Leveraging 21 CFR Part 11 Compliance to Achieve Broader Product/Process Quality

Electronic business processes pervade the landscape of life sciences companies. Without them, the development of new medical devices, pharmaceutical products, nutritional supplements, and other life sciences products would consume more time and resources. Likewise, the absence of software systems to develop such products and devices could stall healthcare advances.

While such electronic tools provide unquestionable value, the risks posed by this pervasive automation cannot be denied. The Food and Drug Administration (FDA) has recognized this dilemma and developed regulations to "permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health."[1] 21CFR11, also referred to as Part 11, imposes mandatory requirements related to the use of electronic records and signatures. These requirements are part of a broader move toward implementing system-wide quality processes. Software solutions can help companies comply with Part 11 requirements as well as provide a solid foundation for building quality-centric processes.

Background

The FDA ensures public health and safety through a myriad of product quality regulations. These encompass wide-ranging initiatives, such as its initiative on Good Manufacturing Practices (GMPs) for the 21st century, as well as more narrow regulations that focus on specific aspects, such as 21 CFR Part 11 (21CFR11). While this white paper focuses on the requirements 21CFR11 imposes on life science companies, it does so through the lens of the broader intent behind this regulation: to ensure product/process quality in pharmaceuticals, medical devices, biotech, and other life sciences. To that end, the FDA pursues an approach that merges science-based risk management with an integrated quality systems approach. What this means for life science companies faced with 21CFR11 compliance is the opportunity to leverage some of the tools and processes needed for Part 11 compliance to implement end-to-end, quality-centric processes.

When first promulgated in 1997, 21CFR11 imposed stringent new requirements on companies using electronic records in their product development processes. As the FDA's official Guidance describes, "Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations."[2] The regulation covers electronic records and signatures for all FDA regulated products, focusing on data integrity and security while providing an opportunity for life sciences companies to more fully utilize electronic processes to streamline product development. Companies maintaining records as required to be maintained but not submitted to the agency may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that relevant requirements are satisfied.[3]

In 2003, the FDA issued its Guidance, a document that contains nonbinding recommendations as well as the Agency's thinking regarding the scope and application of Part 11. In this document, the Agency expressed its intention to interpret Part 11 narrowly, encompassing fewer records subject to Part 11 requirements:

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format…*
- Records that are required to be maintained , based on the predicate rules, that are maintained in electronic format *in addition to paper format,* and that *are relied on to perform regulated activities…*

1 Guidance for Industry Part 11, Electronic Records; Electronic Signatures–Scope and Application. U.S. Department of Health and Human Services, Food and Drug Administration, August 2003. page 1.

2 Id.

3 21 CFR §11.2 (a)

- Records submitted to FDA, under predicate rules… [parenthetical omitted] in electronic format…
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.

(Italics in original. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application)

The Agency also indicated it would exercise enforcement discretion with respect to Part 11 requirements for validation, audit trails, record retention and record copying, as well as all Part 11 requirements for legacy systems (systems operational prior to the effective date of the regulation).[4]

Despite this stated intention, Part 11 compliance is not optional for regulated companies. As the FDA notes:

> *We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:*
>
> - *limiting system access to authorized individuals*
> - *use of operational system checks*
> - *use of authority checks*
> - *use of device checks*
> - *determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks*
> - *establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures*
> - *appropriate controls over systems documentation*
> - *controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)*
> - *requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)*
>
> *We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules. (Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application)*

Automated compliance tools can supplement a well-defined process and help ensure compliance while minimizing the day-to-day impact on business activities. However, each independent compliance application a business deploys increases the risk of malfunction or data loss at integration points. 21 CFR Part 11 management strategies are most effective when the company deploys a comprehensive platform, with pre-built integration among components. A comprehensive means of process automation can log every employee action and comment, from product design to production, providing a compliant audit trail while increasing overall production efficiency and quality.

Process automation allows businesses to enforce their manufacturing and development processes, bringing individual and corporate accountability and issue traceability to their development lifecycle. This increases product quality, resulting in fewer product recalls, shortens time-to-market, maximizes ROI, and provides companies the means to reduce business risks associated with a problematic FDA audit. Automatic logging also provides objective data that companies can use to decide which products make the most efficient use of company time and priorities.

