

## **21 CFR PART 11: UNDERSTANDING COMPLIANCE**

Every pharmaceutical and medical company is affected by 21 CFR Part 11 and the incipient development of Canadian HPFB rules of a similar nature. Life Science Organizations face significant risks if found non-compliant. Enterprises under these regulations should look for ways to make their business processes more effective and efficient as they strive to achieve compliance.



## TABLE OF CONTENTS

<b>INTRODUCTION</b>	<b>4</b>
<b>UNDERSTANDING 21 CFR PART 11</b>	<b>5</b>
<b>THE IMPACT OF NON-COMPLIANCE</b>	<b>6</b>
<b>COMPLIANCE FUELS TIME-TO-MARKET</b>	<b>7</b>
<b>CONCLUSION</b>	<b>9</b>
<b>ABOUT RCM TECHNOLOGIES</b>	<b>10</b>

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## Introduction

Current reports of FDA investigations of bio-pharmaceutical and medical device companies for failure to comply with regulations are a concern of senior management. While the requirements for corporate compliance with regulatory guidelines are well known, organizations in the Life Sciences Industry continue to face mounting challenges based on the need for increased operational effectiveness and improved time-to-market. The challenge is to balance that need with good information technology management, while simultaneously maintaining regulatory compliance.

Life Science Organizations (LSO's) must set standards and effectively communicate and monitor compliance with health protection regulations, assign oversight responsibility, and adopt appropriate mechanisms to avoid noncompliance. Many organizations are now facing a challenge that matches or exceeds that of Y2K. The reason for this new challenge is Part 11 of Title 21 of the Code of Federal Regulations (21 CFR Part 11).

**21 CFR Part 11 establishes the criteria by which the U.S. Food and Drug Administration (FDA) considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.** This also applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in agency regulations as well as

*An **Electronic Record** is any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.*

*An **Electronic Signature** is a computer data compilation of any symbol or series of symbols that are executed, adapted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.*

electronic records submitted to the FDA under the requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. The Canadian Health Products & Food Protection inspectorate is considering similar regulations for Canadian LSO manufacturers.

Since its enactment in August 1997, 21 CFR Part 11 has had a substantial impact on the Life Sciences Industry. In contrast to other government regulations, 21 CFR Part 11 was developed initially as a response by the FDA to allow Life Science enterprises' use of electronic signatures in electronic batch records. 21 CFR Part 11 affects every bio-pharmaceutical or medical device organization governed by the FDA. There are potential risks and penalties if the systems are found to be non-compliant. While 21 CFR Part 11 does not mandate electronic record keeping, it provides the criteria that must be met if a Life Sciences Organization (LSO) utilizes electronic record keeping and electronic signatures.

According to Gartner Group, by 2007 the FDA will actively encourage that all New Drug Applications (NDA's) and equivalent license applications for medical devices and biologics be submitted to the agency in electronic form. Given this mandate, the need for compliance to 21 CFR Part 11 will only intensify. RCM Technologies recommends that LSO's take a proactive approach and develop systems and business processes that will enable the use of electronic submissions as well as achieve FDA compliance.

## Understanding 21 CFR Part 11

**21** CFR Part 11 has established standards for the use of electronic records and signatures as an equivalent or substitute for paper records and handwritten signatures. It is applicable to records identified in predicate rules, such as Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Manufacturing Practices (GMP). The purpose of the regulations is to ensure both the accuracy and trustworthiness of information and data as it is handled and traced throughout a LSO's multiple systems. In August 2002, the FDA launched a major agency re-examination of GMP's as part of a broader shift to risk-based regulation, an approach that aims to concentrate the FDA's scarce resources more on high-risk products and activities.

One of the underlying reasons behind 21 CFR Part 11 was to establish the reliability of data submitted to the agency for drug or device approval process. LSO's can realize many benefits by complying with the ruling but, to truly succeed, companies must incorporate the elements of 21CFR Part 11 into their overall business policies and strategies. Some of the key issues surrounding compliance include where to apply electronic signatures, audit trails, signature and record linking.



