



SAS® Drug Development

*A solution for addressing 21 CFR
Part 11 compliance*

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Introduction

The Code of Federal Regulations Title 21 Part 11 is a significant milestone in the U.S. FDA's unrelenting effort to find improved efficiencies in the new drug development, submission, review and approval process. *21 CFR Part 11 — Electronic Records; Electronic Signatures* has served to require that the drug sponsor perform validation of systems that support the maintenance and submission of electronic records.

While the heart of *21 CFR Part 11* is less than three pages long, the impact on regulated industries has been enormous. The SAS Drug Development solution has been designed to specifically address the issues associated with *21 CFR Part 11* and the FDA's *Guidance for Industry* documents. SAS Drug Development provides these capabilities while offering an enhanced operating environment for managing clinical data, programs, logs, documents and reports.

Careful consideration has been given to the intended performance with respect to data warehousing, analysis and reporting, electronic submissions and related e-Signature requirements. The development of SAS Drug Development adheres to the industry standards for both process and quality management. Application of both process and quality management has assured that the software meets the intended requirements of the system's *21 CFR Part 11* functionality.

21 CFR Part 11 is strongly, but not exclusively, driven by the requirements of the *Good Practices Regulations* of *Title 21* (Part 58-GLPs, Part 312-GCPs and Part 210-GMPs). For example, *Good Laboratory Practices* represent a very good one-off mapping to *21 CFR Part 11* regarding the requirements for signings, archiving and records retention. These specific regulatory requirements (as mandated per the Public Health Service Act and the Food Drug and Cosmetic Act) are known as the 'Predicate Rule'. The controls for system validation are accurately listed in *21 CFR Part 11.10* and *11.30* and the ability of SAS Drug Development to address and/or enable the required controls and procedures are the solutions discussed and reviewed in this paper.

As this paper will demonstrate, the implementation of SAS Drug Development helps ensure that electronic records are "trustworthy, reliable, and generally equivalent to paper records and handwritten signatures."

System Validation for 21 CFR Part 11 Compliance

21 CFR Part 11.10(a) states "validation of systems to ensure accuracy, reliability and consistent intended performance" and is core to the procedures and controls to maintain, sign and transmit/submit the electronic regulatory record. The new FDA draft guidance document on validation clarifies that once the end user's needs and intended uses of the system are established that "evidence that the computer system implements those needs correctly and that they are traceable to system design and specification" must be available.

Strongly concurrent with these elements is *21 CFR Part 11.10(i)* that requires persons have the correct credentials to develop and maintain a system.

System validation can be achieved by developing, maintaining and releasing computerized systems using state of the practice activities throughout the life cycle of the system by qualified personnel. Validation of SAS Drug Development is achieved by ensuring that the system is developed according to a predefined System Development Life Cycle (SDLC) in which tasks are defined, integrated and consistently performed to develop, maintain and release the system. These activities are executed by staff with the knowledge, skills and abilities to perform their jobs effectively. Supporting the SDLC, controls are in place to ensure the ongoing security and integrity of all systems. Following is a brief synopsis of the SDLC, qualified personnel and supporting system controls in place within the Pharmaceutical Software Development Group, a Department of SAS that demonstrates compliance with *21 CFR Parts 11.10(a)* and *(i)*.

System Development Life Cycle

Requirements Gathering and Analysis

The life cycle begins with the development of a concept document that establishes a clear vision of the system and its intended application. Further analysis including user profiling, task analysis and the development of use cases are performed to more fully understand the target users. Once the vision for the system has been clearly established, detailed specifications are developed and analyzed to lay the foundation for all development activities.

Planning

Planning is a critical component of the life cycle. It provides the underpinning for the project's activities and provides a mechanism to track progress and take corrective actions if necessary.

A quality plan ensures that the system meets all quality goals that are outlined by Quality Management, regulatory bodies and customer expectations. The quality plan identifies, at a minimum, project methodology, quality risks, quality deliverables, quality assurance audits, processes, SOPs and an archival plan.

A project plan is developed for performing the work and for managing the project. The project plan identifies, at minimum, tasks, schedule and assignments, tracking and oversight mechanisms, configuration management activities, training activities and a test plan/strategy.

Design and Verification

Design and verification form the coding framework. Decisions made during the design phase affect the success of the implementation, and even more importantly, the ease in which the system can be maintained. The department follows user-centered design methodologies to ensure that the system will indeed meet customer requirements and integrate within the users'

environment. This phase is complete when the design has been assessed with a series of formal technical reviews, design walkthroughs and usability testing.