Principles of Product/Process Quality

While the specifics of 21 CFR Part 11 may be new to the age of electronic business, the principles that inform its mandates are familiar. Exclusive of any regulatory requirements, the principles of accountability, traceability, and quality establish the foundation of efficient, productive, and compliant business practices.

Canfield Scientific, Inc. produces medical imaging software and equipment. Its Clinical Trial division is regulated by 21 CFR Part 11, while its Retail Software division is not. Scott VanSickle, Canfield's Lead Software Architect, replaced the Retail Software division's custom Exchange-based process tool with Seapine's TestTrack Pro in 2002, and the company realized immediate productivity gains. "While we don't have a formally regulated process, TestTrack allows us to define our workflow easily and make sure issues are closed out. It keeps our information in one place, and helps ensure that tasks and change requests flow between testing and development without losing anything else. Between that and the linkage to Seapine's Surround SCM, it's easy to isolate and address issues while still allowing our developers to work on branched code. Our developer productivity has literally risen by several hundred percent since installing both products."

Formal regulations, such as Part 11, create significant business risks in the event of noncompliance, including potential consent decrees accompanied by financial penalties as well as exposure to criminal liability. Computer-related citations have increased annually since 2000. EduQuest, a regulatory consulting organization, reports that

4 Id., page 4.

more than $630 million in penalties have been imposed in consent decrees as well as more than 93 criminal plea agreements.

Accountability

At the heart of 21 CFR Part 11 lies the intent to prevent fraud by ensuring appropriate regulated entities and persons are operating in good faith. Like its counterparts in other business sectors (e.g., Sarbanes-Oxley, HIPAA, and PCI), which mandate a secure level of accountability in business processes, Part 11 requires a secure level of accountability in the use of electronic records and the software used in product development. At the same time, the regulation recognizes the business value of using electronic processes to expedite business. Electronic signatures provide efficiencies, reducing paper and the time necessary to collect and store documents that require sign off from multiple parties. 21CFR11 accepts electronic signatures bearing "the printed name of the signer" and "the date and time when the signature was executed" as a secure, binding replacement for paper signatures, provided those signatures are based on at least two factors, such as a username or unique ID and a password. The regulation also requires that businesses take precautions to ensure electronic signatures and their timestamps are unalterable.

Traceability

The FDA has chosen to enforce 21 CFR Part 11's audit trail requirements with discretion, but regulated businesses must still maintain compliance. For instance, in a 2002 warning letter the FDA sent to an institution, the agency noted "our Investigator noted that the laboratory is using an electronic record system for processing and storage of data…that is not set up to control the security and data integrity in that the system is not password controlled, there is no systematic back-up provision, and there is no audit trail of the system capabilities. The system does not appear to be designed and controlled in compliance with the requirements of 21 CFR, Part 11, Electronic Records."[5] Transparent business processes that allow visibility into their employees' actions will allow businesses to produce the "secure, computer-generated, time-stamped audit trails"[6] Part 11 mandates. The detailed information will also allow businesses to increase efficiencies. The ongoing archive of development-related activity provided by a workflow-enabled software tool allows managers to observe and fine-tune the real-world efficiency of their business processes, addressing complications in real-time, flagging potential expenses earlier, and ultimately, projecting more accurate budgets and schedules in the future.

Quality

The number of domestic medical device recalls has risen each year since 2003, hitting an all-time high in 2005.[7] Each recall costs companies millions of dollars or more and risks users' health, loyalty and business. By enforcing, logging, and automating development and manufacturing processes, companies can improve efficiencies, identify potential weaknesses, and produce higher quality products more likely to meet expectations. In addition to providing an archive of best practices to help businesses react when defects occur, proactive process management increases the likelihood that companies can identify issues before production, reducing exposure to product recalls and public embarrassment.