While 21 CFR Part 11 does not yet *require* the use of electronic records or signatures (paper is an alternative, albeit not a practical one), records and associated signatures submitted to the FDA in electronic form must comply with the regulation's criteria. Compounding the issue of compliance is the fact that the ruling applies to all electronic records created after August 1997, as well as the *systems* that support those records. In practical terms, this means that 21 CFR Part 11 does not "grandfather" any systems or processes.

This is not simply a technology issue – 21 CFR Part 11 applies to all areas regulated by the FDA, as well as all records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any record requirements set forth by the FDA. In other words, *nearly every system or process in a regulated area of a LSO will be affected by this ruling.*

21 CFR Part 11 sets out the procedural and system requirements for controlling and auditing electronic records and signatures. These controls include User Authentication, System Access Controls, Security, Audit Trails, Records Retention, End User Training, and Systems Validation. To make matters more challenging, other government agencies, such as the Securities and Exchange Commission, are issuing similar regulations in their jurisdictions that may necessitate similar controls for records *not* covered by 21 CFR Part 11. This suggests that 21 CFR Part 11 may become a *de facto* standard for electronic records management and control, and raises the implications of non-compliance to a whole new level of importance for LSO's.

## The Impact of Non-Compliance

**N**on-complying LSO's are subject to any number of actions by the FDA: they may receive a Form 483, a Warning Letter, or a more serious reprimand, such as a Consent Decree, that may result in significant delays to regulatory approval, time-to-market, product recalls, or facility closures. Continued non-compliance subjects LSO's to possible criminal and civil actions under various Federal and State statutes.

The impact of the regulations and potential FDA actions extends beyond the United States. A non-US LSO marketing or selling products in the United States is subject to 21 CFR Part 11 regulations *in their entirety, regardless of location*.

*An **FD-483** is An Inspectional Observations form issued to the inspected firm's management. It is typically issued for adverse findings after an FDA inspection. If an FDA inspection yields any Good Manufacturing Practices (GMP) compliance concerns or faults during an inspection, the FDA is required to immediately complete an FD 483.*

*The purpose of a **Warning Letter** is to notify a LSO that it is in violation of the law and that the FDA is ready to take regulatory action if voluntary corrections are not implemented. For computer validation, Warning Letters are usually issued as a result of a field investigator's FD-483 observation that a computer system used to ensure the quality of a product is found to be non-compliant.*

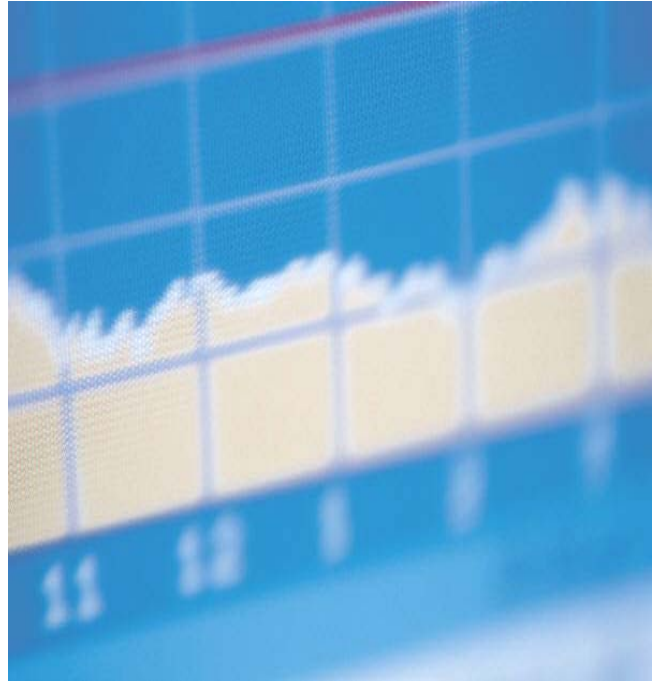
*A **Consent Decree** is a permanent injunction issued by the FDA to companies in violation of current Good Manufacturing Practice regulations ("cGMP"). Violations of cGMP regulations cover facilities, manufacturing, quality assurance, equipment, laboratories, and packaging and labeling.*

Because the FDA is committed to the enforcement of laws designed to protect patients and consumers, an LSO's *continued failure* to comply with cGMP regulations will ultimately result in the issuance of a Consent Decree that will strictly prohibit a company from manufacturing or distributing any products associated with the non-compliant system(s) or process(es). In addition, companies may be required to pay *tens of thousands of dollars per manufacturing process per day* for failure to adhere to corrective actions required by the FDA, as well as *millions of dollars in fines* after a Consent Decree has been entered by the court.

