A Client/Server Solution using the SAS® System for Electronic Submissions to the FDA
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Abstract

In delivering information electronically to the Food and Drug Administration (FDA) for drug review, client/server solutions are now becoming commonplace, particularly in light of expanding technology and space constraints at the agency. The ability to take advantage of hardware already set-up at the FDA as well as provide multiple access to submitted sponsor information is key in agency review of drugs and biologics. The various agency divisions now request, more often than not, client/server solutions or, minimally, information that can be loaded and accessed with software tools already being employed at that division.

This paper will present a real world experience concerning the actual planning, implementation, and delivery of a client/server solution to both the sponsor and the FDA for a New Drug Application (NDA) involving minimal hardware installation. The use of SAS® software as an interface driver, programmed in SAS/AF® and Screen Control Language (SCL), for the system and to store the database will be discussed in detail, as well as technical issues involved in using SAS with other client/server software. Problems and obstacles encountered will also be addressed, as well as how they were handled and resolved. The paper will close with an objective evaluation of the entire process, including future plans concerning this technology for FDA submissions.

At the time of this writing, the implementation of the solution at the FDA had not yet taken place. Thus, the plan by which submission of this technology to the agency will be presented.

Background

Synteract, Inc., a SAS Quality Partner providing data services and software solutions to the pharmaceutical and biotechnology community, was contracted by an emerging biotechnology company to deliver an electronic NDA for the sponsor to the FDA in a 7-month time period. The sponsor thought highly of Synteract’s software, which included the integration of the SAS® System as an interface driver/data review tool and WordPerfect as a document review

and navigation tool within a UNIX-based application. In order to support their submission, Synteract provides the sponsor with a replica of the software application in-house for multiple access by its staff. However, the client/server solutions for the sponsor and the FDA will vary due to the different hardware configurations at each site. Specifically, the sponsor wished to use PC clients with a UNIX server (a Sun Sparc20 machine), while the FDA plans to use UNIX workstations as clients with a UNIX server (Sparc 10).

Electronic submissions, most times identified as Computer-Assisted New Drug Applications (CANDAs), involve the submission of information electronically to the FDA to facilitate a more effective drug review, both in quality and speed. Access to and navigation of on-line clinical study reports, querying of the analysis database, re-run of analysis programs, retrieval of optical images, and report generation and conversion are all key functions of such a system. Client/server solutions have become particularly key in submitting information and providing functionality to the agency due to the following factors:

1. Upgraded hardware/software at FDA
2. Limited space for hardware
3. Multiple access to information

Planning Phase

Before diving right into software development, both the sponsor and Synteract needed to discuss with officials from FDA about the parameters in which hardware and software could be submitted to help review the NDA electronically. These discussions often involve consideration of:

1. Type of hardware and systems used currently by sponsor
2. Type of hardware and systems used currently by FDA
3. Features/functions in a CANDA most useful to FDA reviewers
4. What the sponsor can provide to the FDA in CANDA-form
Clarification of these items is key in establishing the groundwork by which the project can appropriately begin. The sponsor held several discussions with their FDA division about submitting a CANDA. Upon deciding to use the Synteract solution, teleconferences were held that included the FDA division representatives, sponsor staff, and Synteract CANDA personnel. It was in this manner that key items (e.g., functionality, operating platform, available hardware) were covered and agreed upon.

In conversations about computing environments, initial strategy as to developing the best client/server solutions for both sponsor and FDA began to take form. Synteract spoke directly to the IS department of the sponsor and to a designated computer-savvy person within the FDA division where the CANDA was to be submitted. Both environments intended on using a Sun Sparc workstation as a server; however, the sponsor chose to use PCs (MS-Windows OS) as clients, while the FDA had other Sun workstations available as client machines. The Information Systems department for the FDA will usually be involved to some extent in consideration of the finer aspects of the submission. Overall, however, the designated person in the division became the key contact in delivering the full solution to the particular FDA division, providing the necessary information as to how any proposed solution can best be implemented at that division.

The situation at the FDA did not present a problem for Synteract since they intended on using Sun workstations as clients. The sponsor’s use of PCs as clients left Synteract with the challenge of providing a graphical user interface on the client side while maintaining the software on the UNIX server side. Our first and, as it turns out, best option was to go with a PC-X Windows communications package called eXceed for Windows by Hummingbird Communications Ltd. This would allow PC users running MS-Windows to bring up an X-windows session that would fully run the CANDA application from the Sun server. Reasons for choosing this option were:

- Less coding necessary within CANDA software to implement solution
- Full functionality of CANDA realized on client PCs
- Cost of communications package was justifiable and reasonable
- Same graphical user interface on both UNIX and PC maintained

Other options included the use of SAS/CONNECT® to access the information from the server at any client machine. However, this would have necessitated the coding of a graphical user interface on the PC client side (or, minimally, the conversion of the UNIX SAS/AF front-end to MS-Windows). Either choice would have greatly increased project timelines. The eXceed option, as an X-windows emulator, allowed us to perform minimal modification to the CANDA application on the server (UNIX) side in addressing issues concerning the software executing appropriately on the client side. Some of these modifications consisted of:

