRC validation rule for 1736, there were 245 studies which had 1736 error. About 59% of the studies had a "Missing define.xml" and 35% of studies were "Missing dm.xpt and/or adsl.xpt" file when standardized dataset are submitted.

*Figure 7- TRC validation rule 1736 Error Reasons, Missing files (245 Studies)*

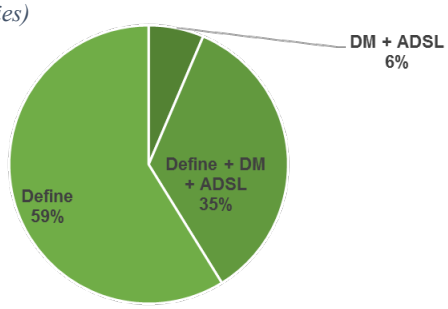
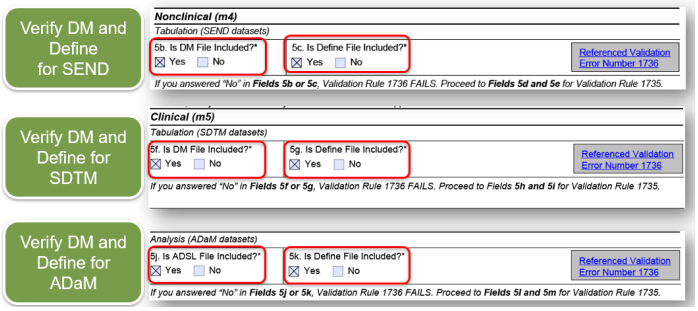



*Figure 8- Self Check Worksheet questions for 1736*




Sponsors can utilize section 5 (5b, 5c, 5f, 5g, 5j and 5k) of the revised Self-check Worksheet to make sure that for all standardized study data a DM and/roads file and corresponding Define file is submitted.

## 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 increase in failure rate. To avoid rejection of submission in future, sponsors need to make sure 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 Ethan Chen, 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

## CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Heather Crandall, CDER
US FDA
WO32, Rm 3160
10903 New Hampshire Ave
Silver Spring, MD 20993
Work Phone: 301-796-6929
Email: Heather.Crandall@fda.hhs.gov