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A Standardized Data Sample: Key to Improving the Submission Strategy

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ABSTRACT

As mentioned in the FDA's study data technical conformance guide, the agency offers a process for submitting sample standardized datasets for validation. Although sample submissions are tests only and not considered official submissions, they can be of a great value to sponsors in various ways. This paper is based on sponsor's practical experience of submitting sample submissions on five different compounds which are currently approved therapies in the market. The paper will walk through the key parts of a sample submission as well as how to plan and implement one. The paper will also discuss excerpts from the regulatory feedback received on sample submissions and how it helped in continuous improvement of sponsor's submission strategy.

INTRODUCTION

As mentioned in FDA's Study Data Technical Conformance Guide [1], there are two types of sample submissions. One is "eCTD Sample Submission" and another one is "Standardized Data Sample". This paper is about "Standardized Data Sample" which is referred to as sample submission in the remainder of this paper. The contents of this paper are based on regulatory references and author's practical experience of multiple sample submissions. The paper describes background about sample submission, typical process, why sample submissions are important, how to plan and implement it, and how author's practical experience has benefitted in continuous improvement of submission strategy. The scope of the paper is to only describe sample submissions to FDA. It is important to note that sample submissions are not mandatory based on author's understanding. Although this paper will highlight how it has benefitted author's organization, it is a sponsor's decision of whether to implement one or not based on various factors described later in this paper. The FDA's sample submission process described in the paper is based on latest information from FDA website at the time of writing this paper [2]. Sponsors should always refer to FDA's resources for latest information. The process described on FDA's sample submission webpage is meant for sample submissions to CDER. To enquire about CBER sample submissions, sponsors should check with respective review division.

WHAT ARE SAMPLE SUBMISSIONS

Sample submissions are submission of standardized study data sample to FDA for validation. They are tests only and not considered official submissions. They are also not reviewed by specific review division at any time. The validation does not involve any scientific review of the content. It is only intended to address conformance to FDA's electronic submission requirements and data standards.

FDA'S SAMPLE SUBMISSION PROCESS [2]

The contents described in this section are based on information on FDA's sample submission validation process page. As per FDA requirement, sponsors must have NDA, IND, BLA or ANDA number and plan to submit an actual submission to the FDA within 12 months of sample request. Once sponsor is ready to submit sample submission, the first step is to request a sample application number by sending an email to ESUB-Testing@fda.hhs.gov. The email should include the following:

- Contact's Name, Company Name, Mailing Address, Phone Number, Email Address
- NDA, IND, BLA, or ANDA number
- Planned Date of Official Submission
- Description of test requested, including application type (e.g., CDISC/SDTM, CDISC/ADaM or CDISC/SEND dataset)

The information in the email request for sample application number should also be provided in the cover letter of your sample submission. Once sample application number is communicated by electronic

submission representative from FDA, the next step is to submit sample of standardized data. Sponsor's should limit the sample submission to one of each data standards (i.e. SEND, SDTM or ADaM). The sample is not submitted via FDA's electronic submission gateway. It should be submitted as per the instructions provided along with sample application number.

After receiving feedback form the FDA, sponsors should review FDA's comments and correct all issues identified before making an actual submission. If there is an explanation for a data issue, it should be documented in the data reviewer's guide. The FDA does not recommend submitting the sample again as it will not be evaluated.

WHY SAMPLE SUBMISSION

Based on author's experience, below are some of the reasons why sponsors may consider doing sample submissions.

- It gives sponsors an opportunity to understand FDA's current thinking on data standards and submission requirements.
- It helps influence improvements to internal data standardization and submission strategy.
- It enhances collaboration and dialogue with internal regulatory team.
- It is a submission dry run opportunity for sponsors especially if sponsors have never done a submission before.
- Sometimes organization's operating model evolves resulting in changes to responsibilities for submission work. The sample submission can allow pressure testing of evolving operating models (if any) as it relates to submission work.