Non-compliance in some systems or applications is more likely to attract the FDA's attention than others. The FDA's focus depends on how data is used, the LSO's history with the FDA, and enforcement trends. Many LSO's understand that external, objective resources are required to better understand the implications of various applications or processes that touch clinical data throughout the value chain. Compliance should be approached not only as a series of projects to address regulatory risks, but as a business transformation initiative intended to deliver real business benefits and improved process efficiencies.

## Compliance Fuels Time-to-Market

**A** medical product marketed in the United States must go through a lengthy development and approval process. For example, the entire process for a new pharmaceutical typically takes 10 years and costs approximately \$200 to 250 million. The FDA approval process can take from six months to 10 years *after* an LSO files a license application; the average time now stands at about 30 months. At any time during a product's development lifecycle (or, for that matter, product sales), LSO's are subject to inspection by the FDA. Because an incidence—or series of incidents—of non-compliance entails a serious business risk, there is a long-term trend toward stronger focus by LSO's on the achievement and sustainability of regulatory compliance. As noted earlier, an LSO's inability to prove regulatory compliance can result in a myriad of costly penalties imposed by the FDA.



In terms of CFR 21 Part 11 compliance, RCM Technologies (RCM) recognizes that many of its LSO clients share common business challenges. Since 1991, RCM has validated hundreds of systems and performed numerous Pharmaceutical Assessments and Studies. Our extensive pharmaceutical experience spans all lines of business, including **Validation and Remediation, Network Management, Supply Chain Systems, Manufacturing Facilities, and Medical Device Engineering.**

For some LSO's, 21 CFR Part 11 compliance will not be mandatory *at this time* if there is no immediate intention to use electronic records or signatures. However, considering that data management and control account for about a third of the time required to prepare a license submission, the potential business benefit of migrating to electronic submissions is substantial. LSO's can capture and achieve these benefits through a robust Assessment and Validation process, which is summarized below.

### Step 1: Define the Opportunity

In the first step of the program, the LSO develops a framework for investigating compliance requirements. This is done to better understand high-level functional requirements for applications and systems, as well as estimate the total project effort. The result of these activities is a proposed structure and plan that describes both the time and cost ranges for subsequent phases. Equally important during this stage is the creation of a **framework to manage the business benefits** and build the business case for a LSO to invest in required changes to applications and systems.

**Step 2: Define the Quality and Compliance Strategy**

The purpose of Step 2 is to engage the LSO in understanding the business and functional requirements needed to achieve regulatory compliance. This is a massive task for most organizations. Many LSO's do not have the time or resources to devote to gathering information, analyzing its impact on existing applications and systems, and creating and documenting a plan that will deliver the changes and business benefits.

Preliminary estimates of systems design changes are also delivered during this stage. This step also documents the LSO's physical infrastructure in order to capture the interrelationships of all applications and systems subject to FDA inspection.

**Step 3: Solution Design and Testing**

This stage encompasses all activities surrounding resource acquisition, project office setup, application design, and systems validation and integration. The end results of this work are applications and systems that are suitable for the Quality Assurance activities that will be performed in the deployment phase.

This phase may be iterative, so each pass reduces defects identified in the solution deployment and unit testing phases. RCM recommends these iterative steps be executed in very rapid cycles to accelerate the design stage and compress the amount of time (and cost) needed to prepare system or application for acceptance.

**Step 4: Deployment**

With all applications or systems now ready, the organization is ready to deploy the **validated solution(s)** into the production environment. The team continues to test and validate the solution within the overall operations. Real time data is now processed in order to identify any remaining compliance issues related to signatures and reporting needs.

