Some Common Programming Errors and Possible Solutions that Could Impact a Successful NDA/BLA

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ABSTRACT

Common errors from the statistical programming function are formatting, traceability, uniformity, completeness of datasets, missing variables, inconsistent data cutoff dates, missed or poor definitions of variables, non-functioning SAS statistical programs, un-executable software, inadequate and/or incorrect annotations within the annotated CRFs, miscalculation, misconducts, etc. All types of errors could not only delay the NDA/BLA approval, even possibly destroy the entire trial, but also hurt financially by take additional time and efforts. This paper illustrates several types of errors from the process of SDTM, ADaM, and tables generation that happened in recent years to help us rethink about the programming strategies and ensure data quality for our NDAs/BLAs.

INTRODUCTION

Data for a New Drug Application (NDA) can be classified into four types: 1) data tabulations, 2) data listings, 3) analysis datasets, and 4) subject profiles. These are collectively referred to as Case Report Tabulations (CRTs). Statistical programming is the function area that generates the CRT. Because data listings and subject profiles usually do not require data computation, so they do not impact the efficacy and safety results as much as the other components of the CRT. The accuracy and completeness of the data tabulations and analysis datasets are more critical to statistical programmers for a successful NDA/BLA.

Statistical programmers have referenced the Study Data Tabulation Model (SDTM) and Analysis Datasets Model (ADaM) to generate data tabulations and analysis datasets, respectively, for many years. There are chances to have errors in this process of generating data tabulations, analysis datasets, efficacy tables, and safety summary tables. Some common errors were mentioned above and are highlighted below.

ERROR TYPE 1. NON-CRITICAL ISSUES OF DATASETS AND/OR SAS PROGRAMS

Non-Critical issues of datasets and/or SAS programs belong to technical deficiencies. They are unrelated to study conduct, interpretability of study results, or validity of study conclusions. An example is Chelsea Therapeutics' NORTHERA™ (droxidopa) NDA Filing [1] in 2013. There were issues that primarily relate to the formatting of certain datasets and statistical programs describing the methods used to generate tables and listings. FDA decided that the six month review clock for the NDA specified under the Prescription Drug User Fee Act (PDUFA) will not start until the matter can be resolved.

Besides consistent formatting, clinical study data needs to be traceable, namely to be able to trace back from ADaM to SDTM to the raw CRF data. All algorithms and derivation processes should be accurate according to the study protocol, statistical analysis plan, and other study directives. For instance, lab test data with abnormal values cannot be populated into the SDTM AE dataset. These observations must be stored in the SDTM LB dataset for traceability by study personnel and regulatory agencies.

In November, 2016, the FDA issued feedback to the NDA for Lutathera® (produced by Advanced Accelerator Applications S.A.) for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults. The FDA feedback identified issues with the format, traceability, uniformity, and completeness relating to the NETTER-1 and Erasmus clinical datasets, which are precluding FDA reviewers from performing the required independent analysis of these clinical studies [2]. What we have learned from this instance is that data issues associated with format, traceability, uniformity, and completeness are usually caused by poor data management and programming.

Poor data management and programming is not limited to small companies. Big companies with solid NDA experience could make similar mistake as well. In 2012, GlaxoSmithKline's melanoma drugs Mekinist (dabrafenib) and Tafinlar (trametinib) lost priority review status [3]. One of the reasons is poor data quality. The data quality problems include data discrepancies resulting from inconsistent data cutoff

dates; errors in the eCTD submission documents; define.XML file containing an inadequate level of detail in the variable definitions and missed definitions of multiple variables; inadequate and/or incorrect annotations within the annotated CRFs; key variables absent in datasets, inconsistent in name or definition across datasets; non-functioning SAS programs (including inconsistent coding of multiple variables and inadequate documentation for statistical analyses). Even though FDA and GSK had communicated very well multiple times prior to NDA submission, FDA reviewers were unable to confirm the applicant's results efficiently and in a timely manner.

