INTRODUCTION

While the vast majority of activities undertaken by individual pharmaceutical manufacturers to introduce new products into the marketplace in the United States occur before the official filing of the NDA (new drug application), the period of time between that filing and FDA (U.S. Food and Drug Administration) approval or denial is critical as well. Accurate and timely response to advisory committee or FDA reviewer inquiries can often minimize or eliminate delays, thereby shortening the overall review and approval process for the compound itself. While there is no substitute for thorough preparation prior to NDA submission, anticipation of every potential concern raised during this process is, of course, impossible. Therefore, some sort of methodology should be set in place that would facilitate the addressing of such concerns.

One of the various methods of optimizing this response time is to maintain a comprehensive record of any inquiries, or requests, made by the FDA. This record, or log, offers such benefits as expected processing of similar or related requests and quick and easy access to newly accumulated data. In addition, this log also provides current information that accurately reflects the state of the review process at any point in time, and may also serve as a projection of FDA concerns, particularly for large development programs consisting of compounds with many indications. This inherent ability to evolve dynamically as a tracking tool will facilitate the anticipation of future requests and further reduce the time needed to respond to them.

The incorporation of SAS/AF® and SAS/FSP® software into a module driven by SCL allows for the development of a single, compact, on-line system capable of tracking, reproducing, and cataloging FDA requests. The Requests Tracking System (RTS) was developed using SAS® software version 6.07 in a VAX/VMS environment. Due to the flexibility of the SAS system, RTS can be easily ported to other computing environments as well.

OVERVIEW OF THE EXISTING PROCESS

Prior to detailing the components of the Requests Tracking System, it is necessary to describe the environment in which it exists. Specifically, what the NDA submission process is, whom the people involved in it are, and the various ways in which FDA requests may be handled once they are received.

An NDA is submitted to the FDA for review for each new compound a pharmaceutical manufacturer wishes to have considered for approval. The submission consists of all necessary paperwork, the data collected to support the claims made as to the safety and efficacy of the compound, labeling and package insert information, and possibly early marketing or advertising strategies. Review of this package is then assigned to an FDA reviewer who examines the data, substantiates or invalidates the claims made for the compound, and scrutinizes the labeling and advertising information for accuracy and completeness. The reviewer is most commonly a medical specialist in the specific area the compound was developed for use in. During this period, questions are inevitably raised concerning perceived deficiencies or inconsistencies in the submission. These questions are then presented to the pharmaceutical manufacturer responsible for the compound as FDA requests and given immediate attention. As the drug review process nears completion, a body of reviewers known as an advisory committee is formed to undertake a rigorous review of the submission. This committee is typically comprised of specialists in the therapeutic area of the drug of interest. During the one day session, known as the "NDA Day," intense review of the submission takes place and quite often results in approval or denial of the compound for licensing. Additional concerns raised by this committee, then, are given the utmost priority by most pharmaceutical manufacturers, and the need to reduce the time necessary to respond to them is even more critical.

Thus, the ways in which such requests are processed take on an added importance. These may vary widely, from no structured method at all, to some concrete, formalized procedure, and can directly affect the amount of time necessary to produce the requested results. To proceed with no structured methodology at all would inevitably lengthen this time and therefore lengthen the review and approval process for the compound itself. Duplication of code, re-creation of data, and re-creation of analysis models are all among the consequences of proceeding in such an unenlightened manner. These pitfalls can easily be avoided by developing a system of request tracking, maintaining not only information about the request itself, but the additional tools developed (i.e., code, statistical models, etc.) to reply to it as well. Both the existing system and the facility developed at Syntex Research to remodel that system are detailed below.

OVERVIEW OF THE NDA SUBMISSION PROCESS

The structure of the existing process for tracking and logging requests at Syntex Research is charted in Figure 1.

Figure 1 - Existing Process Flowchart

- Statistical sends request to programmer for processing
- Copy of request form to programmer
- Copy of request form to statistician
- Final tables/illustrations are completed
- Copy of final tables/illustrations to programmer for filing
The major components of this process include a request form, the Regulatory Requests Log, where the information about each request is stored in a tabular format and can be browsed as a text file or printed to hard copy, the code and/or applications developed for analysis, and the final report quality tables and listings sent as a response to the FDA. The request form is responsible for driving the process and warrants further attention here. A two-part form, the first detailing information about the request prior to the onset of work to complete it such as what statistical models to use in analysis, what data or groups of data to analyze, and what assumptions are to be made, the second detailing information about the request after work has been completed, such as the directories created to store the developed analysis tools, the tools themselves, and the date the analysis was completed. It is on this form that the integrity of the current process hinges.

