Paper 41-28

A Programming Development Environment for SAS® Programs

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ABSTRACT

Organizing the programming effort for large projects can be a daunting task. Programming teams are under pressure to complete work accurately and rapidly, while using standard templates and macros whenever possible. Add to that several levels of documentation and a manager's need for frequent status updates and you have an administrative nightmare. A system is necessary to integrate programming documentation, validation checklists, and real-time status reports.

After deciding to centralize our project management spreadsheet, program header documentation, and validation documents, we found that we had the beginnings of a web-based programming development environment (PDE) for SAS programs. This paper describes a database-driven system for organizing SAS programs written using Active Server Pages, Visual Basic, and Javascript.

INTRODUCTION

PRA International is one of the fastest growing Contract Research Organizations (CROs) providing programming services to pharmaceutical and biotechnology companies. Competitiveness in this industry increasingly requires globalization (Labore and Burger, 2001). Expansion of PRA to Trials Management Centers (TMCs) around the globe has fostered cooperative teamwork and the need to develop standardized, steady-state processes that apply not only to SAS program coding practices, but also to the software used to manage the corresponding documentation and validation processes. The staff in our various offices all use a similar approach, but over time some individuals may add improvements to methods without informing the rest of the company. As Tiggemen (1997) noted, "Learning is often the cumulative result of many small improvements rather than major breakthroughs and tends to vary depending on the amount of management attention devoted to capturing it."

With an increase in workload comes the need for a strategy to maximize efficiency while maintaining rigorous quality standards and adherence to the regulatory requirements of the Food and Drug Administration (FDA). A major challenge for programmers, managers, and administrators is how to efficiently organize an access all the programs and documentation required for the many projects they work on.

As drug companies race to get their products to market, this time pressure is passed along to the CROs to whom they outsource many projects. While companies attempt to shorten development cycles, high quality standards must be maintained and this requires new ways to write, document, and validate programs. How then can a CRO differentiate itself from its many competitors in the drug development arena? A successful philosophy must include the pursuit of new and innovative approaches that streamline operations and yield a competitive advantage.

BACKGROUND

Tools to organize and integrate programs with documentation and quality assurance methods would greatly increase the efficiency of managing projects. However, these programming adjuncts are very specific to an industry, company, and even to the individual programmer, so it is not surprising that such a facility is not a part of the SAS system.

A solution to this predicament requires more than just software – it requires a fundamental change in how team members interface with the information. Success will only be obtained if the people who perform these tasks on a daily basis are involved in remodeling the system. Such an obvious statement may not seem worth mentioning, except for the fact that consensus building is one of the most challenging aspects of development.

The Analysis Programming Department at PRA has well-defined quality assurance methods for code development and program validation. We use a variety of tools to assist us in these activities (**Figure 1**), including:

- Detailed headers in every SAS program
- A "Table of Programs" (TOP) spreadsheet to organize and document programs within a project
- Validation Checklists in Microsoft Word®.

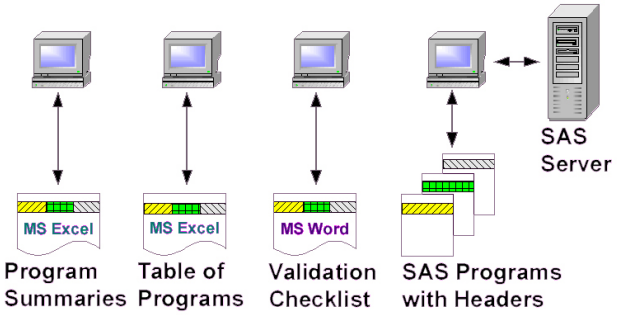

Figure 1 : SAS programs and related files prior to integration.

Program Header Documentation

Documentation of programs is one of the least favorite activities of programmers and is often put off until the last minute. As a result, documentation may be sparse, incomplete, inaccurate, or nonexistent. By making this task an integral part of the project setup and program validation process it becomes a more seamless and less burdensome activity.

Gill (1997) states that narrative documentation of program code is essentially *internal* (such as program headers and in-line comments) and *external* (such as our Table of Programs spreadsheet). Program headers serve not only as a guide to our programmers, but also to our clients who may request the source code as part of the deliverable product. Hence, any documentation stored externally to the program code must become part of the program or be adequately referenced and accompany it.

