

**Achieving Life Sciences GxP and 21 CFR Part 11 Compliance with EMC
Centra CE Solutions**

Dr. Michael Breggar
Tom Beatty
Deloitte Consulting

Table of Contents

Current Life Sciences Regulatory Landscape	3
Deloitte Consulting Opinion on “Risk-Based” Policy Shift Update	3
21 CFR Part 11 Update.....	4
Methods for Achieving “Results”	5
Addressing Regulatory Compliance with EMC Centera Compliance Edition (CE) Solution	6
Deloitte Consulting Viewpoint on the EMC Centera CE Solution (Executive Summary)	7

Current Life Sciences Regulatory Landscape

Life Sciences companies are faced with sustaining operational and innovative success while adhering to the high standards of Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Manufacturing Practices (GMP) and 21CFR Part 11. Today, like never before, reaching these goals requires the melding of efficient, compliant processes with applied and proven technology.

One of the key challenges facing the life sciences industry is the need to meet regulatory data handling requirements in a reliable, scalable, and cost-effective manner. With the industry-wide shift to electronic record keeping, and a new push to fully digitize regulatory data files in anticipation of electronic submission, life sciences organizations are facing a staggering increase in sheer volume of data to be managed and safeguarded. Drug development and clinical trial data must be archived in accordance with very strict regulatory rules, and data is often required to be stored in unalterable form for the life of the product and beyond. This dramatic growth in the need for scalable fixed content storage (static data retained for future reference and use), is significant and will require significant investment by life sciences organizations over the next five years.

The FDA is keenly aware of the need for reliable fixed content storage for the accurate archival of the records they require. From its inception in 1997, 21 CFR Part 11 was, in part, written to address this archival need and provide directional guidance for life sciences and healthcare systems development. Recently, the FDA's stated shift to a "Risk Based" policy, and the related evolution of the Part 11 rule has helped further define what is expected of life sciences data archiving programs.

This paper will review the FDA's recent policy shifts, specifically in their change in orientation to a "Risk Based" approach to GMPs and the new guidance for industry related to 21 CFR Part 11. Additionally, this paper will highlight an enabling technology solution that facilitates life sciences companies' adherence to regulatory requirements and standards.

Deloitte Consulting Opinion on "Risk-Based" Policy Shift Update

On August 21, 2002, the FDA announced a major new initiative on the regulation of drug product quality in its release of *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*. The two-year program, which applies to human drugs, biologics and veterinary drugs, has several ambitious objectives, which include ensuring that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science, and to encourage new technological advances by the pharmaceutical industry. Second, the implementation of "risk-based" approaches, that focus both industry and agency attention on critical areas. One of the first milestones in the FDA's shift towards the "Risk-Based" orientation has been the rewriting of much of their previous guidance on 21 CFR Part 11.

21 CFR Part 11 Update

With the recent FDA release of its new guidelines on electronic records and signatures in February 2003 (21 CFR Part 11), the FDA was clearly responding to the multitude of questions, issues, and problems that the Rule raised since its release in 1997. The release of the FDA's updated Part 11 guidance should not be misinterpreted as a lifting of the rule. The release of this Guidance document provides much needed clarity around the FDA's expectations on issues of validation, audit trails, record retention, record copying, and legacy systems.

Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application, is specifically noted as a “draft guidance” document. This means it is not “officially binding” as regulation or policy. However, it does represent the current thinking of the Agency in these matters (Part 11) and can represent the “current” in “current Good Manufacturing Practices” (cGMPs). The larger issue gleaned from this document's release is a clear manifestation of the FDA's overall re-envisioning of the substantive set of regulations dealing with current Good Manufacturing Practices (cGMPs). The timing of this release coincides with work on the “risk-based” cGMP review approach.

While this document covers requirements and respective results the FDA expects to see - it does not cover methods or the management of the scope to reach these expected results. The document is explicit in noting that the guidance is relative to *scope* – what is and is not covered under the Rule – anything else (such as the requirements for open or closed systems) still hold as written in 21 CFR Part 11.