Unfortunately, this process suffers from many flaws that render it a poor record tracking and management tool. These arise from its multi-step design in which multiple "hand-offs" trigger the various stages of request logging and tracking, including the initiation of a request, the execution and completion of a request, the logging of request information, and the filing of all related request documentation. More specifically, these flaws are: (1) paper based design, (2) manual log maintenance, (3) tracking deficiencies, and (4) labor intensive.

**Paper Based Design**

As mentioned above and shown in Figure 1, each step in the process of logging and maintaining information for a particular request is dependent upon either the receipt or generation of a paper document, most commonly the request form. Portions of this form are completed and drive both the initiation of analysis on the request itself and the initial entry of the necessary information into the Regulatory Requests Log. The remaining portions of the request form are completed once analysis is finished and the form is then used to enter the remaining information into the log. Delays between the time the form is issued and the time the log is updated are common, and often quite lengthy. In addition, the programmer responsible for log maintenance is usually not the programmer who carried out the analysis, so transcription errors, typographical errors, and incomplete information are all very possible outcomes of this paper based design. Thus, the accuracy of the accumulated data as well as its ability to reflect the current state of the review process are compromised.

**Manual Log Maintenance**

The Regulatory Requests Log is updated manually, as a text file, when copies of the request form are received by the person responsible for doing so. Again, this can occur several weeks after the actual analysis or analyses have been completed, so the errors mentioned above also apply here. This limits the usefulness of the log since the most current and accurate information is not always immediately available.

**Tracking Deficiencies**

A consistent method of uniquely identifying each record in the log exists only informally. A request number is assigned by the person responsible for log maintenance independently of the analysis process itself, often after work has either begun or been completed, so that those directly involved in the actual analysis are unaware of the identifier. In addition, the documented request form is often filed without this request number attached, making future reference by others difficult to achieve. Thus when the log is searched for a particular request's information, it is not done by using a commonly known unique identifier, but rather by the date of the request, the description of the request, or some other text that is subject to all those errors mentioned above. This method, then, can sometimes produce incorrect results, and hinder, rather than expedite, the response time to the FDA request.

**Labor Intensive**

As many as three to four technical staff are needed to perform all the tasks currently involved in the requests tracking and log maintenance process. The flowchart above includes the minimum of three -- a statistician, a programmer to maintain the Regulatory Requests Log, and a programmer to perform the analysis. Additionally, the programmer responsible for maintaining the log must file all relevant documentation pertaining to a request, and must do so in an environment where time is often in short supply and a task such as this is assigned lowest priority. Thus, the time delay between the completion of the analysis and the filing of its documentation again often is quite large, making immediate reference to that material impossible.

**SYSTEM REQUIREMENTS**

Recognizing that flaws existed in the current process and realizing the effect they had to hinder its usefulness as a tool for reducing the response time to FDA requests, it was decided that a remodeling was in order. The first step, then, was to outline the objectives, or requirements, of the new system. Obviously the primary objectives were to remove the flaws detailed above and replace them with the necessary procedures to improve the efficiency of the new facility. To do so would be to create a more streamlined system that could exist independently of paper, which has the capability of attaching some type of unique record identifier to the request form and all associated system generated documentation from the point of its initiation, and finally, could automatically maintain the Regulatory Requests Log. With these objectives met, there remained the additional requirements necessary for the system to be an effective tracking and records management tool. These general features include:

**Ease of Use**

The users of the system were defined to be primarily statisticians and programmers with varying levels of computer experience and expertise. Because the overall objective is to reduce the response time to FDA requests, users were not to be overburdened by complexity in system design. Since the experience base of the intended users was varied, the facility had to provide enough flexibility to accommodate them all. Such users would benefit most from a menu-driven system with an on-line help facility.

**Performance**

A tracking/records management system for large development programs can typically log information for well over several hundred requests. To accomplish all of the tasks required by various users on a large database in a reasonable amount of time, the system must be written compactly and efficiently.

**Additional Requirements**

In addition to those general system requirements listed above, the system should specifically be able to:

- provide on-line editing/updating capabilities
The balance between features and performance, then, was to be carefully maintained. A system lacking any of the additional features added at the expense of performance would be an incomplete tool, and one with would be equally undesirable. In proceeding it was meeting all of the requirements of the data tracking/records management process.

