

Tips on Creating a Strategy for a CDISC Submission

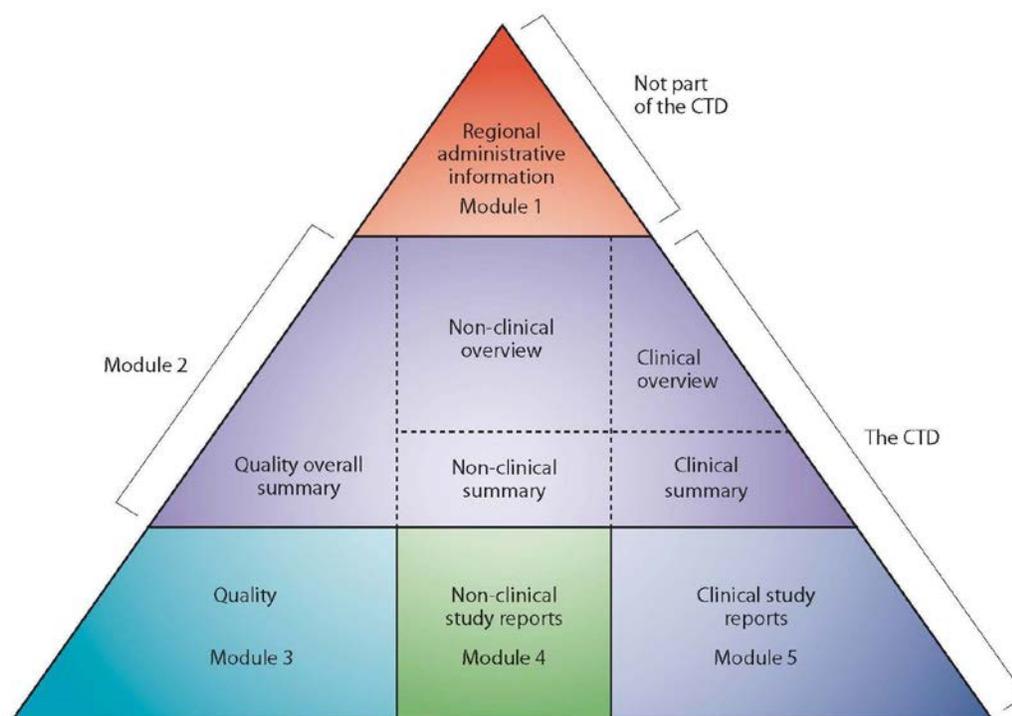
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ABSTRACT

A submission to FDA for an NDA (New Drug Application) or a BLA (Biologics License Application) is very exciting as well as very critical for a company. Companies and programmers who are dealing with submission for the first time are often confused on how to develop a strategic plan and how to do a successful filing. A clear strategy and proper planning is very critical for a timely submission. This paper will discuss on some basics about electronic submission and then it will provide guidance on how to plan things out for a successful filing. This paper will also discuss on what to look out for while working with an outside vendor for preparing electronic submission related deliverables.

INTRODUCTION

The eCTD (electronic common technical document) is CDER/CBER's standard format for doing regulatory submission electronically. Having data in common electronic environment eliminates difficulties with assessing, searching and finding data in paper forms.



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Figure 1. eCTD Modules. (Image Source ww.ich.org)

The eCTD is organized into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions.

Module 1 is not part of the ICH eCTD standard as it has been designated to each regulatory authority to define the contents of Module 1 for the regulatory and administrative documentation it requires with the different types of applications.

Module 2 contains the summaries and overviews of Modules 3 through 5. Everything contained in Modules 3 through 5 must be summarized along with a critical analysis of the findings about the pharmaceutical or biotechnology product

Module 3 contains the documentation about the chemistry, manufacturing, and controls content of the submission.

