How FDA will Reject non-CDISC submission

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ABSTRACT

Beginning **Dec 18, 2016**, all clinical trial and nonclinical trial studies must use standards (e.g., CDISC) for submission data and beginning **May 5, 2017,** NDA, ANDA, and BLA submissions must follow eCTD format for submission documents.

In order to enforce these standards mandates, the FDA also released "Technical Rejection Criteria for Study Data" in FDA eCTD website on October 3, 2016. FDA also implemented a rejection process for submissions that do not conform to the required study data standards.

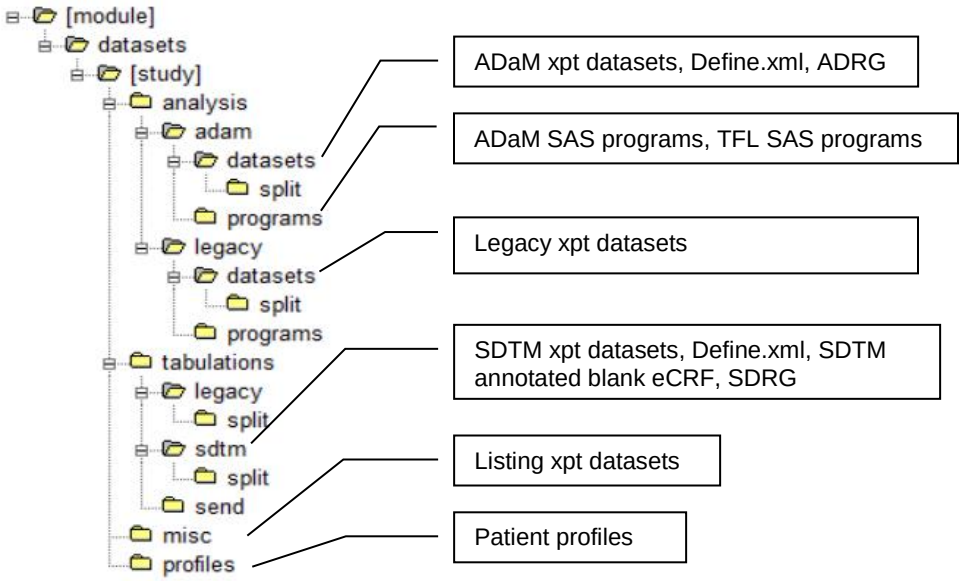
The paper will discuss how these new FDA mandates impact the electronic submission and the required preparation for CDISC and eCTD complaint submission package such as SDTM, ADaM, Define.xml, SDTM annotated eCRF, SDRG, ADRG and SAS® programs. The paper will introduce the current FDA submission process, including the current FDA rejection processes – "Technical Rejection" and "Refuse-to-File" and discuss how FDA uses "Technical Rejection" and "Refuse-to-File" to reject submission. The paper will show how FDA rejection of CDISC non-compliant data will impact sponsor's submission process, and how sponsors should respond to FDA rejections as well as questions throughout the whole submission process. Use cases will demonstrate the key technical rejection criteria that will have the greatest impact on a successful submission process.

STANDARDS (CDISC, eCTD) SUBMISSION DATA AND DOCUMENTS

The following items are usual CDISC data and submission documents used in the preparation for electronic submission.

- Protocol – pdf (e.g., study001-protocol.pdf)
- SAP – pdf (e.g., study001-sap.pdf)
- eCRF – pdf (e.g., study001-blankecrf.pdf)
- SDTM – xpt (e.g., dm.xpt, ae.xpt and ds.xpt)
- ADaM – xpt (e.g., adsl.xpt, adae.xpt and adtteos.xpt)
- SEND – xpt (e.g., dm.xpt, se.xpt, and bw.xpt)
- CSR – pdf (e.g., sutdy001-csr.pdf)
- Define file – xml or pdf (e.g., define.xml/define.pdf)
- ADaM SAS programs – txt (e.g., c-adsl.sas.txt)
- Efficacy SAS programs – txt (e.g., t-14-01-001-ds.sas.txt)
- Study Data Reviewer Guide, Analysis Data Reviewer Guide, Study Data Standardization Plan – pdf (e.g., study001-SDRG.pdf)

Datasets and submission documents are placed in submission folder as shown below.



INTRODUCTION OF CURRENT FDA STANDARD REVIEW PROCESS

Once a submission package is submitted to FDA, there are 4 stages of FDA review process.

- Process submission
- Plan review
- Conduct review
- Take official action

Process Submission

During this stage, FDA do the followings for the first 14 days.

