Practical Guidance for Successful BLA Submissions from a Statistician's Perspective

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Abstract

This paper describes lessons learned from recent Biologics License Application (BLA) submissions. Paper provides an overview of submission packages and requirements by Federal Drug Agency (FDA). A successful BLA submission can be achieved with careful planning, persistent adherence to the plan, and a collaboration between team members. This paper focuses on the clinical section of the common technical document (CTD) components and data submission and tips on how to avoid technical rejection. Paper includes tips on planning, content, technical issues, and FDA interactions based on our experience and a literature review.

Key Words: Guidance, BLA, electronic submission (eSubmission), CTD components

1. Introduction

Submitting a marketing application to the FDA is the first step for the products being approved. Both FDA and sponsors have activities which needs to be completed prior to the product being approved. Any of the steps required for submission which is not complete will lead to delays in product approval. This paper covers 4 key topics for BLA submissions, filing and review process overview, technical rejection criteria, planning eCTD documents for submission, and collaboration between and within teams preparing the submission.

1.1 Filing and Review Process Overview

Once a submission is received, through method of submission, via the FDA Electronic Submissions Gateway (ESG). the NDA/BLA review process proceeds through the following 5 phases. Submission Processing, Filing Determination and Review Planning, Full Review, Official Action, Post-Action Feedback.

After an NDA is received, the FDA has 60 days to decide whether to accept the file so it can be reviewed. If the FDA accepts the file the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. The overall goal of the review process is to provide a thorough but efficient mechanism whereby the safety, effectiveness, and quality of a product can be adequately assessed, and a regulatory decision can be made in a timely manner. The amount of time that applications spend between initial submission and a final regulatory decision varies. Current FDA performance goals under the Prescription Drug User Fee Act (PDUFA) stipulate that FDA

intends to review and act on 90% of standard NDA and BLA submissions within 10 months of the filing date. The goal for priority review applications is 6 months.

1.2 FDA Study Data Technical Rejection Criteria (TRC)

Because all commercial marketing applications are now submitted electronically, the first hurdle is to pass an automated technical review of study data. If a submission is missing key components or the study data fail to meet technical conformance criteria, then the application will receive a technical rejection. 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 (updated in October 2020). Sponsors must conform to standards in the FDA Data Standards Catalog: NDA, BLA, ANDA studies that started after December 17th, 2016. Commercial IND studies started after December 17th, 2017. Technical Rejection Criteria for Study Data developed to help industry understand how FDA is using eCTD validations to check conformance. FDA Data Standards Catalog was updated (March 2021), contains footnote re: Simplified TS.XPT file.

TRC effective date published: Electronic Common Technical Document (eCTD) web page, Specification for eCTD Validation Criteria, and within the TRC document
Warning notice was sent between March 15th and Sept. 15th, 2021 for submissions failing eCTD validations in TRC. Starting Sept 15th, 2021, if a submission fails eCTD validations in TRC, CDER and CBER will reject. The key technical rejection criterions for study data effective September of this year are summarized below.

Error	Description (Reference to FDA Study Data Technical Rejection Criteria March 2021 version)	Severity Level	Effective Date
1734	A dataset named ts.xpt with information on study start date must be present for each study in required sections in Module 4 and 5	High	9/15/2021
1735	The correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections in Module 4 and 5	High	9/15/2021
1736	For Standard for Exchange of Nonclinical Data (SEND) data, a Demographic (DM) dataset and define.xml must be submitted in Module 4 required sections in Module 4 and 5 For Study Data Tabulation Model (SDTM) data, a DM dataset and define.xml must be submitted in Module 5 required sections in Module 4 and 5 For Analysis Data Model (ADaM) data, an ADaM Subject level analysis dataset (ADSL) dataset and define.xml must	High	9/15/2021

	be submitted in Module 5 required sections in Module 4 and 5		
1789	A file has been submitted in a study section without providing an STF file. STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing reports	High	9/15/2021

2. Planning

Planning phase includes eCTD required documents planning. There are many nuances to the eCTD, but in its simplest terms, the eCTD is a standardized arrangement of documents that allows for the consistent and comprehensive presentation of information within a submission. eCTD submissions include 5 parts, termed modules, with each containing a specific type of information.

