

Using SAS® 9 in Clinical Research

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Abstract

For 30 years SAS has been used in pharmaceutical research settings for data management, analytics and reporting. Traditionally, these roles were staffed by the BASE SAS programmer and the statistician. At the same time, dramatic shifts in the research informatics eco-system have occurred with advances in standards, such as CDISC, ICH, and HL7, and the convergence of clinical data management systems and modernization strategies, such as electronic data capture and 21 CFR Part 11.

This paper provides a broad based view of solutions SAS provides across the research information spectrum. We are at an interesting crossroads—on one hand, the power of traditional SAS approaches found in BASE and STAT; on the other, a new range of technologies grown out of the SAS 9 platform, such as the Metadata Server, Data Integration Studio and SAS Business Intelligence products. The SAS Drug Development solution merges the accessibility of the Internet with the clinical trial workflow.

. Whether your focus is beating data into submission or making it sing and dance in reports, this paper will make the connections to the various solutions from SAS and where each solution is most valuable in the pharmaceutical setting.

This paper is appropriate for people at all levels and across the spectrum of job skills, including the production of clinical study reports, pharmacovigilance and safety reporting, sales force optimization, clinical trials management, and laboratory data analysis. It is specifically designed for the programmer, statistician, manager and system administrator.

Table of Contents

ABSTRACT	1
INTRODUCTION	2
THE NEED FOR BI AND DI IN PHARMACEUTICALS	2
<i>BI Defined</i>	2
<i>DI Defined</i>	3
PHARMACEUTICAL VALUE PROPOSITION	3
CLINICAL RESEARCH LIFE CYCLE	4
CHALLENGES	5
USING SAS IN BIOPHARMA	6
INTRODUCTION TO SAS 9.....	6
NON-CLINICAL USE	7
CLINICAL USE	7
SAS, SAS 9 AND SAS DRUG DEVELOPMENT	8
REFERENCES:	10
BIOGRAPHY:.....	10
CONTACT INFORMATION:	10

Introduction

BioPharmas ensure the safety and efficacy of drugs being discovered, developed and approved for the market; enabling drug candidates to be accelerated through the discovery and development cycle; and “killing” underperforming candidates from either entering clinical programs or continuing in the cycle. They do this through enhancing decision-making capabilities for managerial processes (e.g., planning, budgeting, controlling, assessing, measuring and monitoring) and ensuring that critical information is being exploited in a timely manner.

From data management to statistical programming, to the exchange of data between companies in the BioPharma ecosystem, the value of business intelligence and data warehousing is becoming more of a priority—the biopharmaceutical industry is seeing a 13 to 15 percent annual increase in its business intelligence and data warehousing spending.

Since SAS has long been the standard in pharmaceutical research and development, this paper, will review not only the traditional uses of SAS in BioPharma, but also explore some additional capability in and out of the research process for SAS to deliver on the goal of efficiency gains through technology.

The need for BI and DI in Pharmaceuticals

As Tim Furey outlines in “Spending Trends Demonstrate Value of Business Intelligence and Data Warehousing” (Furey, 2006), the value of incremental improvements efficiency—the empowerment of management to make better, faster, higher quality decisions—has a huge potential impact on the bottom line. With enhanced decision-making capabilities, and the ability to respond to health authority requests and inquiries in a more timely manner, the concerted organizational effort leading up to NDA review/approval is being accelerated by up to five days—leading to earlier revenue recognition. Revenue is being estimated at \$1,000,000 per day, each day the review or approval is accelerated.

With enhanced decision-making capabilities, in addition to the ability to utilize all drug discovery and development data in a consistent, accurate and trusted manner, there is potential to “kill” at least one more drug per year earlier in the cycle; and/or prevent one from entering a clinical program.

Note: 9,999 out of 10,000 drug candidates fail to make it to the market; and for the one that makes it the research and development costs are almost \$750 million. The cost avoidance is estimated to be in the millions.