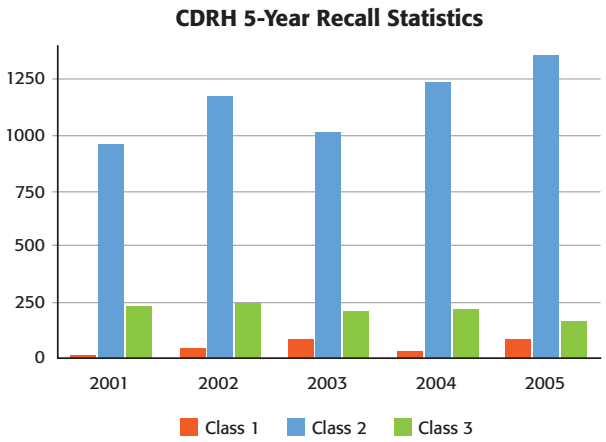

Figure 1: *According to the FDA's Center for Devices and Radiological Health (CDRH), the number of device recalls has risen each year since 2003, hitting an all-time high in 2005.*

21 CFR Part 11 mandates the "use of operational system checks to enforce permitted sequencing of steps and events, as appropriate."[8] To ensure quality and efficiency and meet 21CFR11 requirements, businesses should create and enforce specific, sequenced processes for all routine business activities.

Tools to Assist in Achieving 21CFR11 Compliance and Product/Process Quality

By itself, software cannot create 21 CFR Part 11 compliance, but for businesses following a GMP-compliant process, software solutions can provide essential validation, workflow, and archiving services.

Fundamentally, 21 CFR Part 11 is about control. To comply, businesses must control access, verify signatures with multi-factor authentication, and log user actions in a detailed, secure, unalterable archive. These levels of security and process integration suggest a single, comprehensive solution capable of seamless handoffs, rather than a "best-of-breed" collection of custom-integrated point solutions. The ideal software solution

5 Warning Letter from the FDA Detroit District Office to Earlham College, July 29, 2002, cited in "A Unified Approach to Information Security Compliance," M. Peter Adler, EDUCAUSE Review, vol. 41, no. 5 (September/October 2006): 46–61. http://www.educause.edu/apps/er/erm06/erm0653.asp?bhcp=1, accessed June 15, 2007.

6 21 CFR §11.10 (e)

7 The Enforcement Story, Fiscal Year 2006, US Department of Health and Human Services, Food and Drug Administration

8 21 CFR §11.10 (f)

would provide a number of secure authentication mechanisms, flexible workflow creation and editing, role-based and user-based permissioning, and unalterable audit trails.

Nova Biomedical, which produces biosensor devices, uses Seapine Software's TestTrack Pro to log and track issues. According to Jason Walazek, SQA Testing Automation Manager, the key to process management is traceability. "We need to know everything about an issue—who started it, when it's going to be addressed, and the current status of any open or closed issue." Comprehensive participation is essential. "Everyone involved in development, testing and support is included in the system, letting us examine issues from introduction to resolution. This helps us evaluate the efficiency of the actions, and also becomes a critical part of generating documentation for FDA submission."

Secure Authentication Mechanisms

21 CFR Part 11 mandates that electronic signatures be "… based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified." A compliance solution should therefore offer a signing mechanism based on username / password or a similar authentication scheme. This scheme should be flexible enough to integrate with existing secure authentication mechanisms, such as LDAP directories active directory, et cetera.

Flexible Workflow Creation

To ensure that the system captures all relevant data, administrators must be able to create detailed, relevant functional workflows that capture specific development and business processes, as well as all related comments, suggestions, problems and resolutions. Creating the workflow should be simple enough for non-technical managers to do, ensuring that their processes can be reflected as accurately as possible.

Role-Based and User-Based Permissioning

Administrators should be able to limit actions and access by specific user (e.g., "John and Sally can read issues and create comments but cannot reassign them.") or by user group or role (e.g., "Managers and Directors can access all development records."). The system should also provide multiple forms of notification (e.g., messages on system login or an email to an outside account) to users or groups when issues of importance are created, modified, or resolved.

Unalterable Audit Trails

An ideal system should log all access and actions, attaching a username and a time and date stamp to each change. The system should encrypt its data store and use some form of redundancy checking to verify the encrypted data's integrity.

