



TIBCO Spotfire® and S+® Product Family

Compliance with 21 CFR Part 11, GxP and
Related Software Validation Issues



The Code of Federal Regulations Title 21 Part 11 is a significant regulatory requirement of the FDA's drug application process. The regulation requires drug sponsors to validate performance of systems that support the maintenance and submission of electronic records.

TIBCO Spotfire's product family including Spotfire Professional, Spotfire S+, Spotfire Statistics Services, Spotfire Clinical Graphics, Spotfire Miner, and pharmaceutical specific modules including S+SeqTrial and S+ArrayAnalyzer are widely used for data management, analysis and reporting (including tabular and graphical reporting). TIBCO Spotfire's software supports FDA-defined processes and quality guidelines, as well as pharmaceutical companies' drug development, submission, review and approval processes. TIBCO Spotfire has been audited by top-tier pharmaceutical companies regarding 21 CFR 11 and GxP compliance and has been used within the FDA.

This white paper describes 21 CFR 11 and GxP compliance and software validation issues as they relates to the TIBCO Spotfire product family.



INTRODUCTION

21 CFR Part 11 has a significant impact on regulated industries including the biopharmaceutical community. The TIBCO Spotfire product family works within the framework provided by 21 CFR Part 11 and the FDA's Guidance for Industry documents. S-PLUS 6.2 and all later versions provide supporting capabilities while offering an enhanced operating environment for managing clinical data, programs, logs, documents and reports. Spotfire Professional 3.3 implements tools to aid in validating Spotfire application installations.

TIBCO Spotfire development practices adhere to industry standards (including ISO 9001:2008) regarding software development and quality management. TIBCO Spotfire clearly defines and carefully implements processes to ensure that developed applications meet the intended 21 CFR Part 11 requirements for pharmaceutical analysis systems. This paper provides an overview of how the TIBCO Spotfire product family addresses requirements for 21 CFR Part 11 as driven by requirements identified in Good Practices Regulations of Title 21 (Part 58-GLPs, Part 312-GCPs and Part 210-GMPs).

TIBCO Spotfire has developed processes regarding approvals, archiving and records retention as described in Good Laboratory Practices that are similar to those listed in 21 CFR Part 11 requirements. This paper discusses how TIBCO Spotfire applications address and/or enable the required controls and procedures for system validation as outlined in 21 CFR Part 11.10 and 11.30 (These requirements as mandated per the Public Health Service Act and the Food Drug and Cosmetic Act are known as the "Predicate Rule".) The paper demonstrates that TIBCO Spotfire application implementations ensure that electronic records are "trustworthy, reliable, and generally equivalent to paper records and handwritten signatures."



System Validation for 21 CFR Part 11 Compliance

System validation in regulated environments is a significant challenge for any company. Pharmaceutical companies are required to adhere to 21 CFR Part 11.10(a) requiring “validation of systems to ensure accuracy, reliability and consistent intended performance”. Accurate, reliable and consistent performance is essential to meet FDA validation guidelines. For example, the guidelines require that end user’s needs and intended uses of the system are established and that evidence that the computer system implements those needs correctly are traceable to the system design and specification. Further, 21 CFR Part 11.10(i) requires persons developing and maintaining the software system to have correct credentials.

In accordance with these requirements, validation of TIBCO Spotfire products is achieved by ensuring that the systems are developed according to predefined processes and procedures in a controlled environment with thorough testing. Tasks are defined as part of the software development life cycle (SDLC) and are consistently performed to develop, release and maintain the software system. These tasks are executed by staff at TIBCO Spotfire with the knowledge and skills to perform their jobs effectively. Supporting the SDLC, controls are in place at TIBCO Spotfire to ensure the ongoing security and integrity of all systems. The next section of this whitepaper summarizes the TIBCO Spotfire SDLC and supporting system controls. These processes, controls and qualified personnel provide compliance with 21 CFR Parts 11.10(a) and (i).



Software Development Life Cycle

Requirements and Design

TIBCO Spotfire's software development life cycle begins with a specification for the product in the form of stakeholder requests and supporting information such as use cases, use scenarios, supplementary information, etc. The requirements are driven by customer feedback as well as identified industry needs. This information is reviewed, refined, and expanded from a marketing-level view to a more detailed engineering specification by a designated architect team. The review process may include mock-ups and prototypes.

The software development project plan is created from the approved product requirement specifications. The plan contains tactical information such as cost estimates, resource allocation, and schedule milestones.