Module 4 contains the nonclinical (animal and in vitro) studies that have been conducted to support the company's assertions about the safety of the product. It includes the pharmacology, Pharmacokinetic, and toxicology studies and datasets that are required to be conducted during preclinical development, and phases 1 through 4 of clinical development

Module 5 contains the clinical (human) studies that have been conducted to support the company's assertions about the efficacy of the product. It includes case report forms and datasets. The study types include bioavailability, pharmacokinetic, pharmacodynamic, efficacy and safety studies and any post marketing studies.

In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to the FDA. Most of the programmers have to deal with Module 5.

This paper is geared towards audiences who have little or no prior experience with regulatory submission.

PLANNING AND PREPARATION

Planning out the overall filling strategy for regulatory submission is the most critical and important piece.

Below are few key points to consider while planning for regulatory submission.

CDISC STANDARDS OR LEGACY STANDARDS

Often, sponsor companies are in situation where newer studies are in CDISC format and older studies are in legacy (non-CDISC) format. The question whether to convert legacy studies into CDISC format or not often comes up during the planning phase. The FDA mandate for CDISC submission starts from 2017. All studies that start in 2017 or later will be required to submit their data to the FDA in CDISC standards. For submission happening before this date, sponsor can consider following key points for decision making.

Number of Studies and Weightage

Even though obvious, it is important to determine which studies will part of submission and which studies will be pooled for ISS/ISE. Sponsor need to evaluate - How many studies need conversion? Is pivotal study and key supporting studies are in CDISC standards or not? Sponsor need to evaluate weightage of legacy studies in overall submission. If the legacy studies are not very critical for submission then SDTM/ADaM conversion may not be needed.

Resources and Time

Another aspect to consider is resources and time needed for conversion. Sponsor need to consider cost of conversion in terms of resources and money spent and also whether sponsor has time needed for conversion.

ISS and ISE

If legacy studies (non-CDISC studies) are part of ISS/ISE then sponsor should consider converting legacy studies into SDTM format to make pooling easy.

DATASETS TO SUBMIT

If sponsor decides to convert legacy datasets into CDISC standards then often question comes up on which datasets to submit – Legacy or SDTM or both?

Analysis Consideration

If study is a closed out study and CSR is already written then sponsor need to consider whether there is a real need to convert legacy (non-CDISC) datasets into CDISC standards or not. If these legacy studies are part of pooled ISS or ISE then sponsor can convert the legacy raw datasets into SDTM standards without re-doing the whole analysis .i.e – ADaM datasets, TLF, etc. In this case, sponsor can submit legacy datasets (raw + analysis) as well as SDTM datasets. Also, sponsor should provide proper documentation to aid regulatory review and make sure both SDTM and legacy datasets meets the requirements for regulatory submission.