PRA's Standard Operating Procedures define a structure for our program headers (**Appendix 1**) that includes client and study name, code author, abstract, validation information and other details about the program.

The Table of Programs (TOP)

Our standard TOP Excel spreadsheet allows programmers to rapidly determine program status and dependencies, as well as providing an overview of the entire project. Information for each program must be entered, including most of the items already mentioned in the program header. A summary page allows the team leader to identify project status by summarizing how many programs have been written and validated.

Program Validation Checklists

These checklists are Microsoft Word documents that vary depending on the type of SAS program. Clearly, a program that involves complex data derivations must undergo a different validation procedure than one that simply lists data. In addition to the checklist items, certain redundant elements must be entered into these documents, such as: program author and date, validation author and date, amendment author, etc.

No off-the-shelf solution was available that would allow the integration of our header documentation, TOP, and validation checklists. The choice to develop our own customized solution was an easy one to make and the concept of PRA SAS Manager (PRASM) was born.

COMPLIANCE WITH INDUSTRY REGULATIONS

This paper does not deal with the validation of the SAS system, but instead focuses on how to make programming with SAS more compliant with industry regulations, specifically those in the pharmaceutical industry.

21 CFR Part 11

The FDA provides compliance guidelines for the pharmaceutical industry. "Guidance for Industry. Computerized Systems used in Clinical Trials," (FDA, 1999) addresses the requirements of "Electronic Records/Electronic Signatures" rule of 21 CFR Part 11 (FDA, 1997) and applies to any source documents created; be they hard copy entered into a computer system, direct human entry into the system, or generated automatically by a computerized system. Therefore, SAS programs are governed by these regulations when producing data for submission to the FDA.

Maintaining an audit trail is a critical requirement. The FDA (1999) defines an audit trail as:

> "...a secure, computer generated, time-stamped electronic record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record."
>
> "Changes to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e). Documentation should include who made the changes, when, and why they were made."

These requirements highlight why a compliant system must: (1) allow access only by authorized personnel and (2) provide a detailed log of their activities that result in changes to data or documentation.

System Security

> "Security measures should be in place to prevent unauthorized access to the data and to the computerized system." (21 CFR Part 11, 11.10(k))

By extension, only authorized team members should access a project's programs and documentation. PRASM will capture the Windows 2000 username from the initial workstation logon. The logon name will be looked up in a security table (maintained by the PRASM Administrator) and access to projects is granted to approved staff members.

The staff altering electronic records "…should not be able to modify the audit trails." (FDA, 1999) PRASM will make this possible by storing all actions in a secure log file.

Activity Log

Capturing an audit log is of utmost importance in complying with 21 CFR part 11:

> "Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information." (FDA 21 CFR Part 11, 11.10 (e))

A SAS programming team must accurately record actions that result in changes to data. Many SAS programming environments strive toward this goal, but it often remains out of reach. Documentation of changes to programs is left in the hands of individual programmers whose compliance may fall short of the required standard. A more automated and accurate audit trail is a desirable goal when moving toward FDA compliance.

As stated by Sporon-Fiedler et al. (2002), "A computer system like SAS is a mixture of development and data processing environment with the capability of producing self-contained systems." They further state, "Proving that a log and output file has it's origin from an exact copy of a specific program requires a finely synchronized monitoring tool to prove that no tampering has taken place... Proving that a database (e.g. SAS datasets) is in complete control, requires that all modifications (updates) are tracked."

The FDA guidance details how the date and time of operator entries must be separately recorded for all actions that create, modify, or delete electronic records. While this has become an integral part of the data entry process in many organizations, compliance is often less than optimal for SAS programmers when they make changes to programs that alter data sets or summary displays (tables, listings, and graphs). Such information must be recorded when alterations are made to programs that result in changes to output.

We must ensure that all program amendments are documented and that no alterations remain unaccounted for. PRASM will do this by comparing the file system date on the SAS program with the date of the last entry in the database for the corresponding program. If the file system date is more than one day younger than the date in PRASM, then warnings are issued alerting the lead programmer to investigate the offending program.

Dating of all changes will be handled automatically by the system, which relies on a validated system clock. PRASM complies with the FDA (1999) requirement that, "Dates and times are to be local to the activity being documented and should include the year, month, day, hour, and minute." All actions by staff using the system are logged with staff identifiers and detailed time stamps.

