

Regulations and EDC: Assuring Compliance

Welcome to our third issue! *EDC Today* is an independent publication on current information and issues on Electronic Data Capture (EDC) strategies and technologies for the Biotechnology and Pharmaceutical (biopharma) industry. Each month we examine topic areas related to EDC theory, technology, practice, or implementation.

Our third issue strives to demystify the requirements of 21 CFR 11, clarify the practical and technical implications of the rule, and help companies lay the groundwork for achieving compliance.

Today, many biopharma companies are adopting EDC, a system of data collection and management that promises to accelerate the prolonged process of obtaining United States Food and Drug Administration (FDA)

marketing approval. As companies embrace EDC systems, they are faced with challenging compliance issues. Specifically, all electronic record-keeping systems must address FDA requirements of the paper-based process in the new electronic environment.

In response to requests from the biopharma industry, the FDA issued a regulation that provides criteria for the FDA's acceptance of electronic records. With this regulation, entitled Rule 21 CFR Part 11, biopharma companies can effectively adopt electronic record-keeping systems.¹

Currently, the use and submission of electronic records are voluntary. Despite this voluntary aspect of electronic records, biopharma companies are trying to comply with the rule as quickly as possible, for two distinct reasons.

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In the next issue of
EDC Today:

We explore
technologies used to
create EDC products

About EDC Management:

EDC Management was founded to assist biopharma companies plan, prepare for and implement Electronic Data Capture (EDC) strategies according to their data management goals and objectives. We do not sell or endorse any specific EDC software application or vendor.

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Available **EDC In Depth** Research Reports related to this issue:

“Understanding Regulations, Guidelines, and Predicate Rules”

Whether companies are equipped with cutting-edge technologies or are new to electronic record-keeping, 21 CFR 11-compliance should be a fundamental business objective. In keeping with this goal, we demystify FDA good practices, regulations, guidelines, and predicate rules.

“Getting Started with Compliance, Part I: Drafting Standard Operating Procedures”

Standard Operating Procedures (SOPs) are powerful tools for maintaining data quality across diverse clinical trials, investigator sites, and data management personnel. In this report, we explain SOPs — specifically, when they are required, recommended or not necessary — in regards to both 21 CFR 11 and electronic data capture (EDC).

“Getting Started with Compliance, Part II: Electronic Records and Signatures”

With the implementation of EDC systems, biopharma companies are faced with compliance issues in meeting the requirements of the paper-based process in an electronic system. This report details the circumstances under which electronic records, electronic signatures, and audit trails are required.

“Getting Started with Compliance, Part III: Validation and Change Control”

Federal citation 21 CFR 11 enables biopharma companies to use electronic records and electronic signatures, but requires comprehensive validation of all related computer systems. This report discusses approaches to achieving and maintaining system validation.

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First, companies want to maintain their competitive advantages by streamlining data management processes with electronic records. Second, companies believe that the FDA will migrate entirely to electronic record systems from the more labor-intensive and error-prone practice of paper record-keeping. The FDA has an internal mandate to be able to accept fully electronic filings by June 2003. While this does not require industry sponsors to submit electronic filings, it certainly foreshadows an evolving preference for electronic data over paper records.

Still, some biopharma companies are slow to embrace emerging technologies, in part due to uncertainty about how to achieve and maintain compliance. Whether a company is already equipped with the latest technologies, or is new to electronic record keeping, 21 CFR 11-compliance has become a fundamental business goal. As the FDA has begun enforcement activities around 21 CFR 11, all existing electronic record systems must come into compliance within a reasonable time frame.

Scope of 21 CFR 11

When 21 CFR 11 was signed into law in 1997, its scope was poorly understood. In essence, it was a response to advances in the tools and equipment being used in conducting clinical trials. The regulation's premise was to maintain proper identifiers for electronic data relevant to product safety, purity, and efficacy.

In theory, there is nothing new about 21 CFR 11; regulations found in 21 CFR 11 are only extensions to existing regulations. Part 11 essentially takes rules pertinent to paper documents, i.e., "predicate rules," and applies them to electronic records.