Usually, the FDA and drug companies do not expect all data to be 100% perfect in an NDA/BLA. There will be acceptable rates of data errors for non-critical domains (e.g. physical examination). In fact, non-critical issues of datasets and/or SAS programs are fixable, but will delay the NDA approval, waste company money, and damage a company's reputation.

To eliminate any chances of having non-critical issues in datasets and SAS programming processes, the first and most important thing to do is to establish a series of sound corporate SOPs that standardize programming practices to ensure the quality of datasets and TLFs. Here are a few examples of common SOP topics:

- Specifications for SDTM datasets:
  - include a detailed process of development, review, and approval
  - confirm responsibilities between statistical programmers and data management
- Specifications for ADaM datasets:
  - include a detailed process of development, review, and approval
  - confirm responsibilities between statistical programmers and statisticians
- Specification Guidelines for tables, listings, and figures (TLF):
  - agreed formatting, font size and type, presentation, etc.
- Biostatistical Programming standards:
  - naming conventions, program documentation, general programming guidelines
- Standards of Table, Listing, and Figure programming and validation:
  - Good programming practices, etc.
  - PROC COMPARE, independent replicate programming
- Specification Guidelines Integrated Biostatistical Analysis and Reporting for multiple studies
  - ISS/ISE (Integrated Summary of Safety/Integrated Summary of Efficacy)

Second, make sure these SOPs are practical and applicable and everyone responsible is well trained. SOPs are the directives that everyone must follow. The disagreements over interpretation, responsibilities and adherence to SOPs among data management, statistical programmers, and statisticians are ongoing. There should be clear lines and acknowledgment among these three different functional areas to minimize blurred responsibilities.

ERROR TYPE 2. SPONSOR'S PROPRIETARY SOFTWARE PROGRAMS

Another reason for GSK's voluntary withdrawal of its priority review requests for Mekinist and Tafinlar in 2012 mentioned above was GSK's usage of their proprietary statistical analysis software. FDA systems could not support GSK's proprietary software programs, which increased burdens on the statistical and clinical reviewers to generate analysis datasets in order to verify the reported results.

FDA requires that SAS programs should not contain any macros and every SAS procedure in the program should have comments to explain its purpose. But most SAS programs GSK submitted were not usable. Especially in the tumor assessment derivation program, more than 10 SAS macros were called in loops. None of the macros contained documentation/comments to help understand the logic and algorithms involved.

Many companies probably still use a lot of macros, especially the nested macros in their SAS programs for whatever reasons. Obviously this is not a sound strategy to perform programming work. I personally saw some programmers use nested macros to generate simple common AE tables. It is not necessary and in fact caused a reversed effect because of changes in the AE tables. Any changes made in the table structure would need modifications of the nested macros that would not provide any efficiency in programming.

Health authorities (e.g. FDA) have the power to review your new drug application, but no obligation to learn your SAS macro programs. When writing SAS code, you should put yourself in the shoes of FDA or

other health authorities. You should think about how these agencies will understand your SAS code. In contrast, it is the sponsor's obligation to make the best effort to present your programs in a way that is easy for the reviewer to understand.

ERROR TYPE 3. MISCONDUCT IN CLINICAL TRIAL

Unfortunately, misconduct in a clinical trial does occur. In September 8, 2014, Hyperion Therapeutics stopped development of a diabetes drug following discovery of unlawful conduct by some employees [4]. Those employees engaged in collusion with a third-party biostatistics firm in Israel to improperly receive un-blinded DIA-AID 1 trial data of DiaPep277 and to use such data in order to manipulate the analyses to obtain a favorable result, and continued the improper practice of sharing and examining un-blinded data from the ongoing DIA-AID 2 trial. The company recorded an impairment charge of $25 million-$55 million related to the discontinuation. What a horrible crime!