- Receive a complete application through electronic submission gateway (ESG).
- Perform technical validation within 3 days.
- Issue “Technical Rejection” according to eCTD validation criteria if the submission fails on technical validation.
- Establish review team and distribute submission.
- Confirm user fee payment.

Plan Review

During this stage, FDA do the following from 14 days to 60 days.

- Assure application completeness and inspect readiness.
- Communicate potential Refuse-to-File and correctable filing deficiencies.
- Make filing decision (Refuse-to-File / File application).
- Organize the review tasks, review timelines and review schedules.
- Determine final review classification (Priority or Standard). Priority is 6 months review and Standard is 10 months review.

Conduct Review

During this stage, FDA do the following from month 2 to 8.

- Confirm and validate the sponsor’s conclusion of the drug (safety and efficacy).
- Evaluate the text in the proposed labeling.

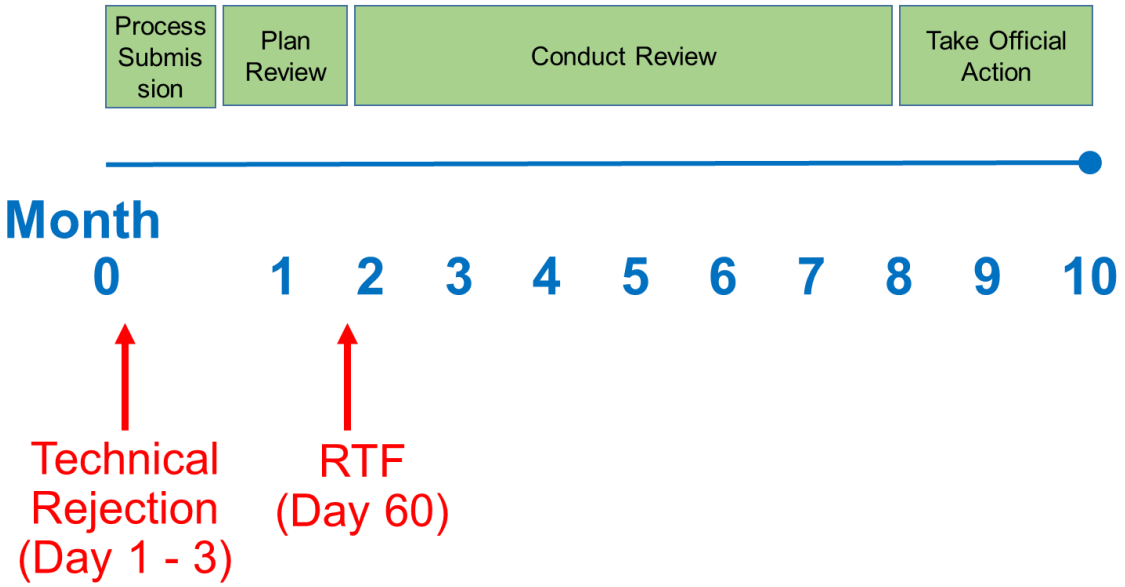
Take Official Action

During this stage, FDA do the following from month 9 to 10.

- Conduct wrap up meeting for any outstanding issues, safety and detailed labeling.
- Inform FDA decision to the sponsors – regulatory approval, an approval with conditions or a rejection.

FDA CURRENT REJECTION PROCESS

During the current FDA submission process, FDA can reject the submission two different ways – technical rejection and Refuse-to-File.



Technical Rejection
Through technical rejection process, FDA can reject the application because of its technical deficiencies. The technical rejection is based on eCTD validation criteria. eCTD validation criteria provide unique assigned number, a description of technical errors, corrective actions, guidance source, effective date and its severity. The severity of technical rejection will lead a different response from FDA.

- High – The error is a serious technical error which prevents the processing of the submission and will require the resubmission.
- Medium – the error may impact the reviewability of the submission, but it cannot be determined without further inspection by the review staff.
- Low – The error is a technical error which may or may not impact the reviewability or the integrity of the submission.

Refuse-to-File
Through Refuse-to-File, FDA can avoid unnecessary review of incomplete applications, and the sponsors can begin repair of critical deficiencies in the application far sooner than late in the submission process. FDA will refuse to file application if the application is in the following categories.

- The application is incomplete.
- The potentially correctable deficiencies cannot be easily modified or have not been modified.
- The application is inconsistent with regulatory practice.
- The application misses clinical data, ISS and ISE, statistical evaluation, CRF, Define.xml/Define.pdf, important variables and protocols.

