Paper DS06

Complexities In Adhering To Data Standards For ISS NDA Submissions

Vidya Muthukumar, IQVIA Biotech, North Carolina, USA

ABSTRACT

Regulation of new drugs in the US has been based on the New Drug Application (NDA). NDA application is the process by which drug sponsors, such as biotech and pharmaceutical companies, propose that the FDA approve a new drug for commercialization. Drug sponsors use the services of Contract Research Organizations (CROs) to help with the complex NDA submission process. The Integrated Summary of Safety (ISS) is a section of the NDA that provides a complete review of safety information through meta-analysis and pooling of data from clinical trials performed with the study drug. The ISS is useful to, 1) Identify rare and/or unexpected trends in patient subgroups, 2) Improve the precision of results with a larger population size by integrating studies, 3) Reach stronger, more defendable statistical conclusions. This paper demonstrates a recent ISS NDA submission to the FDA and the complexities surrounding the process of adhering to data standards.

INTRODUCTION

The purpose of this paper is to highlight essential elements needed for an NDA and ISS FDA submission and the various complexities associated with gathering all the safety data for ISS pooled studies specifically for NDA and ISS FDA submission.

PREPARING DATA FOR NDA AND INTEGRATED SUMMARIES

The actual process of drug development is an extremely complex and time-consuming process. It can be broken down into many phases. The pre-clinical phase usually takes 3 to 4 years to complete. If positive results are seen, this phase is followed by a submission to the FDA as an Investigational New Drug (IND). After the approval of the IND, the next stages are clinical phases I, II, III and sometimes IV, which require about 1-3 years for each stage to complete. The manufacturer, thereafter, files a New Drug Application (NDA) with the FDA for approval. This appeal can either be approved or rejected or the FDA may request further study before making any decision. Following an FDA approval, the agency may request the manufacturer conduct additional post-marketing studies. On average, the entire NDA process takes between 8 to 12 years.

This paper outlines the process involved at a high-level towards the buildup for an NDA and ISS submission to the FDA and the many complexities and roadblocks along the way. Each clinical trial in a program is unique in its objective and design. Some are small safety studies among normal subjects, while others are efficacy trials in a large subject population. This paper highlights the progression and submission of a pooled set of 5 studies for ISS and a stand-alone NDA for FDA submission. One of the pooled ISS studies was a subset of the NDA submission to FDA.

While all the 5 studies had a similar indication, the pooled ISS was a combined set of studies that included data from a legacy study that was acquired from a different Sponsor and data from 2 studies that were housed in an external database with completely different database interfaces.

CHALLENGES IN DATA POOLING

The first major challenge was to assimilate all the data from a legacy study that was acquired by the current Sponsor from another external Sponsor. This legacy study was one of the studies that was part of a pooled set of four studies for ISS. This legacy data was based on a legacy annotated case report form (CRF) and a “non-familiar” legacy database that had already been locked by the original Sponsor. The acquired legacy CRF had been initially annotated by the original Sponsor in PDF format and the CRF annotations acquired from the original legacy sponsor was not CDISC compliant. In that, all CRF annotations had been locked in a PDF file, which entailed cleaning out the annotated CRF and re-creating the CRF as a blank CRF with CDISC compliant annotations.

In addition, the legacy data had data issues which could not be resolved since this was "acquired" data from an external legacy data Sponsor who had since "locked" their legacy database a few years ago and had closed out that legacy data and transferred all that legacy data to the current sponsor. We were tasked with using that legacy data in its current state "as is" and transform the CRF to make it CDISC-compliant. Once the legacy CRF was cleaned and CDISC compliant annotated CRF was created for submission, the SDTM team was tasked to create CDISC compliant SDTM datasets for the pooled ISS studies.

Prior to even starting the assimilation of data for NDA and ISS, we required the Sponsor to come to an agreement for a common pool of ISS domains. Since the NDA-standalone submission had all the necessary SDTM domains per the CRF, the subset of the parent NDA study (which was part of the pooled ISS study) had to be scrutinized for ISS SDTM domains harmonization and only a set of common domains between the NDA study subset and the four remaining ISS pooled studies were included for the ISS submission.