BI DEFINED

Business intelligence (BI) is a broad category of application programs and technologies for gathering, storing, analyzing, and providing access to data to help enterprise users make better business decisions. BI applications include the activities of decision support, query and reporting, online analytical processing (OLAP), statistical analysis, forecasting, and data mining. BI is a set of concepts and methods used to improve business decision-making through fact-based support systems.

In clinical research, we traditionally used DATA STEP, PROC SQL, macros, PROC Report, PROC Tabulate, Data _NULL_ and ODS— all supporting the generation of reports (a subset of business intelligence.)

DI DEFINED

Data Integration (DI) is traditionally known as “data management”. DI involves combining data from several different locations, formats and structures to create a single, credible version of the “truth”. Data Integration is about beating data into submission—getting the data right before it’s used.

As a practical matter, DI is seen in a number of usage areas, such as those found in statistical programming where Data step, SQL, and macros to support the generation of derived datasets and analysis datasets might traditionally be used. Over the last few years, a tremendous uptake in the adoption of CDISC standards and the support from vendors like SAS to aid in the management of the standards process with new generation of tools to support CDISC had been noted. Finally, there are also a number of classic data warehousing strategies that employ the use of DI tools, such as the development of Clinical or Patient Data Warehouses, being used.

Pharmaceutical Value Proposition

Looking at what pharmaceutical companies do, the bottom line is they produce drugs (or devices) that are focused on these key components:

- Prevention
- Cure
- Treatment
- Diagnosis
- Promotion

The figure below highlights the Pharmaceutical Value chain—or what is done to support the development of drugs. Each of the major organizations within a pharmaceutical company focus on solving one of these fundamental problems.

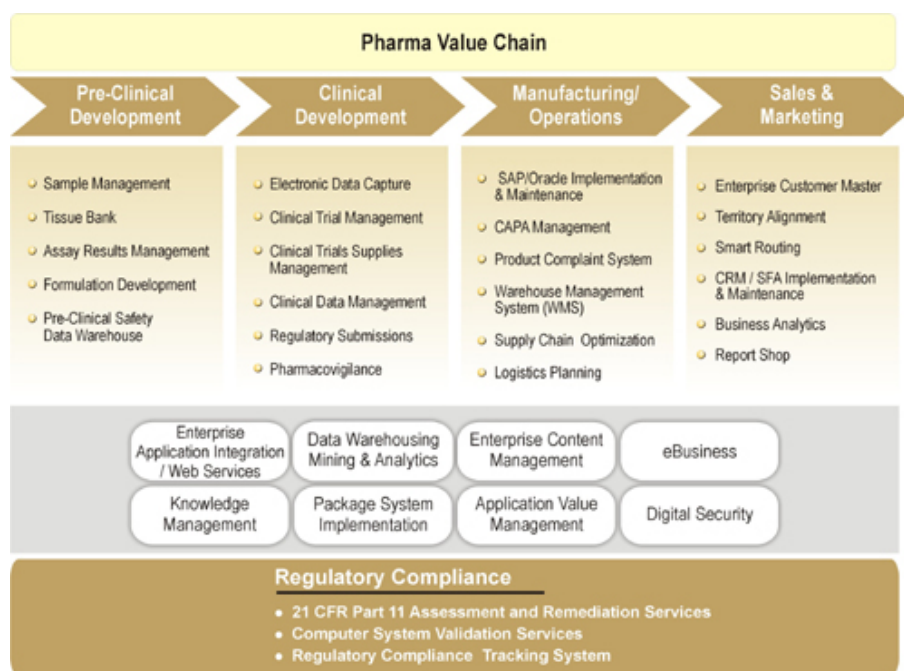


Figure 1. Pharmaceutical Value Chain

Pharmaceutical companies make a tremendous investment in getting drugs or devices to market. These facts highlight the importance of efficiency in this process.

- Only 1 in 10,000 of compounds synthesized ever reach market
- An NDA is approved for 20% of the drugs which had an IND filed
- By the time a drug is approved, generally only 8 years remain on the patent
- Only 25% of all drugs marketed achieve profits that exceed the development costs

Hence, the importance of

- Efficient processes
- Meeting or exceeding timelines

Clinical Research Life Cycle

The clinical research objectives are to provide clinical information useful in the making of business and economic decisions and to provide understandable information that will aid stakeholders in predicting the safety and efficacy of a compound.