SYSTEM DESIGN

The decision to abandon the text file, paper based design of the existing system was immediate. The benefits obtained from establishing a database system for logging FDA requests were known to be many, and the experience the developer already had with SAS software made its selection obvious. Initially, the system design consisted of SAS/FSP software set into a shell of DEC Digital Control Language (DCL) code. The FSEDIT feature of SAS/FSP was intended to handle data entry, and the DCL code would be responsible for all else: I/O, log creation and maintenance, and reproduction capabilities. The limitations of such a design were immediately apparent, as both flexibility and performance were not achievable to acceptable standards. Whereas SAS/FSP could more than handle the data entry requirements, providing additional capabilities such as search/find functions, field specific features, etc., the DCL code was overburdened when dealing with SAS-VMS interactions. As such, the initial system design was abandoned, and a new design developed. That design is presented below.

Facility Options Menu

Since DCL code was ineffective in driving the system, the obvious choice for its replacement was SAS/AF software. The lack of experience with this extension of SAS had prevented its selection in the first place, but the time required to familiarize the developer with the product was minimal. SAS/AF and DCL code was developed to surround the FSEDIT data entry feature of the facility, and allowed for the desired flexibility and performance not attainable with the DCL code.

In addition, the use of SAS/AF and SAS/FSP with one another minimized the number of VMS interactions that are relatively expensive in terms of processing time. It also allowed for a facility that was both aesthetically and operatively cohesive, that is, it both looked like and acted like a SAS based database facility.

Upon initiation of the facility, an initial menu of options, shown in Figure 2, is provided to the user for selection. These options are:

- provide on-line viewing capabilities, particularly for the Regulatory Requests Log
- provide search/find capabilities, again particularly for the Regulatory Requests Log
- provide subsetting capabilities on accumulated data (i.e., request date, study number, etc.)
- provide sorting capabilities on accumulated data (i.e., request date, request number)
- provide reproduction capabilities (i.e., hard copy output)

The user is then presented with a series of three FSEDIT data entry screens designed around a "fill-in-the-blank" format for ease of use. Upon completion of each screen, data is immediately saved to the database, and exists in the format in which it was entered for the life of the compound. The type of information entered through this option typically deals with the details of the request itself, including what groups of data to analyze, what statistical methods to use, and the necessary personnel. Hard-copy output of that information, arranged into a format analogous to the first part of the request form in the existing process, may be obtained if needed. An example of the INITIATE request option data entry screens is shown in Figure 3.

COMPLETE Request Option

Selection of the COMPLETE request option produces a dialog box that prompts the user for the number assigned to the request at the
time of its inception. The facility then checks for the existence of this number, and whether or not the documentation for the request has already been completed, producing legend windows for instructions in either case. With a valid request number, a series of FSEDIT screens are produced in much the same way as those for the INITIATE request option are produced. Again, the data entered is saved immediately to the database and, if deemed necessary, hard-copy output of a document similar to the entire request form in the existing process is available. An example of the COMPLETE request option data entry screens is shown in Figure 4.

Figure 4 - COMPLETE Request Option FSEDIT Screens

The data entered through this option typically includes details about the tools developed to complete the request, their storage locations, and the dates and times of development and completion. This task can be performed either by the person who did the actual analysis, or by the person who initiated it.

BROWSE LOG Option

The on-line BROWSE LOG option enables the user to browse all entries in the Regulatory Requests Log one entry at a time. Only the most pertinent collection of information concerning a particular request is displayed on screen for the users review. The BROWSE LOG option screen is shown in Figure 5.

Figure 5 - BROWSE LOG Option FSBROWSE Screen

Included in the BROWSE LOG option of the facility are the abilities to subset and/or sort the data. Subsetting allows for the selection of particular groups of data based on any of the following variables: the request data variable, either a single date or a range of dates; the area of request variables, the data from studies variables, the source of request variables, and the statistician/programmer variables. These variables may be selected separately, or in some meaningful combination to provide the user with the most desirable set of results.

Sorting allows the user to output the desired information, either on-screen or to hard-copy, in the most useful format. Choices of sort order include by request number, by request date, by statistician/programmer used, or by the study number from which the data came.

Also included in this option are the inherent capabilities of SAS/FSP to search for and find data as requested by the user. This is especially useful when employing the facility as a quick and easy reference to archived data.

The INITIATE, COMPLETE and BROWSE LOG request option data entry screens all make use of the features available with SAS/FSP, such as protected and required fields for data accuracy and completeness.

UPDATE Request Option

The UPDATE request option allows a specified user or set of users access to update the regulatory requests database. Once the data has been entered using either the INITIATE or COMPLETE request options, it cannot be altered except through this option. This ensures the integrity of the accumulated data as well as allowing only the most qualified personnel to modify it.