PLANNING AND IMPLEMENTATION OF SAMPLE SUBMISSION

The process of sample submission can vary in each organization depending on organizational structure, operating model, and resources. The following figure (Figure 1) explains how a process may look like for sponsors planning for sample submission. Usually a trigger for initiating a sample submission is upcoming regulatory submission such as NDA/BLA. Once timing of NDA/BLA submission is established, it is easier to plan timing of sample submission. As mentioned earlier in the paper, actual submission should be within 12 months sample request. This will allow enough time for sponsors to make any changes to data standardization approach based on feedback from the FDA. Secondly, based on author's experience, FDA may ask at pre-BLA/pre-NDA meeting whether sponsor has done sample submission.

As noted before, the review of sample submission is not done by the review division who will review the NDA/BLA application and there is no scientific evaluation involved in this review. Therefore, as soon as feedback is received, authors strongly recommend having a high-level cross-functional meeting with different key stakeholders within the organization to explain context of the feedback received and help alleviate any anxiety about it. The subsequent meetings can be held with relevant departments to develop a detailed plan of action in terms of any potential changes to standardized study data in NDA/BLA.

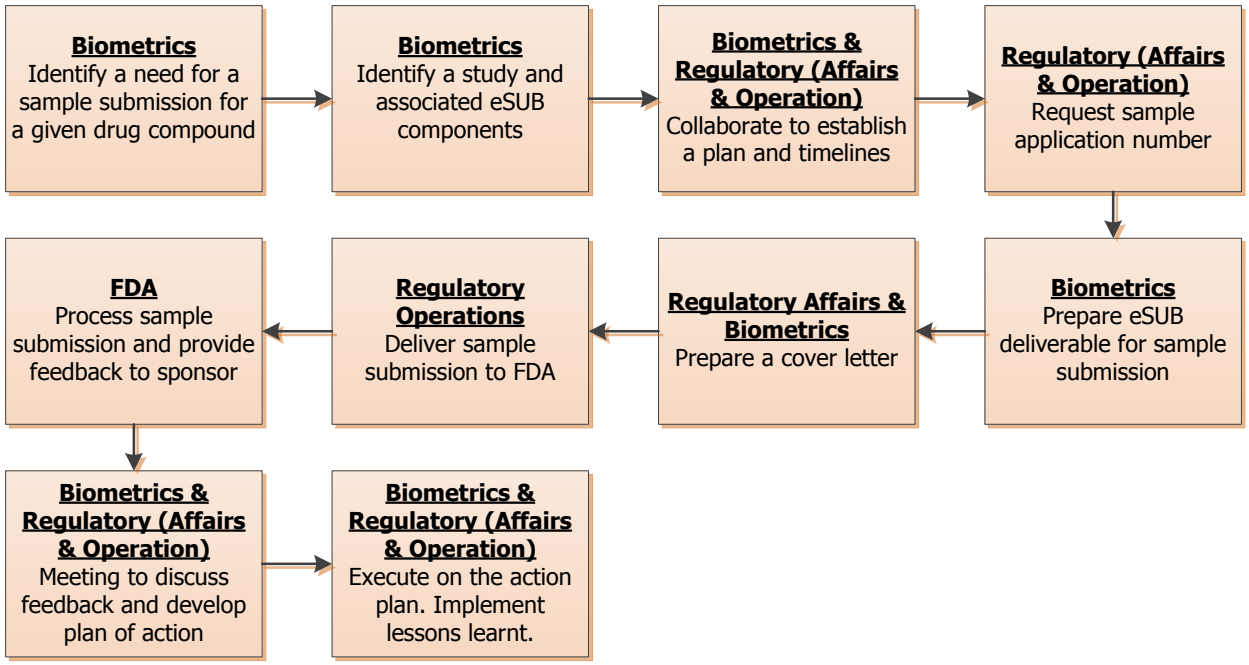

Figure 1. Sample Submission Procee Flow

PRACTICAL EXPERIENCE AND IMPACT ON SUBMISSION STRATEGY

Below is a list of sample submissions done at author's employment organization in the last five years.