HOW FDA WILL REJECT NON-COMPLIANT CDISC DATA SUBMISSION

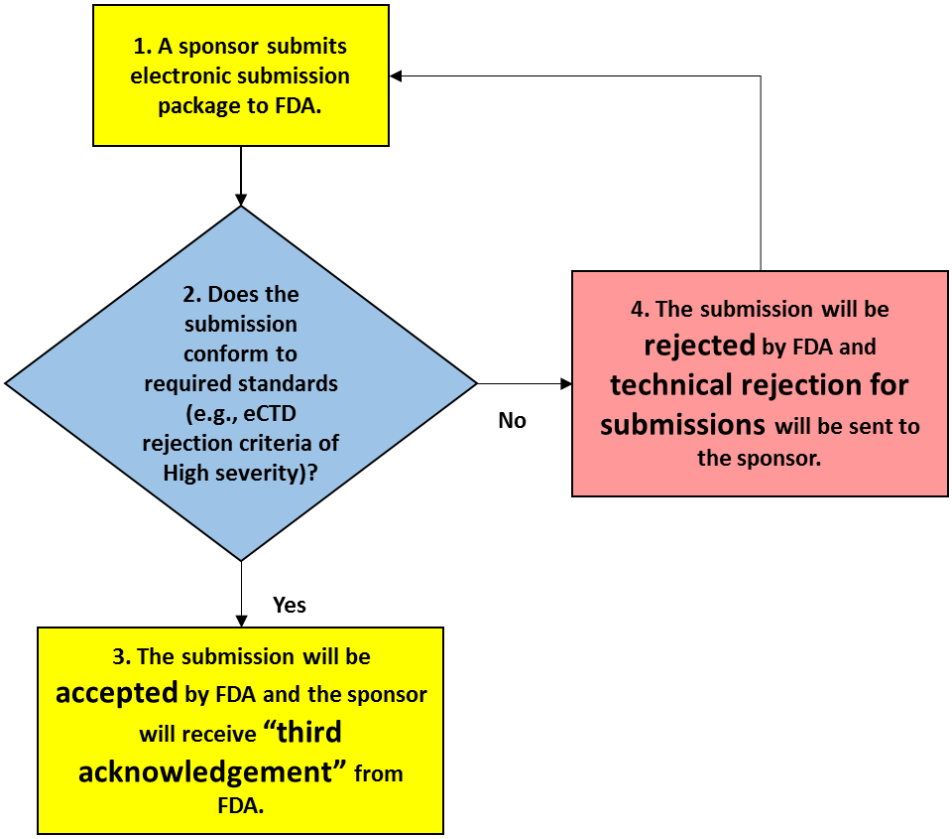
In order to enforce standards, FDA should reject non-compliant CDISC data. The question is how. Will FDA use the current rejection process (e.g., technical rejection, refuse-to-file) or implements the new rejection process specifically for non-compliant CDISC data submission?

Technical Rejection Criteria for Study Data
In order to enforce these standards mandates, the FDA just released "Technical Rejection Criteria for Study Data". It basically adds four additional rejection criteria to “eCTD Validation Criteria”.

- A trial summary (TS) dataset must be presented for each study. (High severity)
- The demographic datasets (DM) and Define.xml must be submitted for SEND and SDTM, and the subject level analysis dataset (ADSL) and Define.xml must be submitted for ADaM. (High severity)
- The correct Study Tagging File (STF) file-tags must be used for all standardized datasets. (Medium severity)
- For each study, no more than one dataset of the same type should be submitted as new. (Medium severity)

According to FDA, these four additional rejection criteria for study data were added to “eCTD Validation Criteria” because FDA wants to use a current rejection process rather than a completely new rejection process. Since first

two are in high severity, the sponsors need to prepare TS datasets for any submission and DM, ADSL and Define.xml for CDISC submission. If sponsors do not include TS dataset for the submission, FDA will reject the submission at Technical rejection.



Why TS domain is important

FDA emphasize TS dataset because study start date (TS.TSPARMCD=SSTDTC and TS.TSVAL="yyyy-mm-dd") will determine whether study started before December 17th, 2016 or after December 17th, 2016. If study started after December 17th, 2016, study should follow CDISC standards. So, this study start date will determine either CDISC data or legacy data.