With 21 CFR 11, biopharma companies must take the existing predicate rules — Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP) — and apply them to electronic records. Just as the predicate rules established documentation requirements for paper-based record content, signing, and retention, 21 CFR 11 establishes the requirements for electronic record-keeping.

Though the spirit of 21 CFR 11 can easily get lost in the blur of technical terms and requirements, it is important to remember the two main goals of the regulation. First, the FDA wants to be able to verify data from the moment of collection through the final statistical analysis. This requires tracking who handled the data, when, and why. Second, the FDA wants to know that software and hardware systems supporting 21 CFR 11 are working correctly. This requires validation. Both of these goals are carried over from the world of paper-based data collection, management, and analysis.

Understanding the Regulation

The tracking of electronic records and signatures is a new concept that biopharma companies may find intimidating and overwhelming. One of the biggest challenges is striking a balance between satisfying minimum requirements and doing too much.

Though Rule 21 CFR 11 is well documented — the FDA gave an interpretation in their preamble to 130 industry comments — information technology (IT) professionals may not be clear about how to implement its requirements.

All biopharma companies employing any form of technology must assess their specific needs for 21 CFR 11-compliance. Because Part 11 has no grandfather clause, even legacy systems fall under its compliance requirements. Older systems, designed before current electronic record-keeping guidelines were drafted, are often more challenging to bring into compliance than new technology. For example, legacy systems were often designed to overwrite data, virtually eliminating the electronic trail. Further, their encryption protocols and user signature capabilities do not meet recent guidelines. Bringing older systems up to speed and integrating legacy systems with newer, compliant technologies are significant challenges for biopharma companies.

Some companies attempt to circumvent 21 CFR 11 by maintaining a paper system to duplicate electronic records. Firms choosing this redundant route — maintaining two record-keeping systems, manual and electronic — are adding unnecessary inefficiencies and time delays to the product development process. Worse, such organizations are not complying with federal regulation. The FDA specifically states that duplicate records should not be kept unless the law requires a paper record. Under 21 CFR 11, even if a paper copy is maintained, electronic records require electronic controls, such as identifiers, audit trails, and metadata. If those controls do not exist or have not been validated, the company is not in compliance.

Because achieving compliance requires a significant investment of time and money, biopharma companies must first understand the practical and technical implications of 21 CFR 11 before developing a plan to meet its requirements.

Electronic Records

Understanding the definition of electronic records is fundamental to understanding 21 CFR 11. According to the rule, an electronic record is "any information in digital form that has been created, modified, archived, or distributed by a computer." Electronic records can take the form of text, pictures, or sound. The FDA makes no distinction between an electronic document and an electronic record.²

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An easy way to clarify whether an electronic record falls under Part 11 is to evaluate its relevance as a printed document. If the printed record would fall under regulation, the electronic record will most likely need to be Part 11-compliant. In addition, any identification on the printed record, e.g., author name, time, and date of development or approval, must also be replicated and tracked in its electronic counterpart. Again, maintaining paper copies of those electronic records is not sufficient to achieve Part 11 compliance.

Each electronic record must be tied to an electronic identifier, such as an electronic signature, e.g., username and password, or biometric, e.g., retinal scan, iris scan, or thumb print. Also called metadata, these electronic identifiers must leave a trail that can be audited should a pharmaceutical product's data or process be called into question. Electronic identifiers are designed to function so that changes to records — including updates, deletions, and insertions — are clearly tracked by username and modification date.

To be considered compliant, audit trails must be generated electronically by the system itself. Though similar to the paper process, automated audit trails replace filing cabinets full of signed documents.

Validation

A key element of creating a compliant electronic record system is system validation. Validation, broadly speaking, is a method or process for testing, documenting, and enforcing the correct and reliable behavior of any system. System validation requires signed documentation created within an organizational context that enforces consistent operations through Standard Operating Procedures (SOPs), process guidelines, plans, procedures, and reports.

According to a 2000 survey published in *Data Basics*, biopharma companies identified several important reasons to pursue data quality assurance procedures.