The qualitative characteristics of clinical reporting include **relevance** (timeliness, predictive value, and feedback value), **reliability** (verifiability, neutrality, representational faithfulness) and **comparability** (including consistency).

There are a number of core functions that are areas for focus when it comes to enabling technologies. These include,

- Protocol Design and Study Start-Up
- Patient and Investigator Recruitment
- Clinical Trial Management
- Clinical Data Management
- Data Analysis
- Clinical Supplies
- Regulatory and Safety

The figure below shows these core functions and highlights the technologies used traditionally to help improve or automate them.

	Key Application Functionality										Integration & Aggregation		Key Infrastructure						
	Portals	Collaboration/KM	Decision Support	Electronic Data Capture	Advanced Data & Database Mgt.	Visualization	Workflow Mgt.	Statistical Analysis & Reporting	Drug Supply & Tracking	Document Mgt.	Project & Portfolio Mgt.	Data Mining	Data Warehousing	Enterprise Application Integration	Stds. Repository	Enterprise Vocabulary	Object Models	Electronic Signatures	Web Services
Protocol Design																			
Recruitment																			
Trial Management																			
Clinical Data Mgt.																			
Data Analysis																			
Clinical Supplies																			
Regulatory & Safety																			

Figure 2. Technologies for Pharmaceutical Business Use

It should be noted, because of its specific strengths, traditionally SAS has only played a role in a few of these functions. For example, Data Analysis, Clinical Data management and Regulatory and Safety. Given the breadth of SAS' current offerings for data integration, business intelligence and analytics, the opportunities to utilize SAS solutions is vast.

Challenges

The road to successful application of technology in BioPharma is not without its challenges however. This is an industry wrought with regulations designed to ensure that drugs that make it to the market are safe and effective. Therefore, the technology challenges of auditability, security, repeatability, manageability, and compliance are ever-present.

Perhaps one of the most significant regulatory requirements is CFR 21 Part 11, which has to do with security, audit trail and version control. This FDA guidance requires the following characteristics for computerized systems used to support medically-based decisions.

- **Validation**—accuracy, reliability, and consistent performance, and the means to discern invalid or altered records
- **Restriction of system access** to only authorized individuals
- **Secure, computer-generated, time-stamped audit** trails to record operator entries and actions to create, modify and delete electronic records—that must be retained and available for agency review and copying for a required period of time
- **Operational system checks** to enforce permitted sequencing of steps and events as appropriate
- **Authority checks** for use, e-signature, access of input and output device, altering a record, and performing operation at hand

In addition, other standards that help deliver safe and effective drugs to the marketplace. These include ICH and CDISC.

ICH

The International Conference on Harmonization (ICH) has been compiling a series of guidelines for the preparation, design, conduct, and reporting of clinical trials with an aim to harmonize the interpretation and application of technical guidelines and requirements for product registration.

CDISC

Consortium of Data Interchange Standards Committee (CDISC) is primarily concerned with developing standards that aid in the exchange of information between companies in the BioPharma ecosystems. These include the following models:

- Operational Data Model (ODM)—operational support of data collection
- Study Data Tabulation Model (SDTM)—data tabulation data sets
- Case Report Tabulation Data Definition Specification (CRTDDS - aka define.xml)
- Laboratory Data Model (Lab)
- Standard for Exchange of Non-clinical Data (SEND)
- BRIDG—Protocol Representation
- Analysis Data Model (ADaM)—analysis data structures
- And others... (For example, LAB, SEND)

Taken together, these standards and guidelines represent challenges of supporting the clinical research process. With these in mind, let's explore what SAS 9 offers us in terms of solutions.