Implementation

Implementation is partitioned primarily into development and testing phases. Unit and iterative testing are components of both. An "Alpha" version of the product may be released that involves a targeted group of designated internal and external users. A "Beta" version of the product may be released towards the end of the project when most features have been implemented and the product is considered stable. Both Alpha and Beta releases provide valuable feedback that can be used to enhance the products.

Software Validation & Regression Testing

A variety of validation & testing methodologies are applied at various project milestones, including hand testing, automated testing, user testing, and regression testing. These processes are iterative and defects are detected, tracked, fixed and retested. It is the responsibility of the Quality Control group to test regularly scheduled builds and feed their findings back to the engineers. Automated smoke tests are performed on daily builds. Test data are generated and results are evaluated to determine if the software meets acceptance criteria.

Certification For General Availability

Certification for release ensures that the product has met the requirements and that all appropriate documentation and testing are complete. The Project Manager reviews the output of the development and validation process to ensure that all requirements have been met, that all reviews have been conducted, and that all testing is complete. A General Availability (GA) signoff form indicating successful review is signed by a cross-functional group representing stakeholders. The source code is archived and securely stored off-site. Once the product has been approved for General Availability, the artifacts and documentation are made available on TIBCO's digital fulfillment site and current customers are automatically notified of the release by email.



Third Party Software

Third party software components included in TIBCO Spotfire applications are components not developed in-house. Supplier products and processes are reviewed and qualified, where necessary, prior to acceptance.

Maintenance, Support and Retirement

Released products fall under the terms set forth in the TIBCO Maintenance Program Guide. This document includes an update and maintenance policy, which provides the foundation for the Technical Support Policy. Mechanisms are in place to ensure ongoing quality and consistency in technical support services. The Technical Support team provides user support and contributes to defect prioritization in subsequent maintenance releases.

Qualified Personnel

Qualified development and testing personnel are critical to creating software products for use in validated environments. Our staff includes both highly developed software engineering skills and significant subject-matter expertise in biomedical informatics. A number of the Engineering team hold doctoral degrees and a majority of the remainder have attained masters degrees. Skills are maintained through training classes, in-depth customer interaction and cutting edge research. Courses developed in-house for customers are made available to TIBCO Spotfire staff.

Systems

Physical and Logical Security

TIBCO Spotfire maintains secure facilities by restricting access to employees and signed-in visitors. Passwords, associated policies and firewalls limit network computer access. Central systems are housed in secure server rooms and access is limited to authorized personnel. TIBCO Spotfire employs a processing checklist for exiting employees that includes disabling usernames and passwords.



Disaster Recovery

TIBCO Software Inc. maintains a Disaster Recovery and Business Continuity Plan to be followed in the event of a disaster. This plan outlines steps based on the size and nature of the disaster to recover business operations. TIBCO Software Inc has multiple offices on several continents. TIBCO Spotfire has a distributed engineering team with offices in Seattle, WA; Somerville, MA; and Gothenburg, Sweden. TIBCO Spotfire's IT infrastructure is located in Palo Alto, CA; Seattle, WA; and Gothenburg, Sweden.

Compliance Functionality

The TIBCO Spotfire product family has been designed and developed to integrate into 21 CFR Part 11 compliant computing systems. Each of these subsections is defined below, coupled with a targeted description regarding how they are addressed within the application. (Note: Subsections (a) and (i) are addressed elsewhere in this paper). Included with these definitions and descriptions is TIBCO Spotfire's 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.

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.

The intent of this item is understood to be that any records used in the system must be accurate, complete, readable and in electronic form. In the context of TIBCO Spotfire products, the word record can be interpreted in several ways, for example.

- A portion of a Spotfire S+ data object that represents one or more specific data elements;
- A Spotfire S+ program object (program, function, log file, image, document, etc.);
- A Spotfire Professional data table or visualization

TIBCO Spotfire products read and write data in a variety of industry-standard formats. In addition, other products offer the capability to read and write data stored in TIBCO Spotfire-defined formats. Thus, all data records can be made available in machine-readable form independent of the use of TIBCO Spotfire products. Further, software products from TIBCO Spotfire and other vendors can be configured to produce human-readable reports directly from these same data.



Spotfire S+ programs and library function definitions are developed in code that is both human and machine readable. In fact, Spotfire S+ “self-documents” its own function code. Spotfire S+ products also generate output and log files which are human readable and can easily be parsed by automated methods. Spotfire Professional has tools available for programmatically comparing application output to “gold standard” output to verify correctness.

By combining these product features with local policies and systems for record retention, the TIBCO Spotfire product family meets the FDA requirements for inspection, review and copying records; given the interpretation outlined above.