Business process changes are monitored and improvements are made to the systems and applications to ensure continued compliance with 21CFR Part 11 and to facilitate the new business processes defined in the business case. This initiates the tracking of delivery of the business benefits that were claimed during the first step in the program.

During this stage, the organization accepts delivery of documentation and Standard Operating Procedures (SOP's), which represent a significant component of 21CFR Part 11 compliance requirements. This part of the life cycle process will continue through user training and the completion of the program. The external advisors in many cases free internal staff for training and change management issues by doing this specific piece of work.

**Step 5: Ongoing Support**

Specific project knowledge must be transferred to the organization during and after a consulting engagement. As compliance and validation project proceeds from execution to turnover, the external consultants ensure that the unique capabilities, skills, and knowledge of developed are not lost to a client's organization.

RCM Technologies works diligently to manage this transition process by:

- Ensuring the process that helps keep SOP's, documentation, and other materials current is established within the LSO.
- Providing (or participating in the provision of) training for the LSO's personnel to ensure that the knowledge and experience gained by the validation and compliance project team is not lost.
- Establishing organizational 'ownership' of the processes as well as the documentation that have been created during the entire program.

As CFR 21 Part 11 evolves, it is reasonable to expect that a LSO will need to assess each system, process, or application. RCM helps LSO's design and audit change control procedures that span product development, quality assurance, and production. RCM can assist LSO's with establishing a program management office to ensure preparedness for future requirements.

## Conclusion

**W**hile the use of electronic records and signatures brings with it a range of compliance challenges, it will also help LSO's realize tremendous improvements in business process flows, increased data integrity, faster regulatory response, quicker time-to-market, and increased data security. In essence, LSOs must learn to:

- Understand the 21 CFR Part 11 regulations.
- Understand regulatory expectations for use and control of electronic records and signatures in computer systems and applications.
- Define 21 CFR Part 11 key issues within the organization.
- Apply 21 CFR Part 11 requirements to specific systems and applications.
- Learn and apply the Good Automated Manufacturing Practice (GAMP) approach to 21 CFR Part 11 compliance.

Life Science Organizations must decide how and when to fully comply with 21CFR Part 11. For some LSO's, compliance is viewed as simply the cost of doing business; for many others, compliance is viewed as an opportunity to significantly improve business processes, capture substantial monetary benefits, and avoid costly and prolonged audits and penalties. To ensure compliance and an improved competitive advantage, forward-thinking LSO's rely on external organizations for their objectivity and expertise in providing:

- A clear and practical interpretation of 21 CFR Part 11
- Guidance on how to implement a 21 CFR Part 11 Compliance Program
- Guidance on features required in systems or processes in order to implement 21 CFR Part 11 compliance.
- Validation and remediation of non-complying systems or processes.

## About RCM Technologies

**E**stablished in 1971, RCM Technologies Inc. is a leading provider of Information Technology and Professional Engineering consulting solutions in the Aerospace, Distribution, Engineering, Financial Services, Government, Healthcare, Insurance, Technology, Life Sciences, Manufacturing, Telecom, and Utilities markets.

RCM has been serving the Life Sciences industry for over 15 years. During this time, RCM has helped its clients transform their organizations from “legacy organizations” to information-driven, biomedical organizations. Our services and solutions embody the technical expertise and business acumen to support complex Life Sciences IT systems and business network infrastructures.

RCM has validated hundreds of systems and performed numerous system and application Assessments and Studies. Our extensive experience in Life Sciences spans all aspects of business information solutions, including:

- Validation & Remediation
- Network Management
- Supply Chain Management
- Laboratory Information Systems
- Manufacturing Facilities Management
- Medical Device Engineering

RCM possesses market and project experience that offers clients a differentiated awareness of the business challenges faced by many enterprises today. We focus on regulated industries, with a thriving business centered on Validation and Infrastructure development and support. Our highly integrated and disciplined approach to 21CFR Part 11 compliance assures LSO's of achieving compliance and real business benefits.

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