In nature, many trials are randomized, and double-blind placebo-controlled. Sponsors are not permitted to have access to either patient group assignments or related product coding information. Sponsors are usually contracted with independent third-party contractors to execute treatment group assignments and oversee clinical trial material coding and distribution according to established procedures. There is a possibility that independent third-party contractors could mishandle the blinded investigational drug used in the clinical trial, such as wrong treatment group coding. Peregrine Pharmaceuticals, unfortunately, experienced major discrepancies between some patient sample test results and patient treatment code assignments after the Phase II trial of bavituximab in second-line non-small cell lung cancer [5] in 2012. The whole trial was a waste, of course, and consequently of no value at all to the company and especially, the affected patients.

Strictly following the right SOPs is important. Any company involved with misconduct in the clinical area should be punished as it does not help in finding new medicines that will improve people's life.

ERROR TYPE 4. MISCALCULATION OF P-VALUE

The P-value is probably the most important indicator for the success of most clinical trials. However, it happens that companies do get wrong p-values by various means. In 2013 FDA declined to approve Hemispherx Biopharma's NDA for Ampligen® for Chronic Fatigue Syndrome [6], because FDA obtained a p-value of 0.10 in one of the clinical studies (AMP-516) while Hemispherx's p-value calculation obtained <0.05. That was a significant difference.

Provenge is the first cell-based cancer immunotherapy for prostate cancer. When Dendreon Corporation submitted its BLA in 2006, the original p-value in the Time to Progression (TTP) data analysis was 0.085. With FDA's help, Dendreon identified data errors and made changes for Subject 9137-014, then recalculated the TTP log rank p-value and Hazard ratio. The final p-value (2 sided, Log Rank) was 0.048 [7, 8, 9]. 0.048 vs. 0.085, this is a significant difference.

To prevent miscalculating the p-value, the clinical data collected must be clean. The methodology used for the p-value calculation must be validated by two independent qualified biostatisticians/programmers.

ERROR TYPE 5. BAD REPUTATION OF ABROAD CROs

WHO, EMA, and FDA found critical data integrity Issues at India-based contract research organizations (CROs) - Quest Life Sciences Private Ltd., GVK Biosciences, and Semler Research, in 2014, 2015, and 2016, respectively [10, 11, 12], and indicated that clinical and bioanalytical studies conducted by them are not acceptable and need to be repeated.

A Chinese government investigation revealed that more than 80 percent of the data used in clinical trials of new pharmaceutical drugs were "fabricated" [13, 14]. The Chinese State Food and Drug Administration (SFDA) found that the more than 80 percent of the data from 1,622 clinical trial programs failed to meet analysis requirements, were incomplete, or totally non-existent.

Many companies are outsourcing their trial and programming work to India or China in order to save costs. However, there are some potential risks associated with these offshore CROs. Company executives should evaluate and implement this type of business model very carefully.

ERROR TYPE 6. UNTRUE PRESENTATION OF CLINICAL TRIAL DATA FOR NDA

Clovis Oncology used immature data sets based on both unconfirmed response rates and confirmed response rates for the NDA submission of its cancer drug rociletinib in 2015 [15, 16]. Per the industry trial standards, however, any unconfirmed responses can be reported in publications with appropriate annotations but are never the primary endpoint in a trial, especially in a pivotal trial designed to seek marketing authorization. The efficacy analysis must use confirmed responses, solely. The response rate of rociletinib dropped from 59% to 34% after removing the unconfirmed response. Clovis Oncology finally withdrew their NDA submission and terminated the ongoing trials. Millions of dollars were wasted, and the company's reputation was jeopardized.

CONCLUSION

To prevent any mistakes in the statistical programming area, in addition to establishing the right SOPs, hiring qualified programmers is extremely important. Like any other professionals, outstanding SAS programmers are not available everywhere. Outstanding SAS programmers not only possess good programming skills, but also good understanding of the clinical trial knowledge and statistical knowledge. It takes many years of practice in this field to gain experience and improve programming skills to become a qualified programmer.

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