Seapine Software: Solutions for Life Sciences

Seapine solutions help life sciences firms track and manage regulatory compliance initiatives, clinical and lab studies, customer complaints, product development efforts, and other mission-critical activities. Seapine provides an integrated software development lifecycle/application lifecycle management (ALM) solution that can include source code control, issue/change management, test case management, and automated software testing. This complete ALM solution can provide superior risk management because each of the individual tools seamlessly integrate with one another. For example, a defect in TestTrack Pro can be linked with the source code file in Surround SCM that contains the defect. The defect can also be linked directly to the test case in Test Track TCM that found the defect. While each tool individually provides a way to decrease software development risk, linking two or more integrated tools makes it easy to automate and enforce workflow processes in order to establish clear accountability and ensure repeatability. Seapine's solutions fill the void between development and quality assurance, provide management insight into the development and testing processes, and help bring reliable products to market more quickly.

TestTrack Pro

Seapine's issue management solution, TestTrack Pro, provides the end-user interface to automated process flows, allowing users to read, modify, comment on, and reassign issues according to pre-set business rules and roles. TestTrack Pro logs every user action in an encrypted, checksum-verified database to ensure a compliant records management process.

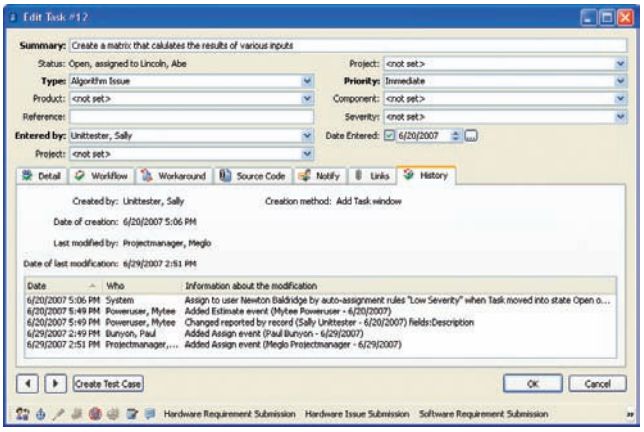

Figure 2: TestTrack Pro provides a detailed, user-level history of modifications to an incident.

TestTrack TCM

TestTrack TCM, Seapine's test case management solution, manages all facets of the testing process including test case creation, scheduling, execution, measurement, and reporting. TestTrack TCM can help demonstrate a repeatable, accurate testing process, provide detailed histories of test cases, data and results, and ensure that this information is secure and protected from unauthorized access.

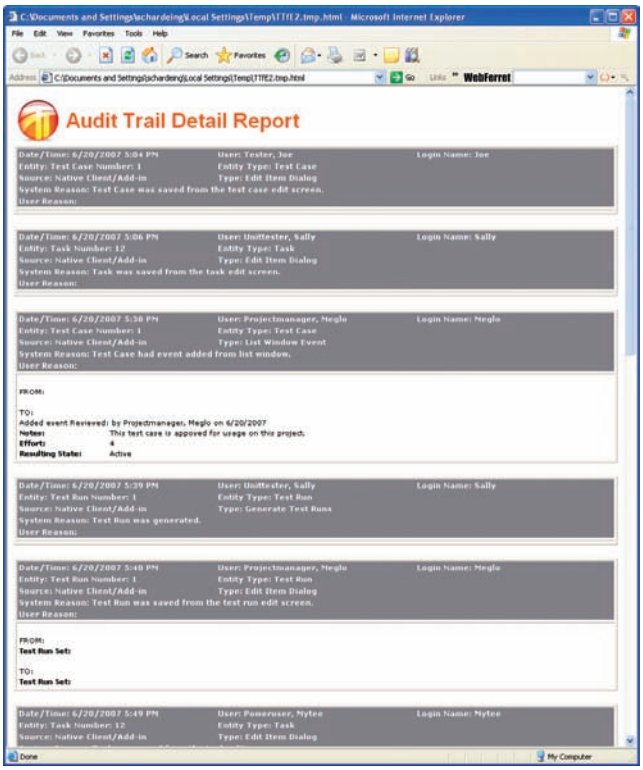

Figure 3: TestTrack TCM provides a detailed, 21CFR11-compliant audit trail of all activities, including date/time, user name, and any comments or notes.