2.1 Planning- eCTD Modules

Below is the list of modules contained in the eCTD:

Module 1 (not technically part of the CTD): region-specific administrative information
Module 2: manufacturing, nonclinical, and clinical overviews, and summaries
Module 3: detailed manufacturing information
Module 4: nonclinical study reports
Module 5: clinical study reports (CSRs)

Chemistry, Manufacturing, Controls-CMC modules (module 3 and summaries in module 2). This part of the dossier covers those aspects that deal with the nature of the drug substance and drug product, the manner in which they were developed and are made, and the control aspects of the manufacturing process. These modules are expansive and can be tedious and time-consuming to complete. Because more documents typically mean more reviewers, it is suggested to combine permitted sections in an effort to streamline the management of authors and versions.
As a general rule, a more simple and clear structure for the documents should be considered in order to avoid issues throughout the lifecycle of the application. The “M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use” can be used as a reference to determine the permitted granularity.
Although legacy CSRs can be submitted as one document, the current recommendation is to divide CSRs into sections: synopsis, report body, and individual appendices.
Preparing a CSR in this format allows reviewers to more easily navigate the large amount of information, leading to more efficient reviews. In addition, by dividing the report into sections, changes can be more easily tracked, as the entire report does not need to be replaced if only one section is updated.
Every study report, both nonclinical and clinical, is required to have a study ID and title inserted into the submission. As such, it is important to ensure that all reports have a unique

ID associated with them prior to sending to publishing team. One of the most common issues that publishers encounter is attempting to hyperlink to a section and realizing that the section either does not exist or that it cannot be linked. Some of this is due to typographical errors during document authoring; however, many instances occur due to a lack of understanding by the authors of what content can actually be linked. As a general rule, hyperlinks can only be made to individual documents and not to section folders. For example, a frequent mistake when hyperlinking is referencing a section that is of a higher level of granularity than that to which the documents are written.

2.2 Planning-Communication

Communication involves, communication with FDA and communication within study team who is involved in the submission activities.

2.2.1 Communication with FDA

In order to communicate effectively with FDA, the FDA has provided formal guidance on best practices for communication between Sponsors and the FDA. This guidance provides helpful strategies for streamlining communication and promoting efficiency for each submission.

Key do's and don't are listed below:

Do contact the Regulatory Project Manager (RPM) assigned to your program.
Do NOT contact the FDA unless you are authorized to do so.
DO NOT contact FDA reviewers.
Do respect the chain of command.
Do establish a communication strategy.
Do set up a secure email.
Do follow-up phone calls with a written communication to the RPM.
Do enlist the help of an experienced consultant with submissions.

2.2.2 Communication within submission-study teams

Planning includes planning within study teams. In order for submission without issues, communicate effectively within submission-study teams via regular meetings.
Prepare a program level analysis packages and submission documents as a template to ensure consistency across studies. Some examples can include table package for CSRs, ADRG, and ARM documents.

2.3 Planning-Tabulation Package

Collected data should be mapped in accordance with valid SDTM version. Valid version can be located on FDA Data Standard Catalog: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources. This clinical package is submitted under the Module 5 of the eCTD under folder: m5/tabulations/datasets/sdtm.

Tabulation package deliverables include:

SDTM datasets

The SAS Transport Format (XPORT). Note that, Version 5 is the file format for the submission of all electronic datasets (e.g. ts.xpt, dm.xpt, etc.). Datasets submitted greater than 5 GB should be split into smaller datasets.

Define.xml, define.pdf

Team needs to ensure all links are working. Derivation rules are correctly documented in plain English.

acrf.pdf

Apply different font and background color when two domains are used on the same page
When data is recorded on the Case Report Form (CRF) but is not submitted, the CRF should indicate NOT SUBMITTED. There should be an explanation in the cSDRG stating the reason data was not been submitted.

cdsrg.pdf

This document facilitates FDA review by describing the standards used in the study; any special considerations; and conformance issues that may help a reviewer to understand the relationship between the study report and the tabulation data.

2.3 Planning-Analysis Package

Datasets within the analysis package are generated using the SDTM data. This package is submitted under the Module 5 of the eCTD folder: m5/analysis/datasets/adam.