Leading reasons to work toward high-quality data include:

- 1) To increase overall quality, including both final clinical and statistical conclusions
- 2) To ensure public safety
- 3) To ensure successful regulatory submissions
- 4) To maintain business integrity³

Validation, a critical step in protecting data quality, helps biopharma companies meet these goals. By improving data quality and productivity, validation reduces business risks. Additionally, by enabling systems to generate better data faster, with less reworking and re-testing, validation more than pays for itself over time.

“By improving data quality and productivity, validation reduces business risks.”

Without consistently executing good standard processes, all other efforts to maintain data integrity lose their power. Validation allows organizations to build quality into their systems while increasing the likelihood that their systems meet user expectations. Accordingly, validation activities should be chosen and designed to overlap with quality initiatives.

Very simply, validation ensures that programs are doing what they were designed to do. The validation process involves checking that operating systems and software packages are working correctly and producing accurate results. This extends from the most basic commands, e.g., "save" or "print," to the more advanced functions, e.g., calculations and reports.

Validation is necessary at both the system level and at the level of individual data sets. Traditionally, extensive effort was expended to manually check and re-check data sets through quality control (QC) procedures and quality assurance (QA) audits at every stage of the process. The paper audit trails were not linked to the data. For example, a Data Clarification Form (DCF) could indicate that data was changed from the Case Report Form (CRF). However, during the QC process, if the DCF form was missing, there would be no way to reconcile why the database values did not match the CRF. Manual processes involved error-prone manual operations. Automating these operations with automatic audit-trail functionality, automatic procedural enforcement, and electronic recording of signatures overcomes some of these issues.

Validating the electronic system provides confidence that the data sets created and transformed by these systems will pass validation testing without requiring remediation. Therefore, the data sets are available more quickly for analysis, monitoring, and submission. Further, if problems are discovered, the electronic audit records provide a trail of legal responsibility, and a method for determining and fixing root causes of data processing problems.

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Biopharma companies work primarily with two types of data systems: 1) commercially available data management products, and 2) systems developed in-house by the company's own IT staff. Both types of programs require validation. Any change to the original program — this can range from product upgrades to customization of commercially available programs — must be tested rigorously.

Motivating biopharma personnel to embrace validation is a difficult but fundamental step toward compliance, according to Steven Svindland and Paula Regan, Senior Consultants with Barnett International in Media, Pennsylvania. In their 2001 *Drug Information Journal* article, Svindland and Regan describe the challenge:

"One of the most important factors for a successful data system validation process is the need for users to understand why they are performing validation and how they need to perform the validation process effectively and efficiently. If users understand the process, the reason why they are testing the software, how to document issues, and what to do after testing the system, they can become more efficient users and improve the overall quality and timeliness of the validation process."⁴

In keeping with this goal, sponsor IT professionals and managers should be educated on validation guidelines pertinent to the sponsor's system. Given their role in system implementation and maintenance, it is critical that members of the IT staff be champions of the validation process.

Third-party IT professionals are also helpful in achieving and maintaining system validation; their objectivity protects validation activities from potential conflicts with internal production schedules or goals.

Once systems are validated, they must be used properly to produce quality data. Like pilots who meticulously walk through a pre-flight checklist no matter how many times they've flown, system users must follow a step-by-step procedure to ensure that they are using validated systems correctly. Such system-specific guides are called SOPs and all users should be directed to follow SOPs.

SOPs are an effective means of maintaining the consistency of data quality across diverse clinical trials, investigator sites, and data management

personnel. SOPs should be written for every step in the clinical data management process and should be updated continually to reflect current practices.

Daniel Y. Tong, PhD, of the Clinical Trials Centre at the University of Hong Kong in Hong Kong, SAR, explained the need for SOPs in his 2001 *Drug Information Journal* article: "With the lack of regulatory guidance on good clinical data management practice, SOPs ensure that a certain level of data quality is consistently attained and maintained."⁵

Ideally, biopharma companies should strive to achieve and maintain validation compliance as a normal course of business. This can only occur if validation is supported by the organization's culture, and if processes are clearly documented, understood, and used regularly throughout the organization.