Surround SCM

Seapine's comprehensive software configuration management tool, Surround SCM, gives teams complete control over source code and other digital assets. Surround SCM extends accountability and traceability from the development process into source code, logging every change to every version of software. Surround SCM controls access to code under development, completed code, reusable code stored for later use, documentation, reports, processes, and any other development artifacts.

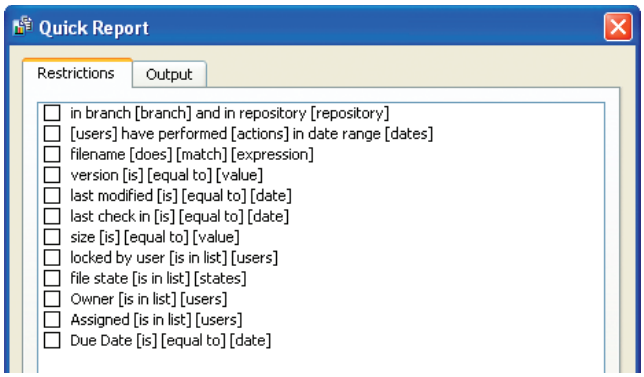

Figure 4: Surround SCM's Quick Reports make it easy for business users to locate and examine specifications, source code, and other process documents.

Conclusion

21CFR11 has evolved during the past decade, and will continue to do so in the future. Despite the FDA's current intention to interpret 21CFR11 narrowly, life sciences businesses should be prepared to comply with all of the regulation's requirements, including data security and audit trails. The future may bring additional regulations beyond the scope of 21CFR11, as well. Automating Good Manufacturing Process with a comprehensive, secure platform will position companies to meet future regulations while providing additional business efficiencies, allowing them to improve quality while reducing time-to-market and expense.

About Seapine

With over 8,000 customers worldwide, Seapine Software, Inc. is the leading provider of quality-centric application lifecycle management solutions. Headquartered in Mason, Ohio, with offices in Europe and Asia-Pacific, Seapine solutions help companies reliably and efficiently develop quality software applications. Seapine's products support best practices, integrate into all popular development environments, and run on Microsoft Windows®, Linux®, Sun Solaris®, and Apple Macintosh® platforms. Visit www.seapine.com for more information.

APPENDIX

21 CFR Part 11 Compliance Matrix

The following matrix provides an assessment of how TestTrack and Surround SCM facilitate compliance with 21 CFR Part 11. Where the regulation contains no notable action required on part of the software, those portions have been omitted.

Feature	Compliance Benefit
Native and LDAP-based username / password authentication	Fulfills requirement that electronic signatures be "trustworthy, reliable, and generally equivalent to…..handwritten signatures."[9]
Security policy management tools allow administrators to specify password standards, session timeouts, and the frequency with which users must re-enter their passwords during use.	Fulfills requirements regarding non-duplication and non-reuse of usernames and passwords[10], as well as requirements regarding mandatory password expiration.[11] Additionally, fulfills requirement that "at least one electronic signature component" should be used for each signing during "a single, continuous period of controlled system access,"[12] and that "each signing shall be executed using all of the electronic signature components" outside of that continuous period of controlled system access.[13]
Username / password authentication determines access level, and all records created by a user are permanently linked to the creator's unique username.	Fulfills requirement that companies maintain "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."[14]
Checksum verification of encrypted data	Fulfills requirement of "Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."[15]
Configurable as an open or closed system	The FDA defines different standards for "closed systems,"[16] in which system access "is controlled by persons who are responsible for the content of electronic records that are on the system," and "open systems,"[17] in which the persons responsible for the content of the electronic records so not control access to the system containing those records. TestTrack and Surround SCM can support either model.

9 21 CFR §11.1 (a
10 21 CFR §11.300 (a)
11 21 CFR §11.300 (b)
12 21 CFR §11.200 (1, i)
13 21 CFR §11.200 (1, ii)
14 21 CFR §11.10 (e)
15 21 CFR §11.10 (a)
16 21 CFR §11.10
17 21 CFR §11.30

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