As Deloitte Consulting has always held, the Part 11 Rule is also applicable to those systems directly relevant to the predicate rule; i.e., if the Agency requires certain records (or data) collected or maintained *and* companies choose to keep these records electronically, the Rule applies. The FDA states that the following “types” of documents (and the systems producing these documents) are subject to the Part 11 Rule:

- Records that are required to be maintained by predicate rules, and those that are maintained in electronic format *in place of paper format*.
- Records that are required to be maintained by predicate rules, are maintained in electronic format *in addition to paper format*, and *are relied on to perform regulated activities...*
- Records submitted to FDA, under the predicate rules (even if such records are not specifically identified in Agency regulations); in electronic format (assuming the records have been identified in the docket as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used in generating a submission, is not a Part 11 record unless it is otherwise required to be maintained by a predicate rule and it is maintained in electronic format.

What is the Predicate Rule?

Pre-existing FDA regulations that define what records the FDA expects an organization to prepare, retain and submit. If these records are electronic, 21 CFR Part 11 regulations apply to them

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.

Methods for Achieving “Results”

The new guidance document goes into a discussion of FDA’s expectation in several areas it sees as key to Part 11 requirements:

- Validation
- Audit trails
- Legacy system
- Copies of records
- Record retention

Validation – the Agency restates here that along audit trails of critical data and security and access, validation is a key to Part 11 compliance. Basically, their point is if a system has been designated as requiring Part 11 compliance, it must be validated.

Audit Trails – One of the key cornerstones of Part 11 is the maintenance of traceable audit trails. As with validation, the Agency will use “discretion” when deciding whether to enforce the requirements on audit trails as noted in the Part 11 Rule (time stamps, computer generated, etc.)

Legacy Systems - the Guidance here is different than what was implied in the original Rule preamble regarding legacy systems. Legacy systems (in use prior to August 20, 1997) *will be “grandfathered”*. This change implies that the FDA will not be focusing Part 11 enforcement on data generated by legacy systems.

Copies of Records – The predicate rules denote what is relevant here ((e.g., §§ 211.180(c), (d) and 108.35(c) (3) (ii)). Inspectors want to be able to retrieve, cross-reference and review relevant documents. The commentary amplifies the Rule and preamble’s request for electronic records in both electronic and “human readable form”.

The Agency asks for “portability”...

- Producing copies of records held in common portable formats where records are kept in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (including PDF)

... and the ability to search and access information in the same manner as the users of a particular system - If you have the ability to search, sort, or trend Part 11 records, copies provided to the Agency should provide the same capability if it is technically feasible.

Record Retention – the Agency expects companies to administer retention policies in a “risk-based” manner. This infers companies document a records retention strategy which includes provisions for electronic as well as non-electronic documents. The issues

What is validation?

”To provide documented evidence that an item of equipment, process, system or method is in a state of control (i.e. that all assignable causes of variation have been eliminated) and is able to consistently deliver specified results.”

related to record retention and important for business reasons as well as regulatory requirements. Indeed, most information of this nature represents the intellectual assets of any particular company. The ability to store records for long periods of time, in some cases indefinitely, coupled with the ability to retrieve these records is business mission critical and should not be minimized. Most records must be kept at least for the life of the product in market.

Though the scope of the Part 11 rule has been clarified, and in certain instances narrowed by the February 2003 guidance, the need for audit trail integrity and security, and post-installation validation remains and will be strictly enforced. While creating a comprehensive plan for compliance with regulations such as Part 11 can be complex and often confusing, such a plan can provide real opportunities for life sciences companies to directly enhance profitability. Compliance with Part 11 can actually add great value by increasing the efficiency and speed of drug development, regulatory approval, and actual production and sale of product. Effective 21 CFR Part 11 compliance can be an opportunity for organizations to achieve future objectives and mandates, in a cost effective manner by using advanced IT-based solutions.

