Implementing 21 CFR Part 11

Workflow Design and Electronic Document Management in Biopharmaceutical Production

21 CFR Part 11 Compliance Is an Opportunity for Productivity Enhancement

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How you implement 21 CFR Part 11 can help justify the costs and recognize the benefits of this new rule.

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Typically, when a new regulation reaches the pharmaceutical industry, manufacturers are reluctant to implement it because of the increased costs — even while seeing the corresponding need. FDA's rule on Electronic Signatures and Electronic Records, known as 21 CFR Part 11 or simply "Part 11," often provokes this reaction. Two camps are forming: One group eagerly seeks Part 11 compliance to increase its productivity. The other group feels burdened by the additional regulation, fearing it will increase overhead without producing benefit.

Millipore believes that the difference between interpreting Part 11 as cost or benefit determines the choice of implementation strategies. This article discusses some workflow considerations of the benefits of Part 11, such as electronic signatures and electronic record keeping and using batch reporting in pharmaceutical production.

Proactive Regulation

In its early years, FDA has been described as doing "regulation by tombstone." This meant the agency would typically act after disasters struck or people were harmed. Only then would FDA issue a regulation to prevent the identified cause of the problem from ever happening again. Milestone legislation on food processing and drug screening, such as the 1938 Food, Drug, and Cosmetic Act, was created in this way. This explains why many people look at 21 CFR Part 11 as yet another one of those reactive regulations. But it's not.

Part 11 is a proactive regulation that the agency enacted to try to help manufacturers use new state-of-the-art tools in their manufacturing processes. It grew from a movement within the pharmaceutical industry itself to realize the productivity gains that are possible with the automation and computerization of pharmaceutical production. The overall goal of this regulation is to speed and simplify the approval of new drugs while maintaining the public safety.

Too much paper. Information pathways within the pharmaceutical industry can be very complex. The reporting required by two existing rulings, 21 CFR Parts 210 and 211, requires detailed records of the drug production process. In applying for the approval of a new drug, a pharmaceutical company may submit as many as 500,000 pages of information to FDA for review. In a paper environment, the time required to produce copies of this mountain of documentation can be considerable. With the advent of automated processing and data acquisition systems, this information either had to be printed out or recorded manually and then verified by handwritten signatures. This represented a significant duplication of effort.

To attempt to address this issue, a group of manufacturers asked FDA in 1991 for direction in the management of paperless records. FDA ruled on the subject and published 21 CFR Part 11, which became effective 20 August 1997. Part 11 outlines the criteria under which the agency considers electronic records and electronic signatures to be equivalent to paper records and handwritten signatures.

The wide scope of the ruling. Part 11 applies to all electronic signatures and records that are submitted to FDA or in response to FDA requirements. The rule applies to all industry segments regulated by FDA and includes areas that work under the following standards: Good Laboratory Practices (GLP), Good Clinical Practices (GCP), and Good Manufacturing Practices (GMP). Part 11, therefore, is directly applicable to research and development, the production environment, and to the medical device industry.

Under Part 11, an approved electronic signature is a unique compilation of symbols that an individual executes or authorizes as the legally binding equivalent of his or her handwritten signature. Part 11 also governs several types of electronic records, including

operation and recipe files. For example, Part 11 prescribes and directs the protection of recipe files after storage by the original author.

Part 11 Compliance Is an Asset

When dealing with Part 11, it's easy to fall into the trap of thinking that it is primarily about technology. In fact, there is a significant technological component to Part 11 compliance that is both obvious and important, such as the requirement for reliable device control hardware and software and for high-quality engineering. But it is important for companies to realize that it's not just your equipment that needs to comply with Part 11. Your organization needs to comply as well.

The "Required Procedures" box lists the steps that must be developed and maintained to meet the requirements of Part 11. Vendors will offer you individual pieces of production equipment labeled as "Part 11 compliant." But does the equipment simply meet the minimal requirements without allowing you to reap the benefits of electronic data handling? Find out.

Demand service beyond compliance. Indeed, customers expect their equipment suppliers to assist their efforts to achieve Part 11 compliance for their entire organization. It's important for vendors to offer compliant equipment, but we would argue that the most critical thing many vendors offer today is their willingness and ability to understand the workflow in which their equipment will operate. Without that understanding they will not be able to effectively assist manufacturers in achieving compliance or in advancing productivity.

Some manufacturers still do not realize that being Part 11 compliant is a property of their entire organization, rather than a buy-in option on any particular piece of equipment. For most organizations, becoming Part 11 compliant will require nothing less than the reengineering of its workflow. (See "What is Workflow?" box.)