After validation of the userid, a series of six FSEDIT data entry screens, the same screens presented in both the INITIATE and COMPLETE request options, are produced which allow for database update. The new information then overwrites the existing data as each screen is terminated.

PRINT Option

The PRINT option allows the user to obtain hard copy output of either the Regulatory Requests Log, or of individual request forms without having to access the INITIATE or COMPLETE request options. The individual request data can be printed using this option at any stage in its development, whether completed or not. The format used for such output is modeled after the request form used in the existing process. The use of SUBMIT blocks embedded in SOL code makes production of such printed output possible. As previously mentioned, the request number assigned to the particular request is printed on the form and all documents generated by the system.

The subsetting and sorting capabilities included in the BROWSE LOG option are also available in the PRINT option when choosing to print the Regulatory Requests Log. This allows the user to select only that information needed, saving time by not searching through superfluous data. It also allows for a more complete monitoring of the FDA concerns, since particular groups of data may be independently examined.

Again, only the most pertinent information regarding a particular request, that displayed on screen in the BROWSE LOG option, is printed. The date of the last log entry and by whom it was entered is also provided for completeness. Samples of the request form and Regulatory Requests Log are shown in Figure 6.
CONCLUSIONS

At the onset of activities to remodel the existing requests tracking and logging process at Syntex Research, the role of SAS was to be limited to data entry using SAS/FSP. This was to be surrounded by a shell of DCL code to perform all other functions. This initial combination was developed but its implementation revealed its inefficiencies. The finished system was almost entirely built using SAS and its many extensions. SAS/AF, SAS/FSP, and SCL code all were incorporated into the design and the interaction between them only enhanced the facility's performance and ease of use.

The remodeled facility effectively eliminated the flaws associated with the original system. This was achieved through a more basic design, one that is more streamlined, less time and labor intensive, and requires less maintenance. Specifically, the new design provided for: (1) on-line existence, (2) automated log maintenance, (3) improved tracking capabilities, and (4) efficient use of personnel.

On-Line Existence

The remodeled facility exists independently of paper. Neither the initiation nor completion of the work needed to respond to the request depends on the issuance of a request form. The request form is now assembled by the system, and is available to all users on-line. The option to produce hard-copy output is, of course, available for filing and review purposes, but it is not necessary as a catalyst to the process. Because the request form is assembled by the system using the data entered by the personnel involved in the actual analysis, the errors that existed in the previous process are no longer present. Transcription errors are eliminated because data is entered directly into the system, not off a form. Incomplete data is no longer a problem because if a field is required, SAS/FSP will not continue until a value is entered. Only the possibility of typographical errors still exists in the remodeled facility, and a method to correct those is provided with the UPDATE request option.

Automated Log Maintenance

Both the INITIATE and COMPLETE request options automatically maintain the log at the time of their use. Information is added to the database as each option is terminated, eliminating the possibility of long delays between completion of analysis and entry of its related data into the Regulatory Requests Log. In this way an up-to-date and accurate collection of information is always available.

Improved Tracking Capabilities

The unique record identifier, or request number, is attached electronically by the system at the moment of request initiation. This allows for the tracking of all requests by all users at all times by a single, commonly recognized identifier. Concerns associated with searching a database by text, such as receiving inaccurate or incorrect information, are no longer present. Furthermore, the request number is attached to all system generated documents, facilitating future reference of request documentation.

Efficient Use of Personnel

Since maintenance of the log is an automatic function of the remodeled facility, the need for an additional programmer for that task is eliminated. Also, the filing of request documentation and related paperwork is transferred to support staff personnel, whose normal, everyday activities include such responsibilities. Therefore, delays between the completion and filing of request documentation no longer exist, and reference to filed information is immediately available. Finally, only those technical staff absolutely necessary for completion of the analysis work itself are included in the records management process. This ensures that a request is received, analyzed, and documented uniformly.

Figure 6 shows the flowchart for the remodeled process resulting from the implementation of the Requests Tracking System. The broken lines depict those steps removed from the old approach, thus eliminating the redundant steps and more effectively streamlining the process.
In conclusion, the Request Tracking System developed at Syntax Research is a powerful tracking, cataloging, and information management system that has a high level of usability and flexibility. Incorporating the features of SAS/AF and SAS/FSP, and the flexibility of SCL to join them, resulted in a compact, on-line system that is easy to use, and accelerates the response time to FDA requests.

ACKNOWLEDGEMENTS

I would like to thank Joe Warlow for his help in reviewing this paper.

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