Addressing Regulatory Compliance with EMC Centera Compliance Edition (CE) Solution

As Life Science firms have invested in advanced information management, there has been an exponential growth in the number of records stored electronically. The current pace of this dramatic growth is overwhelming the capabilities of conventional and legacy technology. Despite changes in regulations data integrity, authenticity, availability and longevity are still at the heart of the FDA guidelines. Life Sciences firms are looking for a new means of harnessing the growth and management of records while maintaining the data integrity and availability core to Part 11 and GxP practices.

The imminence of true electronic submission of NDA's and ANDA's, coupled with the significant monetary incentive for simultaneous worldwide submission via the ICH common technical document (eCTD), creates a compelling business case for investment in large scale fixed content data storage repositories. In addition, the litigious nature of the life sciences industry and the need for low-level cost accounting echoes the need for such archives for legal and internal administration purposes.

Over the last 8-10 years this increased need for online storage strategies has been answered partially with various "home-grown" systems with a patchwork of storage solutions cobbled together with time-stamping middleware, and an ad-hoc security scheme which is often simply an extension of existing network policy. The FDA has been patient with the evolution of such systems, but the agency is clearly trending toward a higher level of enforcement around data products – specifically in the archival and audit trail security realm. With the advent of dedicated platforms, such as EMC's Centera Compliance Edition (CE) solution, the pressing industry need for purpose-built secure fixed content data management has at last been addressed in a single product.

In the Centera CE solution, EMC has incorporated many of the core data archival functionality demanded by global regulatory bodies. While it is impossible to describe *any* product as being “Part 11 Compliant” as shipped (because Part 11 compliance – under GMP rules, can only be achieved after the apparatus is *installed and validated*) Centera CE can be accurately described as “Part 11 Ready.”

EMC’s Centera Compliance Edition (CE) solution is a magnetic disk based storage solution specifically built for fixed content data management. Centera CE’s hardware platform is based on a “RAIN” (Redundant Array/Independent Node) hardware architecture that virtually eliminates hardware failure by removing any single point of failure. EMC’s proprietary CentraStar operating system is the software heart of the product, and introduces new capabilities which are vital to fixed content management, such as Content addressing, which generates a unique digital “fingerprint “ for each record delivering precise digital monitoring, control and audit trail functionality. In addition to Content Addressing, CentraStar offers complete control for document retention management, ensuring that records cannot be deleted prior to their predefined retention period. When these records do eventually expire and are deleted the Centera system will then dispose of the records in excess of federal standards and recapture the vacated capacity. Perhaps the most exciting feature of the Centera CE solution from a reliability standpoint is its self-healing functionality, which greatly enhances failure prevention. To address any security concerns the Centera CE solution offers access and platform security to prevent against potential fraud or malicious intent. The Centera CE solution has been clearly designed as a combination of fail-proof hardware and software for reliable long term fixed content storage and retrieval.

Deloitte Consulting Viewpoint on the EMC Centera CE Solution (Executive Summary)

EMC Corporation, in an effort to provide data archival products that consistently meet the specific needs of clients from varying industries, understands that training and certification of individuals in the FDA-regulated industries is itself a regulated process. Therefore FDA-regulated companies look for products and vendors that will ease the process of computer system validation and the ability to comply with Part 11 regulations.

EMC Corporation has engaged Deloitte Consulting to assess the Centera CE solution for Part 11-readiness and provide a go-forward action plan for remediation of any gaps.

Deloitte Consulting has closely examined the Centera CE solution, its specifications, and the development practice used to create and support it checking for conformance with 21 CFR Part 11 guidelines.