Coding and Verification

Coding and verification are performed to develop and verify code to implement requirements and design. The development staff may choose a variety of development methodologies, including an iterative prototyping cycle. Offering a choice of development cycles is intended to provide flexibility to development groups while ensuring conformance to internal standards. During product development, the software development organization tests the code. Baseline, functional, integration and system testing are performed at various milestones.

Regression Testing and Sign-off

Once the code is frozen, regression testing is performed to ensure that no new errors have been introduced during the final stages of product development and testing. The scope of the regression testing is determined by the project team based on a risk assessment of the system. When the tests have been executed and all exceptions resolved, a final sign-off from the project team and Quality Management indicates final approval for release.

System Acquisition

When computerized systems or portions of computerized systems are acquired through either the purchase of Commercial Off-the-Shelf (COTS) software or through subcontracting for development services, the department gives up the development portion of the process. However, the department still bears the responsibility for ensuring that the design and development methodologies used in the construction of the system are appropriate and sufficient for the intended use of the system. Quality management performs assessments and audits to qualify suppliers' abilities to produce quality systems. Once a supplier is chosen, oversight of the supplier is provided throughout the entire contractual period. Upon completion of the acquired piece of the system, it is carefully evaluated for acceptance and sign-off.

Release

The release phase is where the system moves from Research and Development to production. Processes are in place such that the transition is performed in a well-controlled and validated manner. This phase may include manufacturing of media, configuration of the production environment, installation qualification/operational qualification, and so on. These activities vary and are determined in the planning stages of the project.

Maintenance, Support and Retirement

Once the computerized system is released, it falls under the control of an organizational Configuration Management Plan. This plan includes change control mechanisms to ensure ongoing quality and consistency.

Technical Support coordinates maintenance releases for production software. By working directly with customers, product managers, and software developers, Technical Support personnel prioritize known bugs, approve fixes, track problem resolution, and test the fixes to verify that the reported problems have been corrected and that new bugs have not been introduced.

After all of the groups that are involved in the maintenance cycle are satisfied with the fixes that have been provided, the fixes are distributed to our customers. Customers are notified about new maintenance releases by a variety of methods.

Qualified Personnel

Key to producing a validated SAS Drug Development system are qualified development and testing staff with both highly developed software engineering skills and significant subject-matter expertise in the area of biomedical informatics.

In order to maintain the high-level of knowledge, skills and abilities, a staff of full-time trainers is devoted to the training needs of Research and Development at SAS. Every effort is made to assist the technical staff in keeping their skills current. As new technology is introduced, appropriate training is also made available. Courses developed in-house and provided by outside vendors are made available to SAS technical staff.

System Controls

System controls ensure the ongoing integrity of the work products throughout their life cycle. System controls include facilities management, physical and logical security, and disaster recovery.

Facilities

The 200-acre SAS campus in Cary, North Carolina, is maintained by the Facilities Division. This division has approximately 200 employees in nine departments, including groups responsible for the design and construction of new buildings and the maintenance of existing buildings and grounds. All buildings are designed and built at or above current building code guidelines. Environmental systems are computerized to reduce energy costs, and all computer operations areas are climate controlled with fire suppression mechanisms to prevent loss of organizational assets.

Physical and Logical Security

The SAS Security Department keeps the campus secure by restricting access through gates and into buildings by means of badge readers. Computer network access is restricted by passwords and firewalls. Access to the computer rooms is limited to authorized personnel.

Policy requires employees to change passwords at regular intervals. Passwords must meet complexity standards. A checklist for processing exiting employees includes provisions for disabling usernames and passwords.

Disaster Recovery

Disaster recovery procedures are in place to protect against data loss. The recovery plan specifies prioritized steps to bring back services according to their business impact. This plan is reviewed and tested frequently and updated as needed. The plan includes restoring facilities (buildings, electricity) and support services (telephone service, computer infrastructure) in order to facilitate recovery of critical business functions.

Functionality Required for Compliance

SAS Drug Development has been designed and developed to specifically address the individual subsections of *21 CFR Part 11*. Each of these subsections is defined below, coupled with a targeted description regarding how they are addressed within the SAS Drug Development application. (Note: Subsections (a) and (i) are addressed elsewhere in this paper). Included with these definitions and descriptions is SAS' interpretation of the stated rules.

