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Navigating a Major Regulatory Submission Project to Success

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ABSTRACT

When a SAS® programming group supports a major regulatory submission in the pharmaceutical / biotechnology industry it is like embarking on a voyage of exploration, discovering new worlds and delivering back uncovered treasure. The tasks include assembling a crew, provisioning the ship, gathering the documents that help chart the voyage, setting a course and embarking on the voyage. Along the way, the activities must be re-aligned and the crew kept motivated, while navigating through changing tides and shifting winds. When the treasure is found, it is delivered back to those who initiated the voyage.

For a recent submission, our team embarked on just such a voyage. Working with the Clinical staff, Biostatisticians and Medical Writers, we gathered the documentation and defined the initial analysis plan for our submission. Along the way we dealt with changes in the timeline and the analysis plan, changes in the staff and the need to support other projects.

This paper describes how the team was built and maintained. It also looks at how we set off without a clear analysis plan, programming "at risk" using Base SAS® software in order to meet our timeline and the outcome of that strategy. Finally, it discusses how we monitored our progress, quickly adapted to changing requirements and dealt with competing priorities.

SETTING OUR SIGHTS ON A DISTANT SHORE

Programming in the pharmaceutical / biotechnology industry is different from typical software development projects. The deliverable is information that is presented in tables, listings and graphs that eventually make it into a report for a regulatory submission and leads to an approval to market a new drug or expand the indication of an already approved drug. Under ideal circumstances, the programmers have an analysis plan that points them in the direction they need to go before they begin programming, but the data ultimately guides the final output.

In a sense, it's like embarking on a voyage of exploration, discovering new worlds and delivering back uncovered treasure. The requirements include assembling a crew, provisioning the ship, gathering the documents that help chart the voyage, setting a course and embarking on the voyage. Along the way, the activities must be re-aligned and the crew kept motivated, while navigating through changing tides and shifting winds. When the treasure is found, it is delivered back to those who initiated the voyage.

The crew in this adventure was made up of programmers in the Vaccine and Oncology programming team, those borrowed from other teams, consultants that were hired and a CRO. We gathered special provisions, including purchasing high-end PCs, a dedicated high-speed printer, and putting together a dedicated team room that served as a meeting room and housed the additional hardware. Working with the Clinical staff, Biostatisticians and Medical Writers, we gathered the documentation and defined the initial analysis plan. Along the way we dealt with changes in the timeline and the analysis plan, changes in the staff and requests for support from other projects. At the end, we reached our goal and provided our "treasure" in the form of a submission to the FDA.

This paper describes how the team was built and maintained. It also looks at how we set off without a clear analysis plan, programming "at risk" in order to meet our timeline and the outcome of that strategy. Finally, it discusses how we monitored our progress, quickly adapted to changing requirements and dealt with competing priorities.

BACKGROUND

In the fall of 2005, MedImmune, Inc. completed a major Phase III clinical study to expand the indication of one its vaccine products. Upon the determination of positive results from the study, the company set its sights on

submitting a supplemental Biologics License Application (sBLA). Due to the seasonal nature of the vaccine product, time was a major factor in completing the task.

The submission used the Common Technical Document (CTD) format. This is an internationally accepted document standard and is made up of numerous sections. The programming team was responsible for providing tables, listings and graphs (TLGs) for a number of reports in section 5. These included three new Clinical Study Reports (CSRs) and a series of integrated summaries. We planned to integrate data from more than twenty studies and to create assessments of safety, efficacy and immunogenicity. This required mapping variables and codes to a common dictionary and summarizing the data by a multiplicity of stratification factors including age groupings, race and study design.

One fact that complicated the integration was that the studies were run by three separate companies. The initial submission for the vaccine was made by Aviron, a company that had since been acquired by MedImmune. At one point a partnership had been formed and later dissolved with another pharmaceutical company to gain approval to market the vaccine in Europe. We planned to use at least a dozen European studies that this company conducted in our submission.

EMBARKING THE SHIP AND CREW

This saga begins in December of 2005, near the time that the results from the Phase III clinical study were being unblinded. The overall results were very positive, but additional ad-hoc analyses were required. After analyzing the situation, it was determined that there were two distinct projects that could run in parallel and be programmed by separate teams.