ADaM datasets

The SAS Transport Format (XPORT). Note that, Version 5 is the file format for the submission of all electronic datasets (e.g. adsl.xpt, adae.xpt, etc.). Datasets submitted greater than 5 GB should be split into smaller datasets. Sponsors should submit these smaller datasets, in addition to the larger non-split datasets. The split datasets should be placed in a separate sub-directory labeled split.

Define.xml, define.pdf, csdrg.pdf

Team needs to ensure all links are working. Derivation rules are correctly documented in plain English.

Analysis Results Metadata.pdf (ARM)

ARM Identifies tables, listings, and figures that support the primary and key secondary analysis and provides a link to the analysis datasets and programs. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. At minimum sponsor should submit the programs that create all ADaM

datasets and those that generate tables and figures associated with primary and secondary efficacy analyses.

2.4 Planning-Bioresearch monitoring (BIMO)

The BIMO package supports site inspection and should be provided for all pivotal studies in CDER submissions. This package is submitted under the Module 5 of the eCTD (m5/datasets/bimo/site-level).

Deliverables	Comments
Subject-Level Data Line Listings	For each pivotal study, prepare the subject data listings (PDF) organized by site.
SUMMARY-LEVEL CLINICAL SITE DATASET	A single summary-level clinical site dataset (clinsite.xpt) that contains the pivotal studies used to support primary safety and/or efficacy endpoints
define.pdf	Required to submit for BIMO review
define.xml	XML format is optional Version 2.0 with a style sheet Make sure all links are working Derivation rules are correctly documented in plain English
bimo-reviewer-guide.pdf	This document is optional but can be beneficial for inclusion This document provides FDA reviewers with context to the clinsite.xpt dataset, terminology, and summary of BIMO package. Submission of this document does not eliminate the need to provide a define.pdf file.

2.4 Assembly Review (Contributor Review) of eCTD Deliverables

This review is to ensure that the contents of the assembled submission are complete and contain the correct finalized files and that all links are working. This review occurs once dropped off files are assembled by the submissions/publication team.
Reviewer should confirm that folder does NOT contain any EXCEL, WORD, Text, or Power Point files (e.g. Pinnacle 21 reports, issue logs, mapping specifications), and there is no password protected files.

3. Collaboration

The preparation of eCTD applications requires substantial planning, organization, and resources. To limit the number of issues that arise during publishing, a few key questions should be considered:

- Is the document or application prepared in a way that allows for the most efficient review and navigation?

- If a change is needed, can the relevant section be easily replaced without impacting the structure of the application?
- Is each document written so as to easily fit into the eCTD structure?
- Do all hyperlinks reference a valid target document?

In order to avoid issues within and between submission documents teams should have a final submission strategy plan which will be applied to documents. Teams should stay on track with the plan to avoid the inconsistencies and delays.

4. Conclusion

Even if submission team has years of experience with regulatory submission, small changes in guidance's or specifications that contribute to submission documents can have significant repercussions.
Prior to starting your submission, you should meet with team and plan a strategy for the submission plans and determine the best organization for your program. As there are slight differences between eCTD versions, it is also important to discuss the preferred eCTD version with your team prior to preparing your application.

References

Study Data Technical Conformance Guide:https://www.fda.gov/media/122913/download
Therapeutic Area Information & Specifications, FDA Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (OVRR): https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf
Human Immunodeficiency Virus:https://www.fda.gov/media/112667/download
Summary Level Clinical Site Data for CDER's Inspection Planning: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf
Guidelines for Requesting Waiver to Current Supported Study Data Standard Versions: https://www.fda.gov/drugs/forms-submission- requirements/guidelines-requesting-waiver-current-supported-study-data- standard-versions
FDA Data Standard Catalog: https://www.fda.gov/industry/fda-resources- data-standards/study-data-standards-resources
Technical Rejection Rules: https://www.fda.gov/media/100743/download
eCTD Submission: FDA Guidelines & Avoiding Common Mistakes
Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
The Comprehensive Table of Contents Headings and Hierarchy (FDA)
The eCTD Backbone Files Specification for Module 1
M2 eCTD: Electronic Common Technical Document Specification (FDA Guidance for Industry)
M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (FDA Guidance for Industry)
M4E: The CTD – Efficacy (FDA Guidance for Industry)
M4Q: The CTD – Quality (FDA Guidance for Industry)
M4S: The CTD – Safety (FDA Guidance for Industry)

M4S: The CTD – Safety Appendices (FDA Guidance for Industry)