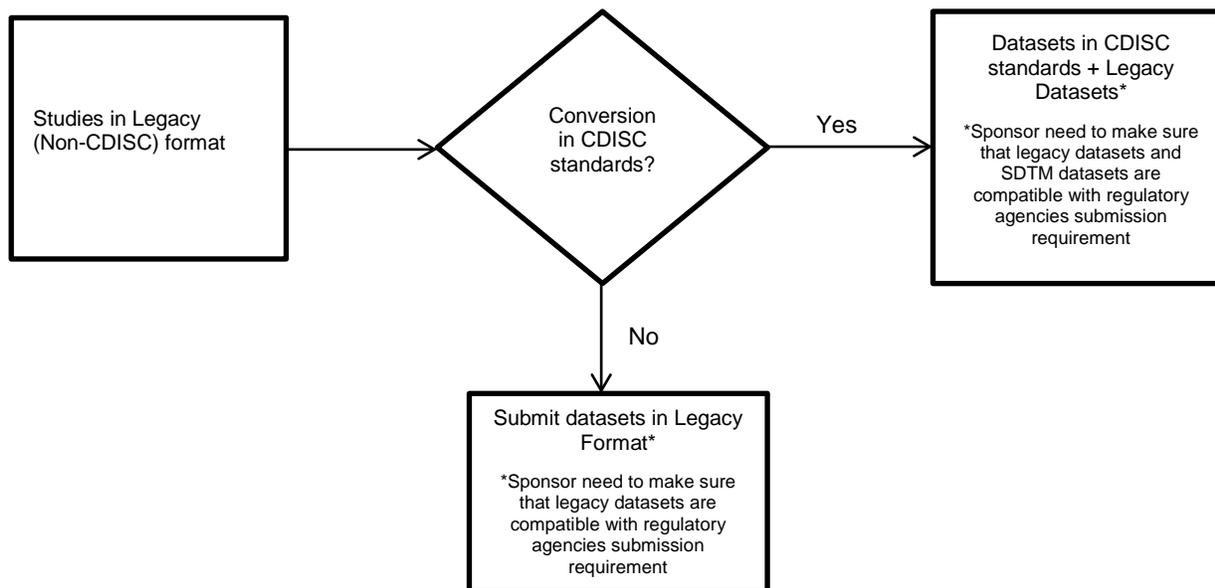


Figure 2. Dataset Submission Decision Making

VENDOR NEGOTIATIONS

It is common for sponsor companies to outsource whole study or part of study work to outside vendors. However, it is sponsor's responsibility to check the quality of deliverables. Many times sponsors deal with more than one vendor which makes it more challenging to co-ordinate; track and review the deliverables. Sponsor can smooth out the whole cycle by selecting capable vendors and as well as effectively negotiating with vendor for deliverables. Below are some tips to ease out the review cycle.

SDTM review

For optimal SDTM review, sponsor can request SDTM aCRF(annotated CRF) from vendor upfront during development phase. Many vendors do not provide SDTM aCRF till SDTM programming is complete and datasets are final. Sponsor has to review datasets using only SDTM specifications. Also, the layout and content of specification varies from vendor to vendor which makes it difficult for reviewer to review SDTM datasets just from specifications. aCRF tremendously helps sponsor as they can see how CRF pages are mapped as well ensures all the CRF pages are mapped. It is also easy to compare SDTM mapping among many studies if aCRFs are available.

Conformance Checks

It is advised to run conformance checks (like OpenCDISC checks) on SDTM/ADaM datasets during development phase and not at the end of the dataset programming. For outsourced studies, sponsor can request vendor to provide conformance check report with each dataset transfers. Running conformance check in advance provides sponsor enough time to address errors/warning originating from conformance checks. It also avoids last minute changes when time is critical.

Sponsor can request vendor to provide explanation for each error/warning within conformance check reports. Also, sponsor need to ensure version of conformance checks are in line with SDTM and ADaM version.

Deliverables Format and Content

Format, Style and Content of deliverables required for submission could be different from vendor to vendor. Sponsor can request vendors to provide a sample of deliverable before initiating actual work to see if it is in line with sponsor's expectation. For e.g. if sponsor needs define.pdf or reviewer's guide for submission, then sponsor can request a sample of these documents from vendor to see if they meet the requirements. Sponsor can then negotiate with vendor to format needed deliverables as per the requirements.

Many vendors have developed their own tools for generation of define documents. These tools needs input for e.g.

dataset specification in certain format. If sponsor is producing specification in-house, then sponsor can provide a sample of specification documents in advance to vendor to see if it's compatible with vendor tools. If not then sponsor can negotiate who can make necessary adjustments to make it compatible.

VERSIONS

While dealing with clinical trials data and with ISS/ISE programmers often have to make decisions regarding which versions to be used for different type of data.

MedDRA

If sponsor is planning for Integrated Summary of Safety database (ISS), then ISS database should be up-versioned using latest version of MedDRA. If legacy studies are getting converted into SDTM format for ISS then there is no need to up versioned individual studies MedDRA version.

CTCAE

CTCAE used for lab toxicity grading can be updated for ISS lab dataset similar to MedDRA. Sponsor can look at the latest version CTCAE version used across all studies and then update ISS lab dataset with that version. While converting legacy studies into SDTM standard, sponsor can stick to the original CTCAE version.

WHO Dictionary

Conmed(Concomitant Medication) can also be up-versioned using latest WHO dictionary version. Again, legacy or closed out studies does not need to be up versioned.