As is often the case, various interpretations of these rules are possible, and additional interpretations and comments can be found in *Section VII* of the final rule (http://www.fda.gov/ora/compliance_ref/part11/FRs/background/pt11finr.pdf).

11.10(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying.

SAS understands the intent of this item to be that any records used in this system must be accurate, complete, readable and in electronic form. In SAS Drug Development, the word *record* has several definitions. These definitions are shown below and are used throughout this document.

- A SAS Drug Development object (program, log file, image, document, etc.).
- An observation(s) written to an audit trail for an object.
- An observation(s) in the actual data that comprises a study, for example, a SAS file.

SAS Drug Development meets the requirements of the FDA for inspection, review and copying records to the extent that the definition of record equates to one of the definitions above. Objects are available in electronic and readable format through the execution of the software. Reports and data transformations produce the source code, log and listing, which are stored in the platform and available for viewing and/or printing. Observations in an audit trail are available in electronic and readable format through the execution of the software. Observations in the data that comprise a SAS Drug Development study are also available in electronic and readable format for printing through the execution of the software.

SAS files can be accessed within the system and printed using procedures available within the SAS software. Also, SAS files can be extracted from SAS Drug Development using validated tools and then accessed from the user's desktop. The data browser within SAS Drug Development enables the complete and accurate copies of the data to be browsed, displayed, and queried in a readable and electronic form. These data displays can also be stored as SAS data files. The Documenter, which is a tool that builds a package of data files and corresponding metadata, can provide readable and printable records through a compressed (i.e. zipped) file containing PDF and SAS transport files. The audit trail keeps a readable and printable history of all modifications made to an object including creation, changes, deletion, and electronic signatures.

11.10(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

SAS understands this item to mean that all records used in the system must be retained in a manner that allows for accurate and ready retrieval. In all cases, specific features of SAS Drug Development will meet the "predicate rule" controls for retention of investigational records in *21 CFR Part 11*.

The definition of records, as provided in item b also applies to this item. SAS Drug Development objects and their associated information can be retrieved through execution of the software. This includes queries, reports, and report outputs. An operator can save outputs from an application to a variety of locations, and the ability to retrieve the output is dependent on where the output was saved and the mechanisms in place to retrieve them (e.g., a HTML page or a SAS file). Also, an operator can ensure the reproducibility of the output by using the Archive function within the system. The operating system will maintain compliance with the applicable "predicate rules" of *21 CFR Part 11* for record retention as long as the system is maintained. SAS Drug Development will not automatically delete or remove objects.

The Archival function in SAS Drug Development puts all records (objects) into an XML structure and stores and locates the archive file in the system. Deleting an archived file can only be done outside of the system and would be a system (not SAS Drug Development) administrator responsibility. Therefore, it is impossible for SAS Drug Development users or administrators to delete archived objects.

11.10(d) Limiting system access to authorized individuals

SAS understands this item to mean that access to the system, in this case a computerized system, must be limited to only authorized individuals.

SAS Drug Development limits user access at several levels to meet this FDA requirement. These are through the use of system, role based and object level security, respectively. A user must enter a user id and password to access SAS Drug Development. The system is configured so that only an Administrator can assign user ids and passwords to a user. In addition, users are required to change their password on initial entry into the system so even the administrator is not aware of their password. Once inside the operating system, users are assigned to user groups, which enable or restrict access to components of the software. Object level security is used to enable or restrict access to individual objects in the system. Finally the Web-based platform is also secured using a secure connection (HTTPS), firewall and 128-bit encryption.

11.10(e) Use of secure, computer-generated, time-stamped audit trails to independently record the data and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

SAS understands this item to mean that a secure, system-generated, time-stamped audit trail, recording when actions create, modify and delete objects, must be in place for all records used in the application of this system.

The definition of records, as described in item *21 CFR Part 11.10(b)*, also applies to this item.

SAS Drug Development records and signatures each contain a secure, computer generated, time-stamped audit trail for actions including, but not limited to create, modify and delete. Modification to previous recorded records will not be obscured by the change. Information from the audit trail is written to a read-only file stored with the object and cannot be deleted. As long as the system is maintained, it will retain investigational records and the supportive audit trail as required by the "Predicate rule" of *21 CFR Part 11*.

11.10(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

SAS understands this item to mean that effective user technology, processes and interfaces must be in place to reduce errors made by an operator to the extent that system errors can be minimized.