As the first project, the completion of the Phase III Clinical Study Report (CSR), including the additional analyses, was already adequately staffed, assembling the team for the second project, the Integrated Assessment Reports became the priority. The first step was to contact a partnered Clinical Research Organization (CRO), with whom we had worked on an earlier submission for this vaccine and which was then working on reviewing and assessing the quality of the data from the European studies. A commitment on their availability to provide the support when we needed it was arranged and a budget was put together.

IDENTIFYING RECRUITS FROM DIRECT REPORTS

A senior person from the Vaccine and Oncology programming team was chosen as the Lead Programmer for the integration team. As many of the team had limited knowledge of the Vaccine area, we had several discussions with the Biostatistics and Clinical groups to help bring everyone up to speed.

HIRING MERCENARIES

Members from outside sources were contracted to work for the project. Two six-month contract positions were approved for this project. Five recruiting companies were contacted and given requirements for the qualifications of candidates. These included at least five years of SAS experience, three of which had to be in the pharmaceutical / biotechnology industry doing clinical research programming, solid knowledge of base SAS and SAS Macro, experience in running SAS in a Windows environment and experience with integrated summaries. Experience in the Vaccine area was a plus. As Maryland has a limited number of companies in the industry, the pool of contractors applying for the positions was small.

Phone interviews were held with several of the candidates. During these interviews, open-ended questions were asked about the various positions listed on the candidate's resume to determine his or her actual experience. Follow on questions were asked to probe deeper into certain areas of interest. References back to the resume were also made. Any hesitation on the part of the interviewee or inconsistency called for additional inquiry.

The interviews lasted between 30 and 60 minutes, depending on the candidate's level of experience. No face-to-face interviews were held. From the candidates interviewed, two were selected and hired "at risk". They were on site before a "Go" decision was made for the submission.

CONSCRIPTING TEAM MEMBERS FROM OTHER GROUP

MedImmune has an independent validation group for the SAS programming function. Two people from that team were assigned full-time to these projects. Occasionally, requirements for these projects required more resources. During these times, members from another team were borrowed. These were usually short-term loans for specific sub-projects which is common practice to help even out the workload peaks and valleys.

IDENTIFYING THE BACKERS AND SUPPLIERS

As many of the people involved in this adventure were new to the therapeutic area and as we were really part of a larger team, it was necessary to identify the roles of the other individuals working on the project. At the highest level were the company executives who were responsible for making the decisions on how the product was to be labeled for use and on the ultimate delivery date of the package to the FDA.

Below them was a multi-disciplinary team mainly responsible for disseminating information and reviewing timelines. The primary team had representation from Clinical (responsible for reviewing the results and providing information to upper management), Biostatistics (responsible for working with Clinical to determine how to analyze the data), Medical Writing (responsible for crafting the documents to be submitted), Regulatory Affairs (our liaison to the FDA), Regulatory Operations (responsible for publishing the various documents into a single submission package) and Clinical Programming.

The working team members were drawn from Clinical, Biostatistics, Programming, and Medical Writing. Initially we had four separate working teams: the Phase III CSR team, the Integrated Assessment of Safety (IAS) Team, the Integrated Assessment of Efficacy (IAE) Team, and the Integrated Assessment of Immunogenicity (IAI) Team. These teams changed as we clarified our requirements along the way.

PROVISIONING THE EXPEDITION (…THE "WAR" ROOM AND ITS TOYS)

Once we had our teams, we needed to outfit them. We looked at our computing environment. At the time, we were using SAS version 8.2 on desktop PCs running Microsoft Windows XP. In addition to SAS, we added the StatXact® version 6 procedures from Cytel Software Corporation. All of the data and programs were stored on a corporate network drive. Knowing that several of the simulation programs took twelve-plus hours to run on the current desktops, we purchased three high-end PCs, with 3.8 GHz Intel® Pentium 4 CPUs and 3.5 GB of RAM.

There was also concern about adequate printing resources for the TLGs. The listings for the Phase III study were over 67,000 pages alone. We acquired a dedicated high-speed printer that had limited access to the rest of the company.

We also needed dedicated space for meetings and to house the high-end computers and high-speed printer. With the help of our facilities people, we were able to procure a Clinical "War" Room for the team which had card-key access. There were tables and shelves around the outside where we installed the PCs and a table in the middle around which people could meet.