Table 1. List Sample Submissions

Therapeutic Area	Type of Actual Submission	Sample Submission Timing	Actual Submission Timing
Hemophilia A (Biologic)	BLA to CBER	2012	2013
Hemophilia B (Biologic)	BLA to CBER	2012	2013
Multiple Sclerosis (Monoclonal Antibody)	BLA to CDER	2012	2013
Multiple Sclerosis (Monoclonal Antibody)	BLA to CDER	Q2 2014	Q1 2015
Spinal Muscular Atrophy (Small Molecule)	NDA to CDER	Q2 2016	Q3 2016

The table below has excerpts from the agency feedback received from some of the sample submissions listed in table 1 and it also has list of some of the actions taken by organization towards submission strategy.

Table 2. Sample Submission Feedback and Action Taken

Regulatory Agency Feedback	Action Taken Towards Submission Strategy
CBER Sample Submission – Response from CBER (Excerpts)	
• The submitted Define.xml was invalid. • The validation errors identified were not explained or were not adequately addressed. • Please resubmit a corrected define.xml to complete the sample submission (DEMO). • If these issues persist in the regulatory submission, it could result in “Refuse to File”.	• Resolved Define.xml errors. • Enhanced quality of reviewer’s guide (i.e. rationale for unresolved errors/warnings). • Resubmitted the sample submission. • Substantiated need for better software for define.xml. • Substantiated need for Biogen’s CRF update (related non-extensible codelist issue).
Multiple Sclerosis Sample Submission (MOAB) - Response from CDER (Excerpts)	
• Reviewer’s guide should be study-specific (versus one guide for multiple studies). • Reviewer’s guide should be placed in the same folder as datasets. • Validation issues should be explained, not just described. • Some warnings can and should be fixed. • Data should be mapped to existing controlled terms if equivalent (e.g. “INCLUSION CRITERIA” in the data is equivalent to “INCLUSION”).	• For actual filing, one reviewer’s guide per study was created and was placed in respective datasets folder. • Datasets were updated to remap data to existing controlled terminologies where possible. • Validation issue rationale language was updated where needed to provide rationale for an issue (versus describing the issue).
Multiple Sclerosis Sample Submission (another MOAB) - Response from CDER	
• Most recent version of data validation software is used. • Variables (e.g. EPOCH) requested by FDA in CDER Common Issues Document should be included in the dataset.	• For actual filing, data for all studies was validated using the latest version of data validation software (i.e. Pinnacle21 latest version). • A decision was made to always use the latest version of data validation software as a best practice.
Spinal Muscular Atrophy Sample Submission - Response from CDER	
• Few instances of confusing and potentially invalid computational method in define.xml. • Missing codelist or external dictionaries where they are expected. • Inconsistency in MedDRA version between define.xml and SDRG. • Codelists are merged across many variables. Codelist is expected to be variable specific (e.g. NY consists of 2 terms (Y, N) but valid values for DTHFL is Y or null). • All datasets should be properly file tagged	• Prepared and sent a response letter to FDA. • Issues identified were either fixed or explained in the actual filing. • Lessons learned in the preparation of submission package were used for working more efficiently under new operating model.

Regulatory Agency Feedback	Action Taken Towards Submission Strategy
to avoid being placed in the “unassigned”. • Other feedback based on Pinnacle 21 validation report.	

CONCLUSION

The sample submissions have been a key to improvement of submission strategy at our organization in the following ways:

- Improvements to internal eCTD folder best practices for study data.
- Software development (i.e. development of internal Define.xml tool to enhance quality).
- Implementation of best practice of using latest versions of validation software.
- Improvements to quality of rationale provided in the reviewer’s guide for validation errors/warnings that could not be resolved.
- Helped better manage internal disagreements and senior management support.
- Helped pressure-test evolving operating model.

The sample submissions are not mandatory. Sponsors should carefully evaluate need for doing it in their organization. To evaluate the need, sponsors can consider various factors such as upcoming submission, size of the group, operating model, decision making framework, resources, management support etc.

REFERENCES

1. FDA Study Data Technical Conformance Guide: https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
2. FDA Sample Submission Web Page: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

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