SAS Drug Development was designed with a technology/processes/interface that provides operational system checks for each feature or functionality. Each of these components provides error-checking to enforce sequencing of the task or function. Sequencing of steps and events is enforced operationally through strict requirements of navigation and the structural hierarchy of the platform. Each tool or application in the platform has enforced interfaces, validated fields, and error checking devices that when coupled with access and security continually enforce operational system checks.

11.10(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

SAS understands this item to mean that the system must provide for authority checks and electronic signatures to be in place for the use, access of input and output device, and ability to alter a record and perform operations at hand.

SAS Drug Development uses a combination of a user id and password to indicate an electronic signature. All objects require that an operator supply a valid user id and password to enter the system. The system will not allow any duplication of the operator's identification and password. Once in the system, the operator's actions are restricted through role and object based security. Security is inherited to all children of the object unless otherwise specified. A system administrator provides all permissions for the operator or user. For example, a user may be allowed to run a report, but cannot modify the source code for the report. Finally, when an operator executes an action on an object, the date, user name, type of change, meaning associated with signature, and electronic signature is recorded in an audit trail. The requirement for an electronic signature and the reason for change are assigned by the administrator as well.

Through the application of both role and object based security, the system can control an operator's specific use of the system features and access to specific input and output functionality and individual objects.

11.10(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

SAS understands that these checks are warranted where only certain devices have been selected as legitimate sources of data input or commands. The device checks would be used to determine if the data or command source was authorized.

SAS Drug Development uses technology other than devices to determine the legitimacy of data input or command. SAS Drug Development combines data source checks, change/signature, permission requirements and security to satisfy this part of the FDA requirements. Invalid and altered checks have been addressed in item *21 CFR Part 11.10(a)*.

11.10(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

It is the responsibility of the customer site, with assistance from SAS, to ensure that the operators using the system have the proper education and experience to perform their tasks, and further to have effective and enforceable policies and Standard Operating Procedures (SOP) in place to govern the operators and their tasks.

11.10(k) Use of appropriate controls over systems documentation including:

- **Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.**
- **Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.**

SAS understands this item to mean that there must be revision and change control in place for system documentation. In the context of SAS Drug Development, system documentation includes documents created for end users who will install, administer and maintain the system. This does not include end-user documentation that provides step-by-step instructions on how to use the software.

System documentation is created for each release of the software and at minimum, includes the following:

- Alert Notes.
- Installation Instructions.
- Release Notes.

Because these are created once per release, they are uniquely identifiable and connected to a specific release of the software. This documentation is published and maintained by SAS for SAS Drug Development.

Section 11.30 Controls for Open Systems — the system shall employ procedures and controls designed to ensure the authenticity, integrity and as appropriate the confidentiality of electronic records from the point of their creation to the point of their receipt. Additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances record authenticity, integrity and confidentiality.

SAS Drug Development provides the following technologies to support the required controls for an open system. These include HTTPS secure sockets, firewall protection, Java level 2 security, VeriSign Digital Certificate, pre-defined authority checks along with a UI design to limit information provided upon the initial log-in screen.

VeriSign Digital Certificates provide a mechanism to ensure user and site authentication. HTTPS secure sockets provide encryption and decryption services to ensure data integrity and confidentiality over the Internet. Firewall protection, Java level 2 security, and authority checks and user interface design provide further authenticity, integrity and confidentiality of the electronic record.

Conclusion

SAS Drug Development provides the means to assure that electronic records are "trustworthy, reliable, and generally equivalent to paper records and handwritten signatures". This capability is not simply an add-on or afterthought designed to satisfy a marketing claim, but has been designed into the product from its very beginning. The ability to address *21 CFR Part 11* begins long before the first line of code is written. In fact, it begins by first establishing a controlled and documented process for software development. As the product takes shape through requirements, planning, design, coding, testing, release, maintenance and, ultimately, retirement stages, capabilities that specifically address *21 CFR Part 11* issues are implemented. SAS Drug Development carefully balances *21 CFR Part 11* needs against usability and implementation issues until solutions that satisfy all user communities are completed.

In working with the clinical research industries through the years, SAS understands the key roles that it plays. SAS further recognizes the need to support the clinical research industries as technology, and the regulations that constrain that technology, continue to evolve. Additional regulations (for example, HIPAA) are certain to impact the healthcare and pharmaceutical industries in the near future. For now, however, the clinical research industries face immediate concern regarding *21 CFR Part 11*. In the case of SAS Drug Development, claims regarding *21 CFR Part 11* compliance are not an outcome of the product, but its foundation.

References

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