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Abstract

The Nonclinical Topics Working group created a project to enable the industry to confidently know what TS files will be accepted and will avoid rejections. We created several sample ts.xpt files that the sponsors might create, submitted them to the FDA in eCTD format, and reviewed the FDA feedback. The results of this project are described here. We expect this information will be very helpful in practice.

Approach

- ❖ An eCTD was prepared as if it were a Commercial IND for CDER with 15 test scenarios
- ❖ The eCTD was submitted in section 4.2.3.2 repeat dose toxicology
- ❖ Unless otherwise indicated, for each test study:
 - Included a ReportX.pdf with Study Tagging File “pre-clinical-study-report” and Study ID of “StudyX”, where X is replaced with the test case letter.
 - A ts.xpt file with Study Tagging File “data-tabulation-dataset-send”
- ❖ The following ts.xpt files served as the baseline for the tests
 - With known study start date: (Test case N)

Name	Obs	Vars	#	Variable	Type	Length	Format	Informat	Label
TS	1	4	1	STUDYID	Character	6			Study Identifier
			2	TSPARMCD	Character	7			Trial Summary Parameter Short Name
			3	TSVAL	Character	10			Parameter Value
			4	TSVALNF	Character	1			Parameter Null Flavor

STUDYID	TSPARMCD	TSVAL	TSVALNF
1 StudyN	STSTDTC	2001-03-13	

- Study start date unknown: (Test case O)

Name	Obs	Vars	#	Variable	Type	Length	Format	Informat	Label
TS	1	4	1	STUDYID	Character	6			Study Identifier
			2	TSPARMCD	Character	7			Trial Summary Parameter Short Name
			3	TSVAL	Character	1			Parameter Value
			4	TSVALNF	Character	2			Parameter Null Flavor

STUDYID	TSPARMCD	TSVAL	TSVALNF
1 StudyO	STSTDTC		NA

- Test cases N and O were created using code from the FDA guidance [Creating Simplified TS.xpt Files](#)

The project results are important because:

- ❖ No one wants to be responsible for a technical rejection.
- ❖ Only sponsor organizations will receive warning messages between the project start and September 15, 2021, when the technical rejection criteria (TRC) will be implemented, AND only if they have a submission before then.
- ❖ Not all organizations involved in creating submission components will have the opportunity to create a test submission before the rejection criteria go into effect.
- ❖ An organized test reduced the burden on the FDA compared to each organization submitting test submissions.

Test Cases

Case	Test	Tool	Result
A	STSTDTC: 2001-03-13, TSVALNF variable missing	XPT Compare	PASS
C	STSTDTC: 2001-03	XPT Compare	FAIL
D	STSTDTC: 2001-03-13, TSVALNF: DERIVED	XPT Compare	PASS
D1	STSTDTC: 2001-03-13, TSVALNF: DER	XPT Compare	PASS
E	SPREFID matches study ID in study tagging file	submit™	PASS
F	STSTDTC: NULL, TSVALNF: NOT APPLICABLE	XPT Compare	FAIL
G	Full SEND 3.1 compliant ts.xpt with study start date	Roche In-house	PASS
H	Variable labels manually edited to incorrect values after file creation	PHUSE R Shiny with manual edits	PASS
K	Baseline w/ study start date	PHUSE R Shiny	PASS
L	Includes TSSEQ and TSGRPID	submit™	PASS
N	Baseline w/ study start date	FDA R script	PASS
O	Baseline w/ TSVALNF: NA	FDA R script	PASS
S	Full SEND 3.1 compliant ts.xpt with STSTDTC: NULL, TSVALNF: NA	submit™	PASS
T	Full SEND 3.1 compliant ts.xpt with STSTDTC: NULL, TSVALNF: NOT APPLICABLE	submit™	FAIL
U	2 nd SPREFID matches study tagging file	submit™	PASS
X	STSTDTC: 2021-07-02	XPT Compare	FAIL

Conclusions

- ❖ All tools used to create the ts.xpt created acceptable datasets
- ❖ Full YYYY-MM-DD STSTDTC required for acceptance
 - Study C
- ❖ When full STSTDTC was present, neither the absence of TSVALNF nor what it was populated with affected acceptance
 - Studies A, D, D1
- ❖ When the study start date was after the date requiring a full SEND data package and only a simplified ts.xpt was provided, the dataset was rejected.
 - Study X
- ❖ Datasets without a STSTDTC were acceptable as long as only NA was supplied in TSVALNF
 - Studies F, O, S, T
- ❖ Incorrect variable labels did not affect acceptance
 - Study H
- ❖ Additional variables and parameters, as specified by SENDIG v3.0 and v3.1, did not affect acceptance
 - Studies G, L, S, T
- ❖ The Study ID in the Study Tagging File can be successfully matched by one of multiple SPREFIDs when the ts.xpt STUDYID does not match
 - Studies E, U

Acknowledgements

Thank you to the FDA for evaluating this submission and the willingness to work with us on this project.
[See more details and links to study files at the PHUSE Advance Hub](#)

Disclaimer: This presentation is not guidance from the FDA. It shares the PHUSE project team’s experience submitting 16 illustrative scenarios on July 16, 2021, to the FDA’s test Electronic Submission Gateway. FDA guidance must be followed to ensure successful submissions.