



 Iris Statistical Computing

Practical Lessons Learned from Recent NDA and BLA Submissions to the FDA

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Outline

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- **Relevant Industry Best Practices**
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Background

- I was the head of a statistical programming group at a pharmaceutical company
 - I have been involved in the approval / clearance of more than 20 products submitted to the FDA – including NDA, BLA, PMA and 510(k) submissions
- Lisa Brooks was hired as a CDISC consultant to help with getting the NDA and BLA submissions ready
 - Lisa has been involved strategically and logistically in 10 New Drug and 2 Biologics License Applications.

Relevant Industry Best Practices

- Sirichenko and Kanevsky of Pinnacle 21 (2015) have identified the most common data issues in FDA submissions as:
 - Metadata Issues
 - Annotated CRF Issues
 - Reviewer's Guide Issues
 - Non-Compliance with FDA Business Rules
 - Programming and Mapping Errors
 - Controlled Terminology Issues

Relevant Industry Best Practices

- Based on this list, sponsor companies have a lot of responsibility in fixing issues related to submitting data to the FDA.
- With the new requirement by the FDA to follow CDISC standards for studies starting on or after 17Dec2016 the bar for submitting data to the FDA has been set even higher.
- Thus, sponsor companies need to follow good practices like those mentioned above.

Relevant Industry Best Practices

- What are the best practices for managing multiple CROs? There are many best practices, but Nataraj and LaPann (2017) provide some valuable insights with respect to data standards, including:
 - Create a Standards Roadmap with long and short-term goals
 - Discuss and provide CDISC standards interpretation
 - Implement Sponsor Standards Library and release after UAT
 - Share in the evaluation and implementation of CRO Processes and Tools

Relevant Industry Best Practices

- Managing multiple CROs (continued)
 - Ahrweiler, Mathur and Ignacio (2015) also realize the importance of a sponsor defining SDTM and ADaM implementation for CROs.
 - Mabe (2011) has developed a method for developing a company standard for SDTM implementation.
 - One of the benefits that Mabe (2011) mentions for developing a company standard is facilitate traceability for integrated analyses, such as ISS / ISE.

NDA Lessons Learned

- Prior to our (Lisa Brooks and myself) engagement at a mid/sized Pharma company, a large CRO was selected for biometric services in support of a very large and long running pivotal trial:
 - Our main objective was to ensure that the electronic data was compliant with CDISC standards and eSubmission ready for an NDA.
 - Up until our involvement, almost no guidance had been given to the CRO on implementation of SDTM or ADaM.
 - Consequently, the first time that we ran Pinnacle 21, there were hundreds of thousands of errors and millions of warnings.
 - We developed and implemented a strategy to address the numerous errors and warnings

NDA Lessons Learned

- Our first step was to review the Pinnacle 21 report to identify possible sources and causes of the errors and warnings:
- Mapping Specification Findings included:
 - Time consuming data review
 - Easy to medium programming changes
 - Unit conversion for local labs
- Open CDISC Validator Findings
 - Missing domains
 - Duplicate records
 - Date inconsistencies
 - Controlled Terminology Messages
 - Data inconsistencies (like expected variables missing, I.e., EPOCH)

NDA Lessons Learned

- Action Item Tracking
 - From a careful review of the report's Issue Summary and Details tab (Pinnacle 21 Report), we categorized each type of issue and placed in a tracker. The types of action items are listed below:
 - Controlled Terminology Error
 - Domain Structure Error
 - Duplicate Error
 - Missing Value Error
 - Visit Error

NDA Lessons Learned

- Actions included:
 - Document in SDRG after database lock
 - Items that could be implemented immediately (this includes data cleaning and programming changes)
 - Items that could be implemented after a dry-run was completed (this includes data cleaning and programming changes)
 - Controlled terminology issues that needed to be reviewed and implemented
 - No action to take

NDA Lessons Learned

- Results of actions taken:
 - An immediate and dramatic 68% reduction in error and warning messages within 6 weeks.
 - We tracked continued efforts over a total of 3 months, there was only an additional improvement to 69% reduction.
 - In total, we went from 1.7 million errors to 524,000 errors which were mostly addressed in the first 6 weeks of a targeted and planned effort.
 - In the end, all though we had many unresolved issues, we were able to adequately understand and explain each warning and error to the agency in the clinical SDRG.
- This NDA was approved by the FDA.

NDA Lessons Learned

- Main lesson learned:
 - Sponsor companies need to give early input to CROs on dealing with Pinnacle 21 findings.
 - When I joined the company, database lock for the pivotal Phase III study was about one year away.
 - The problem was primarily with the sponsor company as the scope of work with the CRO did not include resolving Pinnacle 21 issues.
 - Once the scope of the work included resolving Pinnacle 21 issues a lot of effort was put into resolving the Pinnacle 21 findings.
 - It would have been much better for the company to properly scope the work by the CRO from the beginning and to not need a Herculean effort towards the end of the study.

BLA Lessons Learned

- Prior to our engagement at a mid/sized Pharma company, two CROs were chosen for a product that would be submitted to the FDA as a BLA.
 - The two CROs were asked to implement the most recent version of the SDTMIG which at that time was SDTMIG 3.1.2 Amendment 1.
 - No guidance to the two CROs on implementation of SDTM.
 - Consequently, the two CROs made implementations of SDTM that were different.
 - Thus, when it came to do the ISS/ISE, the SDTM and consequently ADaM datasets were incompatible for integration.
 - Thus, one of the CROs SDTM and ADaM datasets had to be re-done for the ISS/ISE to proceed.

BLA Lessons Learned

- Main lesson learned:
 - The lesson learned here is that companies should not simply ask CROs to implement the most recent version of SDTM.
 - Ideally, companies should develop an internal standard of SDTM implementation and then provide the company standard to CROs to implement.
 - Multiple CROs may still make slightly different implementations, but the sponsor company is more likely to get back compatible SDTM and ADaM when they give the CROs a company standard.
 - Thus, ISS/ISE is likely to be easier when a company standard is followed.
- This BLA was approved by the FDA.

BLA Lessons Learned

- Note:

- It is important to note that this situation of two different implementations of SDTM is not an issue which would be found by using a tool like Pinnacle 21.
- Each implementation of SDTM may conform to the SDTMIG and not have any significant Pinnacle 21 errors which need to be fixed.
- Thus, the problem here is that the two implementations (which were ok by themselves) was that they were incompatible for integrated analyses (i.e., ISS/ISE).
- The way for companies to avoid this incompatibility is to develop a company standard (a standard way of implementing SDTM) and provide the company standard out to CROs

Conclusions

- Under the best of circumstances (when best practices are followed) putting together a quality submission to the FDA is challenging.
 - However, when best practices are not followed then the challenges may become insurmountable.
- Ignoring fixing Pinnacle 21 findings till the end of a study is costly in terms of time to fix the problems.
- Developing an internal company standard is truly the best way to have consistency in terms of receiving SDTM from different vendors.

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