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FDA View: Technical Rejection Criteria for Study Data

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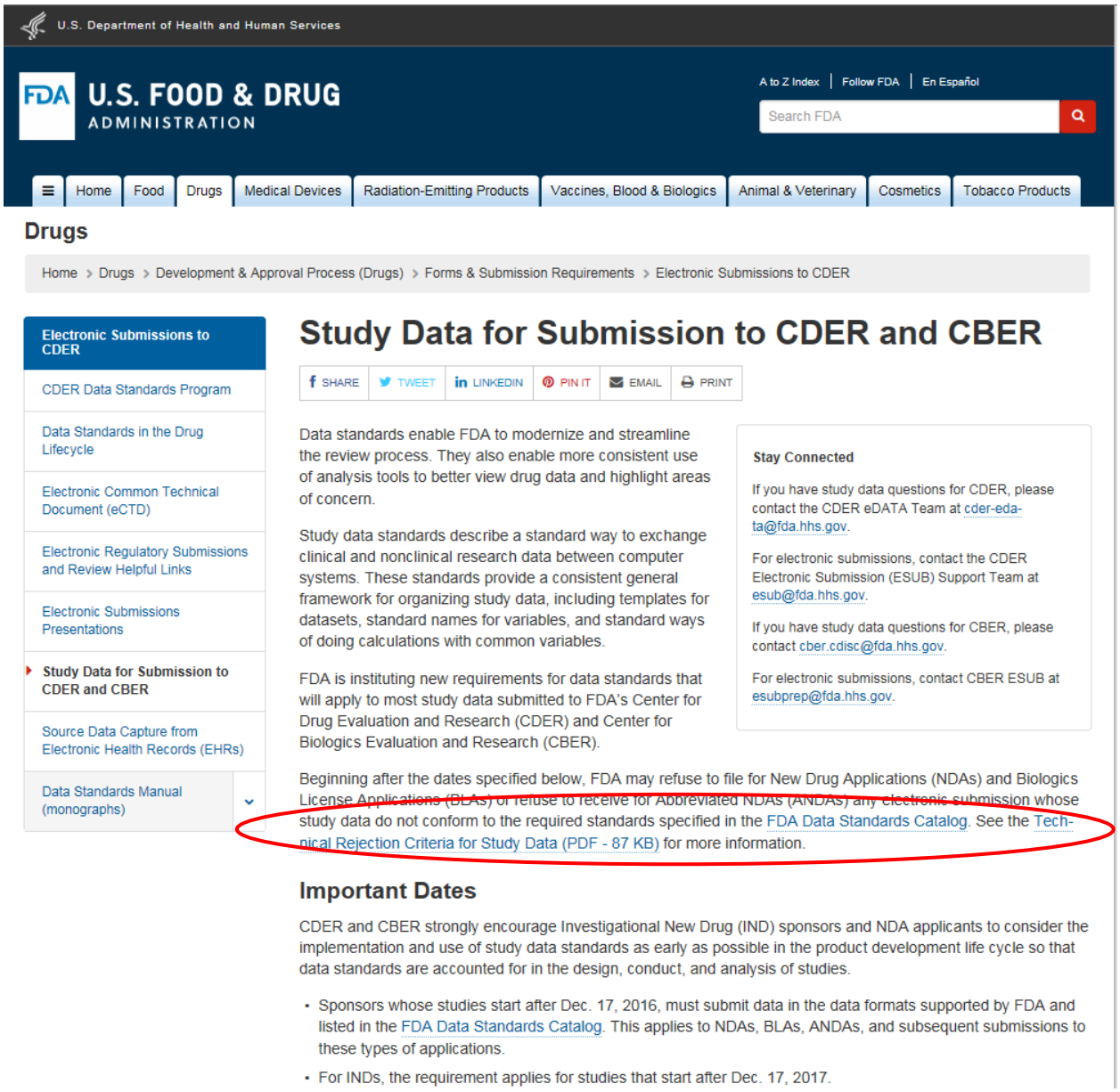
ABSTRACT

Study Data Standards listed in the FDA Data Standards Catalog are required for clinical and nonclinical studies that started after December 17, 2016. Technical rejection criteria have been added to the existing eCTD validation criteria to enforce compliance to the required study standards. Through the technical rejection process, FDA can reject an application because of its technical deficiencies, based on the severity of the eCTD validation criteria. eCTD validation consists of a unique assigned number, a description of technical errors, corrective actions, guidance source, effective date and its severity. FDA has identified two types of errors for the technical validation of study data in electronic submissions. High errors flag a serious technical error which prevents the processing of the submission and will require the resubmission. Medium errors flag an impact on the reviewability of the submission, but require further inspection by the review staff. FDA will implement a process to assess high-level study data standards conformance at the time the submission is submitted and validated.