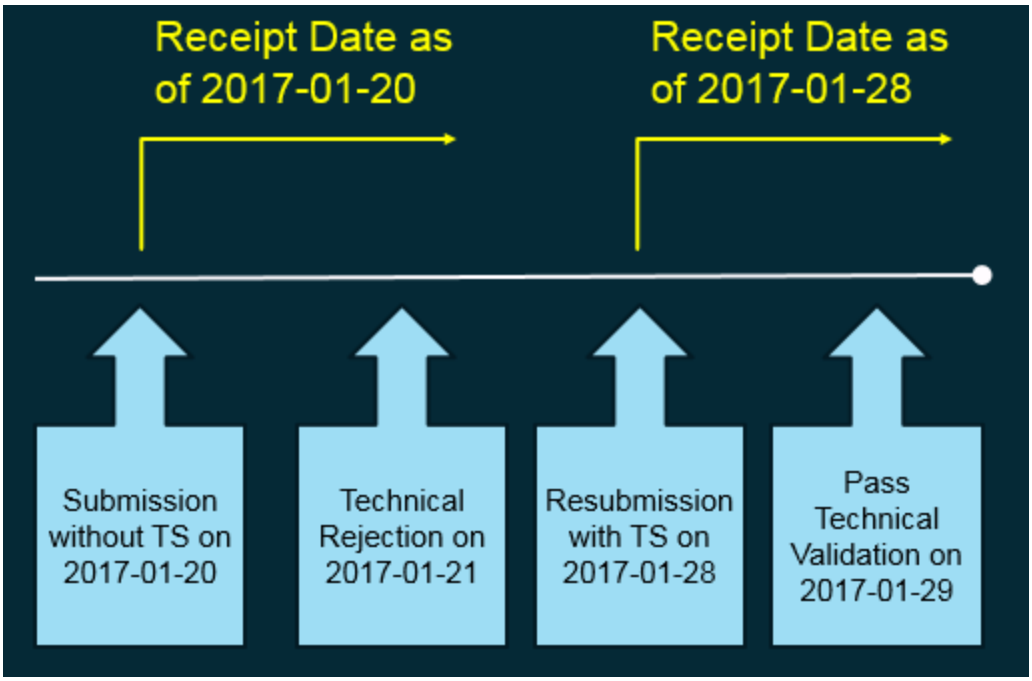
How to Respond to Technical Rejection

According to FDA, about 1% of submission fails in technical rejection. FDA will send "Technical Rejection for submissions" to the sponsors through ESG and also provide eCTD validation criteria error number (e.g., 1734 for missing TS). Sponsors should correct the issues (e.g., adding TS domain) and resubmit the package.

Use Cases for Technical Rejection

Below use cases can provide more clear pictures on how to respond to technical rejection.

1. A sponsor submits without TS on 2017-01-20.
2. A tentative application receipt date is 2017-01-20.
3. FDA rejects on 2017-01-21.
4. A sponsor re-submits with TS on 2017-01-28.
5. Now, a new tentative application receipt date is 2017-01-28.
6. FDA passes technical validation on 2017-01-29.
7. Now, an application receipt data is finalized as 2017-01-28 and FDA will start 2nd stage of submission process.



For any technical rejection, the sponsor can just simply fix the issues and re-submit the application. The issue of technical rejection is a delay in submission process. As seen in above use case, the sponsor loses 8 days, which means that this drug can't help patients earlier and the sponsor will lose 8 days of revenue.

HOW TO PREPARE

To avoid the technical rejections, the sponsors need to prepare TS domains both for legacy data and CDISC data and include Study Start date in TS domain. The sponsor also need to prepare DM, ADSL, Define.xml for CDISC data.

FUTURE REJECTION CRITERIA

"Technical Rejection Criteria for Study Data" contain only 4 rejection criteria. There are a lot more to validate CDSIC data. There are FDA CDISC business rules, SEND validation rules, SDTM validation rules and ADaM validation rules. So, FDA should include all the validation rules. It is not clear if FDA will add other CDISC validation rules to "eCTD Validation Criteria" or "Refuse-to-File" or if FDA add another rejection process specifically for CDISC data. One thing clear is that there will be more rejection criteria or rejection process in the future.

CONCLUSION

If the sponsors understand new FDA rejection criteria and process for CDISC data, the sponsors can prepare fully CDISC-compliant submission packages to avoid FDA technical rejection and in any rejections, the sponsors can quickly respond to FDA. In addition, to avoid any regulatory compliance issues, the sponsors need to keep up with any upcoming FDA updates on Standards (CDISC, eCTD), compliance validation and rejection process.

REFERENCES

Technical Rejection Criteria for Study Data
eCTD Submission Standards
Specification for eCTD Validation Criteria v 3.2
Study Data Technical Conformance Guide v 3.3
FDA Data Standards Catalog v 4.5
Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A (a) of the Federal Food Drug, and Cosmetic Act
Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data
Electronic Common Technical Document Technical Conformance Guide Version 1
Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Revision 3
Portable Document Format (PDF) Specifications Version 4
Specifications for File Format Types using eCTD Specification Version 1

Providing Regulatory Submission in Electronic Format – Receipt Date
Good Review Practice: Refuse to File

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CONTACT INFORMATION

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TRADEMARKS