Using SAS in BioPharma

Introduction to SAS 9

The SAS 9 architecture is fundamentally different from any prior version of SAS. In the SAS 9 architecture, SAS relies on a new component, the Metadata Server, to provide an information layer between the programs and the data they access. Metadata, such as security permissions for SAS libraries and where the various SAS servers are running, are maintained in a common repository.

By providing a single point of access for this kind of information, SAS servers can be located practically anywhere (consolidated or distributed) and on any platform (operating system and hardware), to be accessed by SAS clients. The SAS client tools now take on the form of special purpose applications designed to satisfy the needs of various types of SAS users.

The SAS 9 platform can be configured in any number of ways, including a myriad of server topologies and client offerings. For example, management of SAS metadata can be done through the SAS Management Console and Information Map Studio. Or management of data can be done through Data Integration Studio in addition to the existing SAS products, such as SAS/Access and Base SAS. Tools used to access information now include a substantially improved Enterprise Guide, the new add-in for Microsoft Office,

and the web-based clients (Information Delivery Portal and Web Report Studio), as well as Base SAS components.

From a clinical programming perspective, SAS 9 can be used in much the same way previous versions of SAS were used. SAS is still SAS. That is, if you are a lone SAS programmer doing base SAS kinds of tasks like Q & A, Reporting, Macro, data analysis, you can still operate the same way you always have. For example, you can still use Display Manager although it is highly recommended you at least move to Enterprise Guide. However, to really leverage the technology and take advantage of the way SAS has become more useable, scalable and integrated, then you are going to have to leap into this new client/server world.

Non-Clinical Use

As discussed above, there are a number of ways in which SAS as a technology platform can be used to support the Pharmaceutical value chain. There is ample evidence to show SAS used successfully in a number of areas including:

- Sales and Marketing
- Manufacturing
- Finance
- Human Resources
- Information Services
- Executive and Portfolio management

Clinical Use

Within clinical research, the strongest use of SAS in pre-clinical research, clinical, STAT/programming, and supporting other groups such as:

- Data management (patient profiles)
- Medical writing
- Finance
- Project management
- Patient registries and post-marketing surveillance

Looking across these uses from an architectural perspective, it becomes more apparent the centralized metadata repository is the key to an effective managing the metadata, data, people, processes, and technology services. The figure below shows some of the clients and how they interface with SAS servers.