When programmers work across TMC's in multiple time zones, the time stamps will reflect local time where the change was made. As a browser-based system, the time stamp is obtained from the clock on the programmer's workstation, which in turn is synchronized with the validated time-server on their local network. Hence, all times in the system are local to the programmer making the change.

Version Control

A compliant system contains:

> "Revision and change control procedures to maintain an audit trail that documents time sequenced development and modification of systems documentation." (21 CFR Part 11, 11.10 (k))

SAS programming lacks a strict means of version control (Williams, 2002) because it takes place outside of a formal Integrated Development Environment (IDE). Implementation of such a controlled environment adds additional overhead to the process and may not be readily accepted by some programmers. Making version control an integral part of program documentation and validation procedures will avoid the perception of increased workload. Version control becomes part of the programming process with little or no additional input from individual programmers.

PRASM will not include a full-scale version control solution. It will, however, provide automatic archiving of files. The time-stamped backups can be compared using version comparison tools, such as the freeware utility ExamDiff (PrestoSoft, 2002), in conjunction with a log of program amendments that exist as part of the program header.

Separating Development and Production Environments

Another important aspect of compliance with FDA guidelines is the separation of development or *testing* code from finalized *production* code. By using separate folder structures for finalized, validated programs, we can ensure that the programs and the output they produce are synchronized. Once programs have been validated the system will allow the programmer to *move the file to production* at the click of a button. If a file requires editing, it is removed from production folder and placed back in the development folder until the changes have been validated. Additionally, programs, log files, and output will be automatically archived into a time-stamped shipment folder each time output is sent to a client.

The key points of compliance with 21 CFR Part 11 – data security, audit trails, and management of programs and documentation, can all be attained to some degree through the use of PRASM along with a standardized management methodology. Much of PRASM's approach to the data security issue is indirect, controlling access to the programs that produce SAS datasets, instead of controlling access to the SAS datasets themselves.

Audit trails are dependent on programmers accurately documenting amendments to programs. Automatic backups of programs provide a means of comparing previous versions of code. Documentation exists by integrating the program header information with validation documentation in a single location - the PRASM database.

DEVELOPING THE SYSTEM

CONCEPTUAL FRAMEWORK

Related elements of the coding process will be integrated into a web-based system as illustrated in **Figure 2**. A centralized database will hold information about each program for display and updating through a dynamically generated web interface. These pages will also provide the ability to launch programs into a code editor or submit them to various remote SAS sessions.

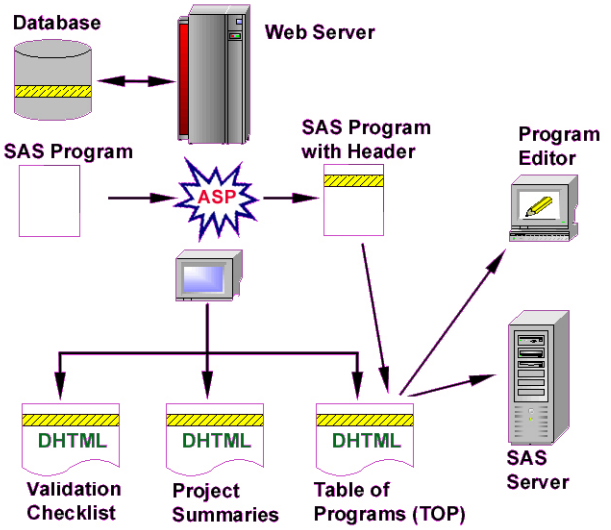

Figure 2 : Integrated approach to managing SAS programs and related files.

Our goal is not to produce a full-scale Program Development Environment (PDE). We already have tools for code editing and syntax highlighting (UltraEdit (Mead, 2002) and the SAS Enhanced Editor). Other software adjuncts are available for diagramming program flow (ComplementSoft, 2002) and our Standard Operating Procedures govern our code writing methodology. The main goals of our system are to:

- Standardize and reduce redundancy in validation and documentation procedures
- Link programs to their documentation and validation information
- Facilitate rapid programming using inter-office programming teams
- Rapidly communicate project and program status
- Increase compliance with FDA requirements.

The scope of the project quickly expanded from merely a documentation tool to a more integral part of our programming methodology and philosophy. It will allow us to review our processes and answer such questions as: "How many hours are required for a Phase III Oncology trial versus a Phase III Anti-Infectives trial?"; "Which offices are under or over staffed?"; "Are the code writing and validation tasks shared equally among programmers?"