FDA conducted an analysis based on submission with study data for applications (NDA/BLA/ANDA) received after December 17th, 2016 and commercial INDs received after December 17th, 2017. This presentation will describe the sample dataset and the results of using the technical rejection criteria to determine a potential technical rejection. The FDA will also communicate recommendations on how to correct issues and avoid validation failures.

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 submission 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. FDA published "Technical Rejection Criteria for Study Data" which specified the criteria to be used to assess conformance to the required Study Data Standards. When a submission is technically-rejected, the submission sequence is not transferred from the FDA Electronic Submission Gateway into the FDA electronic document rooms.



ECTD TECHNICAL REJECTION CRITERIA FOR STUDY DATA

"Technical Rejection Criteria for Study Data" specified the four technical rejection criteria to be used to assess conformance. Among them, two (Errors 1734 and 1736) are designated as High severity and the other two are designated as Medium (Errors 1735 and 1737). These technical rejection rules are being used check all FDA received NDA, ANDA, BLA, and Commercial IND. High severity rules will be used for refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs.

The technical rejection criteria are:

- Error 1734 (High severity): A Trial Summary (TS) dataset 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
- Error 1735 (Medium severity): The correct STF file-tags must be used for all standardized datasets 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
- Error 1736 (High severity): DM dataset and define.xml must be submitted in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4. DM dataset, ADSL dataset, 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

- Error 1737 (Medium severity): 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, no more than one dataset of the same name should be submitted as new

This paper describes the conformance statistics and the most common cases of validation failure against high severity rules.

COMFORMANCE STATISTICS TO (HIGH SEVERITY RULES) TECHNICAL REJECTION CRITERIA

OVERALL COMFORMANCE STATISTICS

Failure Rate	All	NDA	ANDA	BLA	Comm. IND
Total Number of Submissions	85,493	24,837	38,346	7,601	14709
Total Number of Submissions with Study Data	3,221	1,126	1,446	473	176
Total Number Submissions with Critical Errors	1,032	302	551	138	41
Error 1734	968	290	506	137	35
Error 1736 *	84	14	63	1	6
Failure Rate *(% among submissions with Study Data)*	**32.04%**	**26.82%**	**38.11%**	**29.18%**	**23.30%**

* Error 1736 validation is not performed if a study has Error 1734

Note
- One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments.
- NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2018
- Commercial IND Submissions received from 12/18/2017 to 3/31/2018
- Submission contains multiple studies can report both Errors 1734 and 1736

COMMON TECHNICAL REJECT CRITERIA VALIDATION FAILURE

TOP ERRORS FOR ERROR 1734 (968):
- Missing ts.xpt file for a study (753)
- No study start date (231)
- Invalid Study Start Date. Study Start Date must be in the format of (yyyy-mm-dd) (75)
- Study files in index.xml are not correctly linked to contents in study tag files (4)

TOP ERRORS FOR ERROR 1736 (84):
- Missing adsl.xpt or corresponding define.xml for a study (52)
- Study Definition File define.xml with file tag name key analysis does not exist for study (38)
- Missing define.xml for a study (36)
- Missing dm.xpt or corresponding definition.xml for a study (23)

*Multiple errors can co-exist in the same study

CONCLUSION

Based on the analysis, less than 70% all submissions were received with non-critical errors. However, identified errors are not difficult to correct. FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog. FDA has not rejected any submission that contains errors as reflected in this analysis. FDA plans to use technical rejection criteria 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

"Study Data Technical Conformance Guide"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

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

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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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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

CONTACT INFORMATION

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