1. Changing the font size for PC use rather UNIX workstation use
2. Re-situate SAS windows on PC to eliminate overlaying within the application

Testing/Development Phase

Upon making the decision on the type of client/server solution to go with, testing began on the particular configuration and hardware set-up necessary for the solution to perform appropriately. This is done in the offices of Synteract as a prototype. Application response time is a critical factor since the primary objective of an electronic NDA is to expedite the drug review; thus, benchmarking of functions provided within Synteract’s software was done for the eXceed solution, employing various factors such as load (3-5 users) and contention (accessing the same files). SCL constructs and application start-up programs were modified to gain efficiencies and address various differences encountered on the client side, such as monitor size, font size, and color schemes. Indices for SAS datasets were used to gain better response time when accessing datasets through system functions. Moreover, the testing allowed Synteract to determine the best PC configuration to be used on the client side (i.e., 486, Pentium, memory allocation, monitor). Pentium-class, 75-Mhz PC with 8Mb RAM and 15" color monitor was chosen as the best price-performance machine for this solution.

(The servers for both the FDA and the sponsor were already purchased prior to the sponsor’s NDA submission and thus, were to be used by Synteract for housing the CANDA software.)

With the decision made on the system parameters to work by on the project, the software development plan was initiated.
Implementation/Delivery Phase

Software development continues virtually until the application enters the validation stage. However, a prototype of the application is demonstrated to the sponsor for acceptance, compliance with the software requirements, and discussion on any modifications to be coded. After sponsor acceptance, and making the requested software changes, installation of the application is installed at the sponsor, with planned updates to both the information database and the software itself. Actually, the sponsor's IS staff let us "borrow" their Sparc20 machine to perform the installation at Synteract's offices. This provided Synteract with more time and resources for troubleshooting any system problems concerning the software load. Installation of the application at this time allows the sponsor staff to become well-versed in using the CANDA before submission to the FDA, resulting in quick turnaround time in responding to questions and request from FDA reviewers when the agency uses the system.

Speaking of the FDA, the game plan is slightly different. The system will be delivered to the FDA fully-validated and complete in content. However, the FDA, as previously stated, will be using Sun workstations as clients, thereby easing the installation procedure for Synteract. The plan calls for Synteract to load the necessary vendor software along with the application on the Sun server within the particular division that the NDA is being submitted. Accounts for FDA users are already set up on the server and Synteract will place application start up programs in the personal (home) directories of these accounts. These start-up programs will be different than the programs for the sponsor's clients again due to the different client machines.

Note that this version of the CANDA application ran in an X-windows environment under Solaris 2.0. It should also be understood that Synteract maintains replica systems for both the sponsor and FDA at its offices to provide on-going support and maintenance. For the FDA, 3-5 days for installation, and 1-2 days of training are planned. Paperwork must be filed with the Information Systems department of the FDA specifying exactly what will be delivered, when, to what division, and approximately how long the system will be in use by that division. The IS department can actually perform or assist in performing the load of the software; either way, their involvement in the process is important.

Validation Phase

Every system had to be run through a validation procedure, which also included a quality control check of system contents (i.e., data, documents, images). Even with the various types of systems, only one procedure was necessary since the functionality and interface of the CANDA remain the same whether the user accessed the application on a PC or Sun workstation client.

However, the procedure itself would be executed a number of times. Two runs are performed at Synteract: once on the Sun workstation side, another on the eXceed (PC) side. When the complete system has been loaded at the sponsor, a validate run is performed on the PC side. Finally, upon installation at the FDA, another validation is performed for one Sun workstation client.

(Note: The validation procedure is written by an independent auditor.)

Evaluation

Overall, the project is continuing successfully at a smooth pace, despite tight timelines. The sponsor is excited about using the CANDA application in-house to query, graph, and report data, providing a level of technological benefit not present previously. The FDA division that will receive the CANDA has used the software before and already holds the application in high regard.

Concerning the methods in which the client/server technology was implemented at the sponsor site, it is key to remember the timelines for this project (roughly 6-7 months to develop and validate a CANDA). Due to this timeframe, decisions had to be based on what could be reasonably achieved within deadlines. Use of the eXceed product achieved our objective of providing the application to multiple PC users at the sponsor offices.

However, Synteract does have a graphical user interface running under MS-Windows 3.11, with development starting shortly for Windows 95 and Windows NT. Along with UNIX, the flexibility to provide sponsors with multiple platforms should help tremendously in implementing various client/server solutions. SAS/AF® is still being used for the front-end coding of each version of the Synteract CANDA. With SAS/CONNECT®, SAS/ACCESS®, and an ODBC driver, SAS now provides the capability to
access many different formats of data from different operating platforms. Regardless, Syneract feels that pervasive use of SAS within the industry and the FDA make it a valid option in developing these types of solutions. More often than not, sponsors have their clinical data residing in SAS datasets, specifically to do statistical analysis. This fact, along with progress in SAS OOP technology and the aforementioned client/server access products, provides Syneract with the rationale for maintaining its CANDA software within SAS.

Of course, Syneract plans to follow the on-going development of FDA guidelines for electronic submissions over the next couple of years. Still, it is assumed that the SAS® System will play a large part in any standards that the agency may establish.

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