PUTTING THE PIECES TOGETHER

We are following, "7 Practices for Excellent Software," (Barnes Nelson and Grasse, 2002) during construction of the application. Early development has started on a workstation running Personal Web Server and a Microsoft Access® database. We are applying the principle of "Orthogonality" by using structures and naming

conventions that will facilitate later porting to an Oracle database and the .NET architecture.

Our initial focal point was one of the most critical areas of the system: the linking of program header documentation to the SAS program. Each time the program header page of PRASM (**Appendix 2**) is updated, the ASP code reads in the appropriate SAS program file and starts searching for a standard marker line:

```
/*!!--DO NOT EDIT THIS LINE OR ABOVE--!!*/
```

When it finds the marker, all code above that line is discarded (deleting the now outdated header information) and the new header information is written in its place. The application appends the remainder of the program below the marker line. Only the header is updated and the program code itself remains intact. A time-stamped backup copy of the program is also created and archived.

Once the program header issue was solved, we turned back to the topic that had started our development in the first place, the linking of validation checklists to each SAS program. Our Microsoft Word checklists account for additional redundancy, so we can further streamline our processes by making them part of the new solution as forms in the web application.

Programmers and team leaders also need a quick way to check the status of a program and determine if it:

- Has been written
- Is ready for validation
- Has been validated
- Is *in production*.

This will be available to programmers at a glance on a web page that provides status *traffic lighting* for each program in a project. (**Appendix 3**).

Once the documentation is linked to the program and its status is easily determined, we can launch a selected program into a code editor and remote SAS sessions. This presented a technical obstacle, since browsers are generally not permitted to launch desktop applications due to security concerns. We overcame the challenge by using "Launch-In-IE" (RockinFewl, 2002). After installing the supplied .DLL and making minor changes to the Windows 2000 registry, we set up a trusted URL for the PRASM website. We can now send SAS programs directly into our code editor and to local or remote SAS sessions from a web browser. Since our database associates projects with offices, PRASM will automatically know which SAS server to use for running the program.

STATUS

Our staffing and workload constraints lead us to adopt the staged delivery model of software development (McConnell, 1996). Staged delivery, also known as incremental implementation, makes content available to users in successive stages as the application is developed. In this way our staff will see tangible benefits of the system without having to wait for its full implementation.

In the current version of PRASM, programmers are presented with an initial screen where they select a client and then drill down to an individual project. From there, a list of all programs within a project and their individual status appears on a web page that resembles our original Table of Programs (**Appendix 3**). On this page programmers can quickly determine the status of a program based on a series of traffic lighting indicators. They will know at a glance if a program has been completed, if it has been validated, and if it has been moved from the development folder to production. At the click of a button they can: edit and update the program header (**Appendix 2**); fill out the program validation documentation; move the program into a production directory; send the program into the program editor; submit it to a remote or local SAS session; or archive all programs, logs, and outputs into an archive directory.

At this time we have identified a small project on which to pilot test the system. A small group of programmers will run through the project, provide feedback, and assist in further refinements to the application.

FUTURE DIRECTIONS

Future enhancements to PRASM may include: parsing SAS program log files to identify ERROR, WARNING and user-defined problem statements; reporting summary information such as the number of programs written, checked, validated over a specified time period; forecasting the amount of hours required to finish projects; customizable templates for program headers and validation checklists.

CONCLUSION

The PRA SAS Manager System is currently in its infancy but shows great promise. What started out as an idea to link program and validation documentation has grown into a much larger endeavor.

Our program documentation will soon no longer exist as disconnected elements, but will instead share fields with the Table of Programs and SAS program headers in a database. Redundancy of data entry will be greatly reduced as the entire process becomes streamlined due to the centralization of information. Programmers can spend more hours on client-oriented project work and less time laboriously filling out redundant information.

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ACKNOWLEDGMENTS

I wish to thank the Analysis Programming staff at PRA International for their continuing feedback and assistance.