FDA AND CDISC GUIDANCE DOCUMENTS

The Agency provides several guidance documents to help sponsors and clinical research organizations prepare their submission material in an effective and timely manner. Many sponsors use services of specialized companies that only work towards getting the FDA submission docket thoroughly reviewed and organized for an Electronic Common Technical Document (eCTD) submission. The eCTD technical conformance guide provides specifications, recommendations, and general considerations on how to submit eCTD-based electronic submissions to the Center for Drug Evaluation and Research (CDER).

For the NDA submission, the following are the key FDA Guidance documents that were used as reference documents:

a) *"Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug and Cosmetic Act"* indicating that most NDAs will need to be submitted electronically in eCTD format.
b) "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data".* This document studies initiated in the relatively near future must utilize specific data standards for the collection, analysis and delivery of clinical and non-clinical trial data and results as endorsed by the FDA as documented in the Data Standards Catalog.
c) *"The Study data Technical Conformance Guide"* provides specifications, recommendations, general considerations on how to submit standardized study data using FDA-supported data standards located in the FDA Data Standards Catalog.
d) In addition, CDISC also has some guidance on NDA submissions. "The CDISC Submission Metadata Model" is used as a guidance document by sponsors in the preparation of data that is to be submitted to the FDA. By following the principles of this model, any FDA submission can help reviewers accurately interpret the contents of submitted data and work with it more effectively, without sacrificing the scientific objectives of clinical development.

PUTTING IT ALL TOGETHER

Once the partner CRO along with the Sponsor had a good understanding of all the required FDA and CDISC guidance documents, the sponsor and the study team prepared a solid project planning blueprint that gave the entire process a two-year window to complete the NDA and ISS submission. The additional benefit for this submission was that the Sponsor had already had pre-FDA review meetings to discuss the NDA application and had a handle on the FDA review process and questions posed by the agency.

For the ISS FDA submission, the main objective was to provide an overall analysis and summary of the safety data. The ISS analysis described study results, with tables, listings and Figures (TLFs) of important endpoint analysis which detail all aspects of statistical approaches defined for the integrated summary of data. Following are some of the key elements of an ISS submission:

a) A summary of the safety data from all the integrated clinical studies including Phase I trials.
b) Exposure data of the integrated studies which includes the number of patients (by gender and other demographic subgroups) that are exposed to various doses for specific durations.
c) Demographic and other characteristics of the study population – age, gender, race, body weight, primary & secondary outcome measures, and other relevant variables identified by the study Biostatisticians.
d) Adverse events.
e) Overall analysis of AEs including event rates, deaths, and other serious adverse events (AESERs)

f) Laboratory assessments.
g) Analysis of adverse effects relating to dose-response information, including any evidence of dose-response variations relating to age, sex or any other subpopulations including PFS (progression-free survival).

CHALLENGES

For the NDA submission, the sponsor had a varied mix of external agencies providing analytical models and forecasting projections of the study data that would often result in re-analyses, re-work of analyses, and reruns of SDTMs/ADAMs and TLFs by the partner CRO. The complexities grew even more when the sponsor had a myriad of external reviewers re-checking and perhaps re-validating the efforts of the partner CRO. Often, a CRO is at the receiving end when it comes to dealing with sponsors who would like to have it “their way or the highway”. This often results in partner CRO study team members having low morale and early panic about study deliverables and hurriedly preparing unrealistic timelines. The study team realized that in order to have low turnover of study team members, it was imperative to keep a steady set of team members who would essentially know the ins and outs of the study. For this ISS submission, the Sponsor and the partner CRO realized the inefficiencies as the study progressed and found time-bound solutions to remove bottlenecks and roadblocks during the study implementation process.

CONCLUSION

In all, some of the key lessons learned with the NDA and ISS submission were that both the Sponsor and the CRO partner needed to have a viable and realistic roadmap during the entire submission timeline even if it meant drawing up new and efficient sub timelines to be able to meet the final deadline. A good and thorough understanding of the FDA requirements and submission process is needed not just by the Sponsor but also by the partner CRO even before creating study timelines for an ISS submission.

REFERENCES

https://www.fda.gov/drugs/types-applications/new-drug-application-nda
https://www.fda.gov/media/98907/download
https://www.cdisc.org/FDA-Final-Binding-Guidance-on-Standards