In May, we initiated daily lunch in the "War" Room for the multi-functional teams working on the Phase III study and sBLA. The original purpose was to give the teams "one less thing to worry about" and focus them on getting the work out. These actually turned out to be extremely valuable opportunities to get questions answered and ensure all functional areas were in agreement. Often, individuals would overhear a conversation at lunch and add their functional perspective which may not have been otherwise considered. It was also an opportunity to share information quickly as new requests that arose out of a morning's strategy meeting would be discussed and the teams informed of new directions the submission was taking. It was also an opportunity for upper management to stop in and "break bread" with the teams and add encouragement to their efforts.

THE ADVENTURE

Preparation for the submission actually began late in 2005, but it was not until the blind was broken and the overall results analyzed that we knew whether or not we had a reason to move forward. For us, that came in mid-December. Given the seasonal nature of the vaccine, we were charged with completing the submission by the end of June. With the proposed twenty-plus studies to integrate and the complexity of the data being from three different company standards, this was a major undertaking. However, with everyone's attention focused on cleaning and unblinding the Phase III study, little attention had been given to specifying the Integrated Assessments until the time of the "Go" decision.

SAILING INTO THE UNKNOWN (…PROCEEDING "AT RISK")

While the Phase III CSR team set off in search of understanding the additional analyses, the programmers on the integration project began to look at what was needed. With a deadline looming and facing a massive amount of work, the programming for the integrations had to begin even though the specification process had not begun.

In order to get the specifications completed as quickly as possible, the three multi-disciplinary teams met weekly to identify the studies, data, analyses, table formats and sub-groupings for the submission. While these meetings were taking place, the programming team was busy gathering documentation that mapped the data and began to create the analysis data sets based on the data set specifications from an earlier submission. Translation dictionaries were built for common data items with varying decodes and passed up for review by the integration teams. Knowing that it'd be easier to drop rather than add later, every study and every data item that could be analyzed or used to sub-group the data was included in the integrated analysis data sets. The expectation was that when the specifications were completed, a new data set would be created that would provide flags for each sub-group analysis, dropping studies, sites or individual subjects as was called for in the final analysis plan. Priority was given to the studies and data elements most likely to be included in the submission.

The programmers were assigned specific studies to convert based on the type of study and the origin of the data (from one of the three companies). The programmers were also assigned specific data domains as priorities and were coached to develop robust programs and macros that could be shared by all team members. One of the first macros written created standard variable definitions (name and attributes). A second macro calculated the subjects' age in both months and years in a uniform way.

CHANGING TIDES AND SHIFTING WINDS (… THE INEVITABLE STORM)

By early March, the Phase III CSR team had completed their analyses and prepared for a Pre-sBLA meeting with the FDA. The meeting was held in early March and was the first major shift in the project. The agency clarified their requirements for the content of the submission. While adding some additional data, they reduced the number of studies and integrations.

Our programming "at risk" with prioritization had paid off, as little effort had been expended on the studies and integrations that were dropped and it was easy to add the additional data that was requested. We had a new course, but had lost little time and were closer to our goal.

A week later we lost the Lead Programmer on the Phase III CSR team. Fortunately, contingency plans were in place and another programmer was able to act as a temporary back up. Meetings were immediately set up with the Phase III CSR team to review the outstanding requests and develop a plan to complete them. A senior programmer was conscripted to take over the lead of the Phase III CSR programming effort. The team worked closely with the new programmer to ensure that everyone understood what was needed and that deadlines were met.

In early April we delivered our first draft of TLGs for the IAS. That small victory was quickly overshadowed by an additional analysis which was added for the Phase III study. An outside consulting group was hired to perform the analysis with the understanding that we would provide all of the programming support. As this analysis had not been planned, the Phase III CSR team was hit with a massive request for additional tables with very little notice. Due to the looming submission date, we needed to drop all other programming activities and focus both teams on completing this request. The tasks were divided up among both teams. To coordinate the activities and reaffirm timelines, the idea for "Scrum" meetings was borrowed from the Agile methodology by the same name. These "Scrum" meetings were ten to fifteen minute meetings every morning in the "War" Room with all of the programmers to review the day's deliverables and ensure everyone was on the same schedule. We delayed questions and discussions about issues for later and focused only on what was needed for that day. Not only did this help keep the programmers focused, it provided daily tracking each morning of exactly where we were in relation to our due date.