OpenCDISC for Conformance Checks

OpenCDISC is commonly used to run conformance checks on SDTM and ADaM datasets. It is advised to use latest available OpenCDISC version pertinent to SDTM/ADaM version sponsor is using. Sponsor need to pay attention to the version updates for OpenCDISC and work with vendor to use the appropriate version.

SDTM/ADaM

Situation where few studies are in CDISC standards and few others studies are in legacy standards, if sponsor decides to convert legacy studies, then it is advised to choose SDTM/ADaM version with utmost consideration. Studies with different versions may require extra efforts while pooling for ISS/ISE.

Controlled Terminology

For studies which are on-going, sponsor can the use latest version of CDISC Controlled Terminology. Since CDISC controlled terminology is released periodically, it is possible to have some variations across studies if they were carried out at different time frame. For ISS/ISE sponsor can use the latest version of Controlled Terminology to address study specific differences.

STRATEGY FOR INTEGRATED DATABASE

Integrated safety or efficacy database are often built for regulatory submission. There are many different ways to build these databases. Below are few approaches with their pros and cons. Sponsor can access and choose an approach which best fits their needs.

Pooling SDTM Datasets

ISS/ISE datasets can be built by first pooling individual study SDTM and then stacking them and creating an integrated SDTM database, which could then be used to create integrated analysis datasets. The advantage of this approach is that it might be relatively easy to up-version MedDRA, CTCAE, WHO dictionary, etc. using this integrated SDTM datasets. Programmer can also look at the data and easily search data for queries. It is easy to spot differences among studies just by navigating through the integrated database.

However, there are some cons to this approach. It may be need more time programmatically to build integrated SDTM database. If the studies pooled into ISS/ISE are on-going at the time of building integrated SDTM database, then programmers need to be aware of constant changes in the data at individual study level.

Pooling ADaM Datasets

Another approach to create integrated database is by pooling individual studies ADaM datasets instead of SDTM datasets. The main advantage of this approach is that it may take less time than the first approach. However, programmer may need to wait till individual studies ADaM datasets are available and stable. Also, navigating and

searching source SDTM datasets to spot differences may not be that easy. Programmer may need to spend more time to understand analysis dataset specifications from individual studies.

Programmatically

Third approach is to create an integrated database programmatically without first creating integrated SDTM or ADaM database from individual studies. If there are not many studies pooled for ISS/ISE then this may be good approach. However, programming may get complicated if more number of studies are pooled into ISS/ISE. Verification of programs may become challenging with this approach. Future changes and enhancements to the programs can also be challenging especially if original programmers are not part of the team.

DATA CUT

Often a cut is applied to studies based on number of events or to use data up to certain time point. It is important to make sure a consistent logic is applied across studies to cut the data. Whether to cut the data at SDTM level or ADaM level is something programmer needs to decide. While pooling data for ISS/ISE, it is critical to make sure that appropriate data is pooled. Data gets updated frequently while preparing for submission to make it submission complaint and it is possible in the rush to forget to cut the data and use incorrect data.

INVENTORY AND TRACKING

The most critical and often overlooked piece of planning from programming side is a good project management. Technical team needs a strong mechanism in place to take deliverables. It is very easy for deliverables to slip through the cracks without good tracking system and things can get very messy very fast. If many studies are outsourced then sponsor need to make inventory of what is expected from each vendor and track them diligently. Sponsor need to consider review timeline, milestone dates and status of each deliverables. It's pretty challenging and it could be very daunting to track deliverables, especially if there are on-going in parallel. A good tracking system is absolutely critical for regulatory submission. Sponsor need to carefully evaluate and prioritize deliverables and should provide sufficient time for project management.

CONCLUSION

Although preparing for regulatory submission could be a challenging task but with proper planning sponsor companies can ensure smooth submission and can eliminate last minute stress. Tips outlined in this paper are to help sponsor companies to form sound strategies for regulatory submission and become more efficient in the process.

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