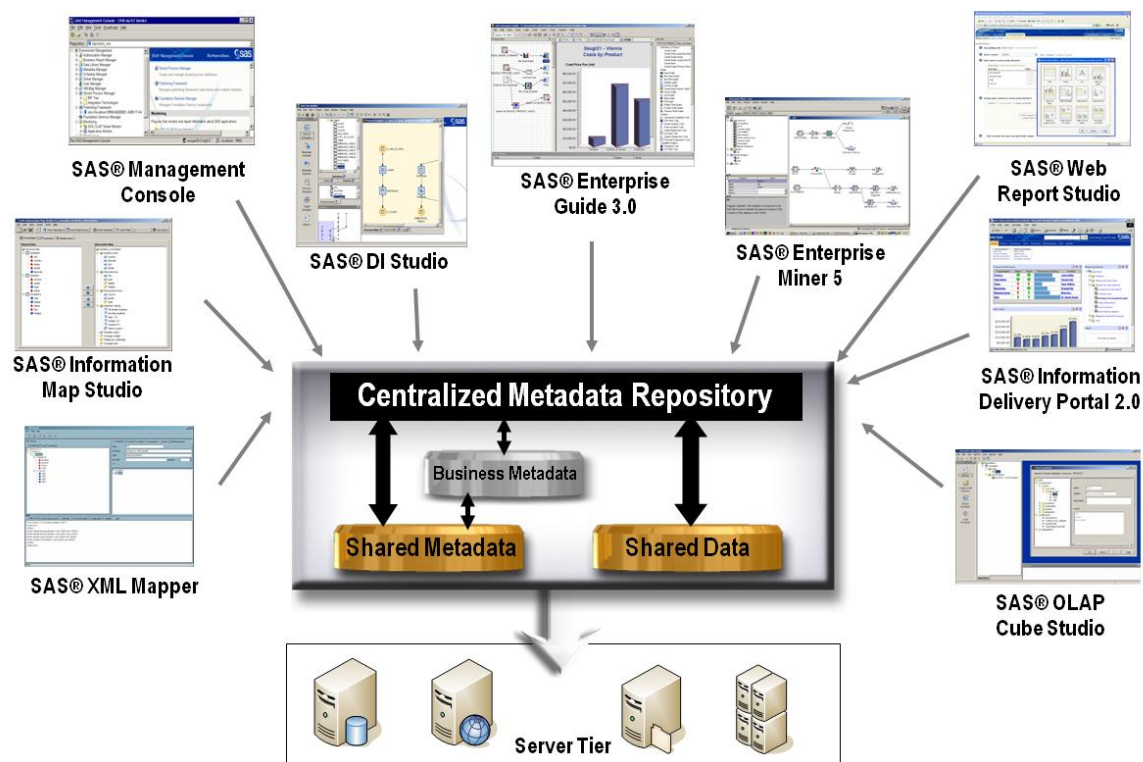


Figure 3. SAS Clients Interacting with the SAS Metadata Server

There are a number of benefits the new SAS multi-tiered architecture provides:

- Delivers immediate productivity benefits to SAS users, particularly those currently working with a variety of SAS interfaces, such as display manager (X-windows, telnet, PC SAS), because of the user-friendly tools appropriate for the job at hand.
- Efficient use of both the desktop and the server. The desktop is used for code editing, reviewing results, and data exchange. The server is used for SAS computations, which are the most CPU and disk intensive operations.
- Excellent support for centralization of SAS, consistent with both the business vision of a global system and the overall IT consolidation strategy.
- SAS Management Console allows management of license information, installation/configuration information, which servers and applications currently in use, and some ability to monitor SAS servers.

Regardless of the client interface an organization uses, all contribute to the same place. But it's not just about centralized storage. The repository is also capturing intelligence through the submission process that can be easily reused from study to study. A statistician who creates a new method for analyzing adverse events can add this to the metadata so other statisticians can easily re-use it with little to no modification. It's hard to underestimate the value of standardizing certain routines and the impact on quality and efficiency that can be derived from that reusability.

SAS, SAS 9 and SAS Drug Development

One of the lingering questions is how to decide which solutions are most appropriate. Much like anything in technology, it depends. For example, there is the traditional data analysis environment used consistently for

the past 30 years and mostly based on SAS (BASE, STAT, macros, etc.). Most large pharmaceutical companies, CROs and Laboratories have infrastructure built around the concept that SAS is a programming tool and the Display Manager is the development environment.

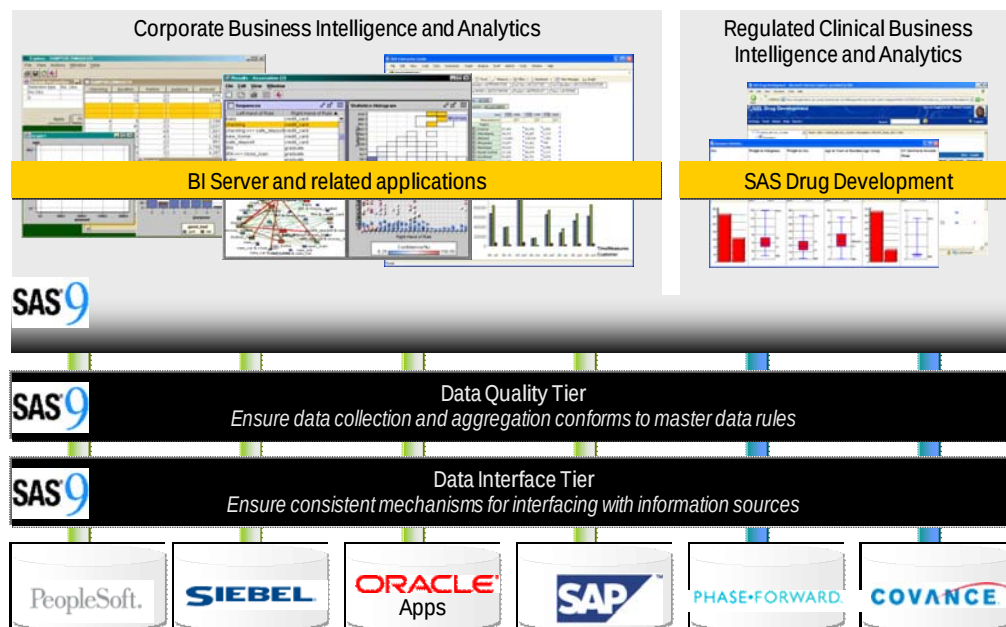
Incremental improvements on that architecture might mean moving it to the server and using Enterprise Guide as the client, but leaving the programming processes in tact. However, some of the most critical imperatives for the use of technology in pharmaceutical research center on improving security, auditability, compliance, validation, and change control. To simply forklift a decade old processes to SAS 9 would merely ignored the potential risks with that approach.