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

TIBCO Spotfire 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 the TIBCO Spotfire product family 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.

Objects generated by the TIBCO Spotfire product family can be retrieved through execution of the software or other commonly available tools. This includes data, program output, log files, and report outputs. An operator can save outputs from an application to a variety of locations, and the retrieval of output is dependent on where the output was saved and the mechanisms and permissions in place to retrieve them. The host 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. The TIBCO Spotfire product family will not automatically delete or remove objects.

11.10(d) Limiting system access to authorized individuals.

TIBCO Spotfire understands this item to mean that access to the system, in this case a computerized system, must be limited to only authorized individuals. The TIBCO Spotfire product family layers on top of the host environment and operating system mechanisms which provide the user access control required by this FDA requirement. Applications within the TIBCO Spotfire product family provide richer, and more robust user access control.



This requirement is typically accomplished through the use of system, role based and object level security. A user must enter a valid user id created by a system administrator in combination with a valid password known only to the user in order to access the computer system. Once connected to the system, users are assigned to user groups or roles that define which applications and directories are available. Object level security is used to enable or restrict access to individual objects in the system such as data files or program code.

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.

TIBCO Spotfire 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.

Spotfire S+ software supports the generation of audit trails by producing verbose log files and operating within the directory and object-based security models implemented for a particular environment. In addition, Spotfire S+ maintains audit and history files detailing information for particular user sessions. Spotfire S+ also includes a date() function that can timestamp any Spotfire S+ output.

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

TIBCO Spotfire 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.

The TIBCO Spotfire product family was designed with an architecture, technologies, and interfaces that provide operational system checks for software features and functionality. Sequencing of steps and events is enforced operationally through the Spotfire S+ object model and through user requirements regarding navigation and scripting workflow.

All components in the TIBCO Spotfire S+ product family include error-checking devices that continually enforce operational system checks. Note that these features need to be supported in a production environment by the use of either validated code libraries and/or independent review of source code and output results.



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.

TIBCO Spotfire 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 devices, and ability to alter a record and perform operations. TIBCO Spotfire products support the host environment in providing these capabilities [see previous discussion, especially 11.10(d)].

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.

TIBCO Spotfire 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. TIBCO Spotfire products support the host environment in providing these capabilities [see previous discussion, especially 11.10(d) and 11.10(f)].

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 to ensure that the operators using the system have the proper education and experience to perform their tasks. It is also the responsibility of the customer site to have effective policies, processes, and procedures governing the users and their tasks. TIBCO Spotfire can provide assistance with this through its professional services organization.

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.



TIBCO Spotfire understands this item to mean that there must be revision and change control in place for system documentation. All releases of products in the TIBCO Spotfire product family include documentation covering installation, administration, programming and user guides. Because TIBCO Spotfire documentation is created once per release, these documents are uniquely identifiable and connected to a specific release of the software. This documentation is published and maintained by TIBCO Spotfire in a revision control system. This documentation is provided to clients in electronic formats. The maintenance and distribution of this documentation at the client site is the responsibility of the client and should be handled in accordance with their training and other policies, processes, and procedures [see previous discussion, especially 11.10(b, d, f, g and j)].

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.

TIBCO Spotfire products support the host environment that provide these capabilities [see previous discussion, especially 11.10(d)]. It is the responsibility of the client to ensure that the appropriate safeguards are implemented for a particular system.



CONCLUSION

The TIBCO Spotfire product family provides systems and enables the processes and systems to ensure that electronic records related to TIBCO Spotfire software are trustworthy and reliable. This capability is integral to the software development life cycle of the Spotfire product family, which provides the underpinning to 21 CFR Part 11 compliance. As development and upgrades continue in the TIBCO Spotfire product family through ongoing requirements gathering and refinement, planning, design, implementation, testing, release, maintenance and, ultimately, retirement stages, capabilities that specifically address 21 CFR Part 11 issues are implemented.

The TIBCO Spotfire product family carefully balances 21 CFR Part 11 needs with usability and implementation issues so that TIBCO Spotfire solutions thoroughly satisfy the user communities. TIBCO Spotfire has been serving the clinical development industry for more than 16 years, and takes its role in this regulated industry very seriously. New regulations that constrain technologies used in this industry continue to evolve and features specifically addressing the clinical community will continue to be a part of new releases of the TIBCO Spotfire product family.

REFERENCES

FDA, 21 CFR Part 11, Electronic Records; Electronic Signatures; Final Rule. Federal

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FDA, General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 11, 2002.



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