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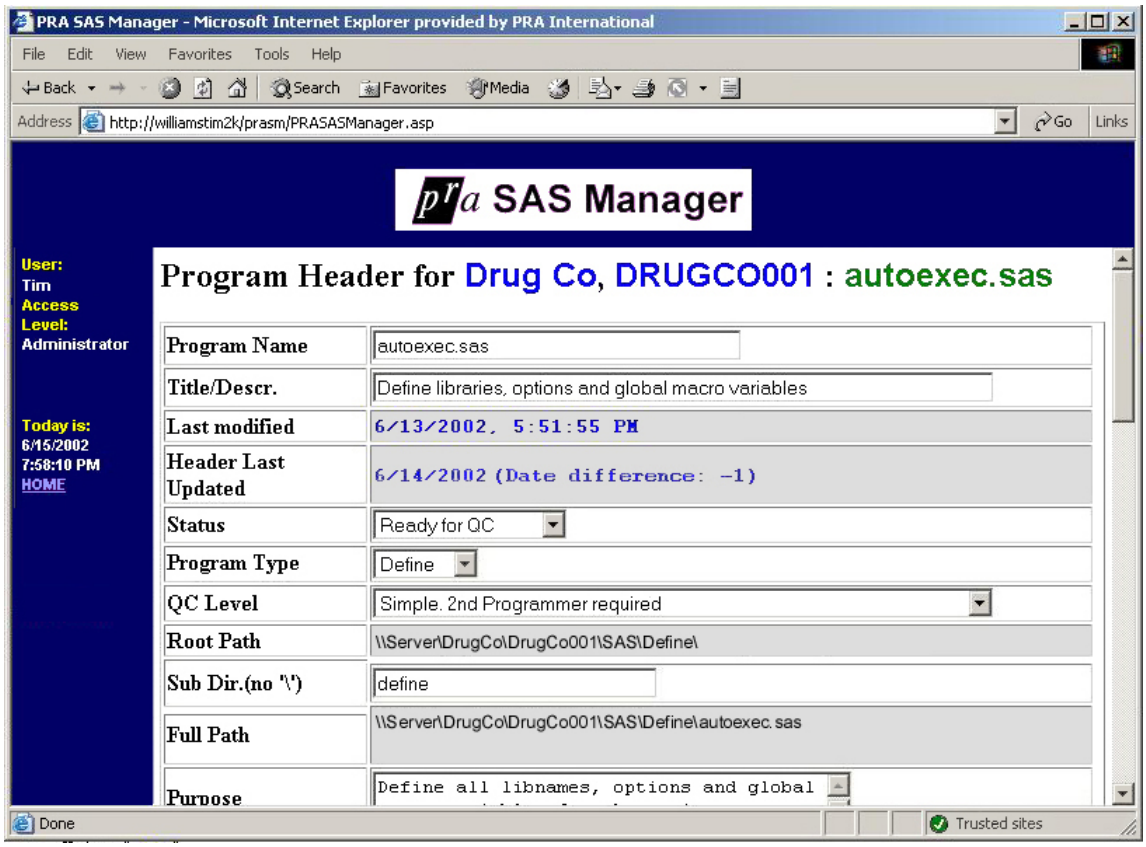
APPENDIX 1 : EXAMPLE SAS PROGRAM HEADER

```
/*************************************************************************
STUDY           : Drug Co, DRUGCO001
PROGRAM NAME    : m_demog.sas
PURPOSE         : Derive Demographic data set.
PROGRAMMER      : Tim Williams
DATE            : 08/12/2002
QC        BY,DT : Jimbo Jones, 08/13/2002
INPUT FILES     : //FileServer/DrugCo/DrugCo001/data/datasets/raw/demog.sd2
OUTPUT FILES    : //FileServer/DrugCo/DrugCo001/data/datasets/final/demog.sd2
MACROS USED     : %CI, %AGECALC
NOTES           : Derived data set is used in l_demog.sas and t_demog.sas
                :
AMEND[1]BY,DT   : Nelson Muntz, 08/20/2002
AMEND[1]DETAILS : Added age calculation to Demog data set
AMEND[1]QC BY,DT: Jimbo Jones, 08/22/2002
                :
Header last updated 11:19 Thursday, August 22, 2002
Copyright (C) 2002, Pharmaceutical Research Associates, Inc.
All Rights Reserved.
*************************************************************************/
/*!!--DO NOT EDIT THIS LINE OR ABOVE--!!*/

data _null_;
   put "Example data step...";
run;
```

APPENDIX 2 : PROGRAM HEADER (PRASM WEB PAGE)



APPENDIX 3 : TABLE OF PROGRAMS (PRASM WEB PAGE)