Until now, upper management had supported us in asking other project teams to understand that their timelines might be affected by the efforts needed for the sBLA. While most of our efforts were focused on the sBLA programming, we tracked other projects' requests and provided some level of support to keep them moving. In the brief pause after producing the second additional analysis, we received a critical request to summarize a set of data needed for a pre-IND (Investigational New Drug) meeting with the FDA for a new oncology drug that we were planning to begin studying later in the year. Failure to get the data ready for this meeting would have caused serious delays for the drug. As the team was used to "crisis mode", we continued the division of tasks and "Scrum" meetings to complete the summarization in less than a week.

In May, the second additional analysis led to another round of intense programming by both teams to clarify and understand what the data was telling us. In early June, a final decision was made on the product label. This required a change to all of the TLGs for both the Phase III CSR and the IAS. Our original timeline was to submit the sBLA package at the end of June. With the new label, management gave one additional month to complete the whole package. Programming the TLGs for both the Phase III CSR and IAS were the first deliverables needed on this final leg of our journey. This change went smoothly for the IAS as only the flag data set needed to be modified. The CSR programs however, which were created months before and were not programmed as robustly, required significant modifications. We returned to the "Scrums" and the division of labor and got everything out in time for the teams to complete and submit the package three days early.

KEEPING THE SHIP AFLOAT

In retrospect, there were a number of things that worked well for us. The functional areas worked seamlessly together, we kept focused on our goal and were able to navigate through the numerous changes in our course. Looking specifically at the programming function, we would not have made our dates if it hadn't been for the hard work and dedication of the team members and the sacrifices made by them and their families. There were numerous late nights and week-ends spent by everyone. One of the major challenges was keeping moral high and the number of disruptions low.

It was important that questions and issues could be quickly addressed. When they arose, priority was given to answering them as quickly as possible to ensure the work sailed on. Spreadsheets and other documents were shared in common areas where everyone had access to keep track of the outstanding requests and note the status of each request. There were other common areas for the various study documents and IAS specifications.

Formal meetings were kept short and to a minimum. Adjusting the length and timing of meetings made for efficient use of our time. Early on meetings were held every other week for one hour. As the specifications were finalized, we moved to weekly meetings and when things got critical we went to the daily "Scrum" meetings. In addition to meeting with the internal team, weekly teleconferences were held with the CRO to ensure they were on schedule and understood the specifications.

We also took time to celebrate the small victories. Before the daily lunches began, we had a number of lunches where we had food inside or went out for lunch with the teams. At the end there were numerous parties, including a happy hour with upper management and numerous deserts bought by various departments.

As the programming dragged into May and June, people had vacation plans that needed to be taken into account. Contingencies were made and everyone was allowed to take their vacations as planned. Based on individual contribution, compensation time was offered to extend the normal amount of vacation, to be taken after the submission.

Finally, the Programming and Biostatistics teams sponsored a week-end "retreat" to a nearby resort for the programmers, statisticians and their families. The company paid the expenses and hosted a banquet where humorous award certificates were presented.

DISEMBARKATION

The voyage to the sBLA submission was an exciting and challenging adventure. Work on the submission project spanned nine months and in then end, the programming team wrote more than 8,100 SAS code files. The project succeeded mainly through the Herculean efforts of the team members, but the effort may have been wasted without the agility and risk-taking that was built into the project.

In addition to the hard work of the team, the success was aided by selecting the right people for the right positions, supporting them, encouraging them, and rewarding them. They were mentored on the areas that were new, provided tools to track the outstanding requests and delivery dates, their questions were answered in a timely fashion, and they had the information they needed to get the job done. The other project teams whose work was not getting done were dealt with and solutions were devised so their projects could continue, even if at a slower pace. Upper management was kept informed of where we were on the timeline and of any roadblocks in our way. This kept everyone feeling more comfortable.

While the submission was made at the end of July, the work didn't stop. There were additional analyses required for publications and preparations for the advisory board. And there was the backlog of requests that had languished while nearly everyone was focused on the sBLA. As one adventure draws to a close, the next is at hand.

ACKNOWLEDGMENTS

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