With SAS 9, we have two complementary options: SAS 9 as a platform and/or SAS Drug Development. SAS 9 as a platform is taking the traditional benefits of using SAS and layer on security, centralized management and metadata management as well as use tools most appropriate to the task.

For example, the data management expert might use DI Studio instead of Display Manager found in BASE SAS. The programmer would use Enterprise Guide and management would use the SAS Add-in for Microsoft Office, the Information Delivery Portal or Web Report Studio. Because things are managed centrally and applying security appropriately, those reports can be repurposed for consumption outside of traditional departments like STAT/Programming.

Some companies have taken that a step further and adopted SAS Drug Development (SDD) as their platform for programming. SDD was built with the notion that compliance, security, and auditability is essential to the clinical research process. The SDD platform uses the same underlying foundational pieces of SAS to produce the output, but does so in a managed environment.

Enterprise Strategy



* Image provided by SAS

27

Figure 4. SAS' Enterprise Strategy for Pharmaceutical Companies

In the figure above, the newer strategies (Business Intelligence and Data Integration) can coexist with a compliant SDD environment that rests on the foundation SAS pieces used for years.

Conclusion

The pharmaceutical industry needs efficient business intelligence and data warehousing solutions for its clinical developments to be successful. The SAS 9 platform is providing interesting concepts to address these future challenges and has been consistently used and supported in the industry.

SAS 9 can take clinical data from early discovery to post-marketing safety and efficacy studies, to supporting sales and marketing. As stated earlier, this is now a financial priority and it is important to realize the value of technologies like the solution proposed by SAS .

However, as with any technology, the *right* solution must be applied. Therefore, it is imperative those using and looking for future opportunities in BI—from managers to programmers—know current technologic offerings and applications, and its impact on efficiency in this process. Whether those processes involve compliance, validation, security, auditing or just improving programmer productivity or sharing of relevant information, SAS provides a number of options to support all pharmaceutical needs.

References:

Furey, Tim (January 24, 2006) *Spending Trends Demonstrate Value of Business Intelligence and Data Warehousing*. <http://www.b-eye-network.com/view/2242>

Biography:

Greg Nelson, President and CEO

Greg has recently started his third decade in the SAS eco-system as a programmer, analyst, architect and teacher. Greg is the President and CEO of ThotWave Technologies where he supports customers in a variety of industries. Prior to ThotWave, Mr. Nelson spent several years in consulting, media and marketing research, database marketing and large systems support. Mr. Nelson holds a B.A. in Psychology and PhD level work in Social Psychology and Quantitative Methods.

About ThotWave

ThotWave Technologies, LLC, is a Cary, N.C.-based consultancy and market leader in real-time decision support, specializing in regulated industries such as life sciences, energy and financial services. ThotWave recognizes the difference between simply accessing data and making data work for business. ThotWave commands the juncture of business and technology to help companies improve their operational and strategic performance. Through products, partnerships and services, ThotWave enables businesses to leverage data for faster, more intelligent decision making.

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