Achieving Compliance

Like all laws, FDA regulations and guidelines are subject to interpretation. Though both requirements and guidelines make up the predicate rules referred to by 21 CFR 11, biopharma companies must follow only requirements, not guidelines. Guidelines are merely suggested ways to fulfill requirements. Achieving compliance requires interpretation of the regulations to address the specific systems and context in which the clinical research sponsor operates.

As a primary step toward achieving compliance, biopharma companies should draft a Master Plan that demonstrates a commitment to 21 CFR 11-compliance, and details the steps necessary to achieve it. Deciding whether to follow guidelines requires a careful risk analysis. For some biopharma companies, following guidelines may demand too drastic a change in established business processes. These biopharma businesses may be able to meet the requirements of 21 CFR 11 by alternate means, as long as the alternate means are well documented.

However, not following guidelines entails a certain degree of risk. The farther companies veer from FDA guidelines, the heftier the risk involved. The FDA will likely look favorably on biopharma companies that have a clearly defined approach to 21 CFR 11 compliance, especially those with specific goals structured around specific time frames.

Performing a comprehensive systems assessment, which routinely includes an inventory of all computer systems, is the first step in generating a Master Plan. On the basis of systems assessment findings, necessary actions toward compliance can be defined.

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Traditionally, comprehensive Master Plans include:

- List of computer systems in use
- Determination of whether the system needs to be in compliance
- Determination of the level of compliance needed
- Determination of risk if system is non-compliant
- Prioritization of systems to be corrected based on risk
- Statement of what the corrections will be
- Statement of when the corrections will be made

Regardless of the specific plans, the most important factor in establishing and sustaining compliance is a clear and consistent message from corporate leaders on the value of compliance. A timely Master Plan to be executed in accordance with new and/or updated SOPs is a good way to communicate this message.

Benefits of Compliance

While a significant investment of time and capital is required to establish 21 CFR 11-compliance, the benefits to the industry are immeasurable.

First and foremost, compliance ensures that critical equipment and systems are functioning at peak performance. This avoids any catastrophic problems, such as breaches in data integrity that can cause the FDA to reject a submissions application for a drug product.

Further, compliance protects system data from unauthorized users who may accidentally or maliciously seek to manipulate or destroy electronic records. Attempts at unauthorized modification of data are not only blocked by security protocols, but the electronic identifier is essentially a fingerprint of the individual who is attempting access. Part 11-compliance adds value by requiring security protocols to protect the integrity of data from unauthorized modifications that could sabotage test results or eliminate proof of change.

Finally, the audit trails and security protocols required by 21 CFR 11 serve as built-in QA tools. They not only plot workflow and manage accountability, but also pinpoint performance issues specific to individual users and minimize the potential for liability. With Part 11 regulations in place, each user

is identified, hierarchies for data approval or modification are established, accountability is managed, and paperwork, storage, and handling are reduced.

When companies achieve and maintain 21 CFR 11-compliance, they do much more than meet FDA regulations. Companies with compliant systems are able to generate better data faster, protect data integrity, and reduce costs associated with redundant functions and system snags. With these improvements, companies are better able to meet a fundamental goal: bringing products to market faster.

¹ *United States Food and Drug Administration. 21 CFR Part 11. 1997.*

² *Brandt Clarkson C. The Not-So-New Rule: Understanding 21 CFR 11. Contract Pharma. 2001;12.*

³ *Andrus J. Leading an organization toward quality. Data Basics. 2000;6(2):7-9.*

⁴ *Svindland S, Regan P. A User's Perspective on Data Systems Validation. Drug Information Journal. 2001;35:819-825.*

⁵ *Tong DY. Data Management and Quality Assurance. Drug Information Journal. 2001;35:839-844.*

Who's behind the research?

Our lead researcher, **Kirk Mousley, PhD** received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

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Robert Pearsall received his BS in Electrical Engineering from MIT and his MS in Nuclear Engineering/Biomedical Instrumentation from The Ohio State University. He is Senior Consultant and Vice President for Business Development at Mousley Consulting, Inc. He has been involved with a variety of clinical data system projects for biopharma, including data management systems, electronic data capture (EDC), electronic submissions, validation compliance, and knowledge management. He was team leader and design architect for pilot projects in FDA/CBER electronic submissions.



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