Deloitte Consulting reviewed the following major elements that are central to Part 11 compliance

- Validatability (i.e.: the ability to be validated once installed by the customer)
- Accessibility (access rights)
- User authentication
- A time-stamped audit trail
- Security and secure environment

- Policies and procedures
- Training
- Electronic signature capability

It is important to understand that the results of Deloitte Consulting’s work cannot certify a product as “21 CFR Part 11 compliant”. This can only be done once it is installed and validated at a User site. Rather, it is a statement that the system has been (or has not been) designed in a manner consistent with the Part 11 regulations. (I.E., “Part 11 – ready”.)

Deloitte Consulting Findings

<p>Access rights 21 CFR Part 11.3 (b)(4),(8); 21 CFR Part 11.10 (d), (g), (i)</p>	<p>The Centera CE solution requires “local” client administrators to define and set access rights, user identifications and password parameters. System access for development servers and application servers is strictly controlled through both logical and physical security procedures and methods. The administrator or designated Supervisor has read-only access to status reports. Only logged-in Users (see below) can do relevant data entry. Change control for all content and software is managed and documented through procedure.</p>	<p>The customer is responsible for defining access privileges, signing privileges and authorizations for Users of the system. Password control remains under the aegis of the client or client developed procedures.</p>
<p>User authentication 21 CFR Part 11.300 (b), (d)</p>	<p>The Centera CE solution has implemented system administrator level User Identifications and Passwords for authorizing application and/or server access.</p>	<p>The customer is responsible for implementing procedures and processes for physical and logical security for their access to Centera applications.</p>
<p>Audit trail 21 CFR 11.10 (e), (k [iii])</p>	<p>From a data tracking perspective, a secure computer-generated time-stamped audit trail is created.</p>	<p>The Centera CE solution uses a method of identification called “Content Addressing”, which generates a unique digital “fingerprint” for each record to maintain complete control over data changes and auditability. Coupled with built in integrity checking, we believe the audit trail functionality of Centera CE is secure and compliant. It is the customer’s responsibility to use encrypted passwords so that the audit trail is not accessible outside of the application.</p>
<p>Validation 21 CFR Part 11.10 (a)</p>	<p>Because of the comprehensive nature of audit trail documentation generation, it is believed that the Centera CE solution is a <i>validatable</i> system</p>	<p>The Centera CE solution must be validated in the user’s environment for fitness of use.</p>
<p>Security 21 CFR Part 11.300 (and others)</p>	<p>The Centera CE solution provides a method for controlling access rights and levels. System is built utilizing an architecture that makes unauthorized access very difficult</p>	<p>The customer is responsible for implementing procedures and processes for physical security, such as back- up of data, safe storage, and disaster recovery.</p>

	and controllable.	
<u>Policies and Procedures</u> <u>21 CFR Part 11.10, 21 CFR Part 11.30, 21 CFR Part 11.300 (c), (k [ii])</u>	EMC Corporation maintains a multitude of policies and procedures regarding the development, management and support of their products EMC Corporation can recommend to their clients relevant procedures and provides necessary training and user manuals for both systems administrators and users.	The customer is responsible for writing and implementing all standard operating procedures for the usage and management of any electronic learning management system. The Centera CE solution is equipped with record retention policy enforcement functionality.
<u>Training</u> <u>21 CFR Part 11 (i)</u>	EMC Corporation can provide training for all of its products developed and sold in full compliance with 21 CFR Part 211.25:	The customer is responsible for ensuring that all persons implementing, maintaining or using this technology have the appropriate training and that the requirements have been identified, implemented, and appropriately documented.

EMC's Centera CE solution has been evaluated by Deloitte Consulting in terms of the above criteria to determine whether the product has been designed in a manner consistent with 21CFR Part 11 requirements. We believe that the Centera CE solution has clearly been designed to be consistent with Part 11 requirements and after installation and validation at a User site, could be reasonably expected to achieve Part 11 compliance. In addition we believe that the Centera CE solution offers many advantages over existing magnetic and optical storage media solutions for purposes of compliant fixed content data management.