The important thing is to recognize that it is not actually a change. The effectiveness of paper-based systems is rooted not just in the technology employed, but in the workflows that have evolved in the context of paper-based systems. Take, for example, something as simple as the operator's signature on a batch record. So-called "wet signatures" have many security advantages: Their position on the page can help indicate the end of the batch data and thus be a safeguard against unauthorized changes or additions. The distinctive marks of pen on paper can help distinguish between original documents and photocopies. Handwriting helps identify the person who signed a document.

Signed documents also provide security

Required Procedures

When considering the integration of a system into the plant, the design of the system must be examined along with the operating procedures that are, or could be, put in place to ensure the following:

Authenticity, integrity, and confidentiality of records. The software system must be robust and designed to prevent corrupted data. The security methods for accessing the system must be foolproof. Procedures must cover who can access the system and who can view records generated by the system.

No repudiation by signer as genuine. The system must allow no possibility for users to change logins during critical processes without recording these activities. Procedures must be in place to make sure that user identification schemes cannot supply duplicate identities and that operators cannot share their critical user identifications with others.

Limiting system access to authorized individuals. Other than the basic security measures of requiring user identification before operation, this process is all procedural.

Use of authority checks to ensure that only authorized users can operate the system. Once again, other than basic security requiring adequate user identification, this security must be handled by procedures and SOPs.

Determination that persons who develop, maintain, or use systems are properly trained. This area should be covered by procedures. Most vendors provide some level of training on the system operation; however, the owner is ultimately responsible for determining what is adequate.

Written policies to hold people accountable. Such policies probably already exist in larger companies; all companies should designate the responsible individual in writing.

Adequate controls over equipment documentation. It is interesting to note that access to the operation and maintenance information for the system also must be limited to authorized individuals. In the case of online systems, an operator ID system can achieve this control. With paper versions of this information, the designation of the authorized person as well as the method of controlling access must be handled with procedures and SOPs.

Change control over system documentation. In this area, the vendor must have a method of notifying and updating the system owner of changes in the documentation package. As with any other critical piece of equipment documentation, the owner must control the documentation with an internal revision-control system and with access controls.

Verification of the individual before assigning electronic signatures. This solution can be as simple as a background check or as complicated as fingerprinting. However, the solution must be fully covered by owners' procedures.

Certification to the agency that electronic signatures are being used and where. This letter must be sent to FDA before the use of electronic signatures or electronic records. The regulation is very specific about the requirements governing this letter.

Provisions for the logging and managing of attempted logins. Such logins can reveal the attempted use of someone else's electronic signature. FDA recognizes that it is not always possible to make a system entirely secure. This requirement must be met by a combination of SOPs or procedures on the part of the end user, along with some capability in the software to detect and log attempted logins.

What is Workflow?

Workflow is a business process during which documents, information, or tasks are passed from one participant to another for action, according to a set of procedural rules.

In the context of pharmaceutical production, workflow includes all activities around the production, packaging, and quality control of a pharmaceutical product, and the requested authorizations and records that document the process.

An increasing number of pharmaceutical organizations use networked equipment and software tools to accelerate the exchange of documents, authorization, and information to unleash the productivity gains made possible by a complete reengineering of their workflow.

in a context of workflow. In this simplest case, a signature is verified by the fact that the person signing the document carries it by hand to the recipient. In other cases, a context of conversations and other signed communication helps establish the identity and intent of the signer. And the ways in which we mark our paper records with observations, explanations of observations, additional notes, and so on automatically brings all of this information into a particular sequence that reflects the timeline and rationale for the actions taken. To understand the workflow of a paper-based process all you need to do is follow the paper record as it is carried from one step to the next.

The electronic document path. This process is very different in the electronic domain: Messages travel independently of and much faster than a paper document and its originator. But this benefit comes at an expense: The connection between content and signature disappears, and the position of the signature no longer verifies content. This disjunction creates the need for electronic identification that can travel with the actual document and that is just as safe as sample signatures or identification papers.

But that's not how we usually communicate. We are much more casual, and that's reflected in the tools we use. In many popular formats, such as Microsoft Word, Excel, or plain-text, the content can be changed after the original file was created, and there is no record that the document has been modified. Many word processors do not have a document structure that allows users to freeze content, prevent changes or additions being made to a file after the original file is created, or even identify those changes as separate from the original text.

Numerous solutions are available today that address these issues. In all such solutions the connection between content and signature is built into the electronic document model. Although such concepts make sense as one tool among others within the Part 11 realm, many of these authorization concepts were heralded over-enthusiastically as self-contained, technical "solutions" to the perceived new "problems" of being compliant with 21 CFR Part 11. Often such solutions were advertised to address the needs of all those who prefer to hang on to and optimize their paper-based workflow rather than reengineer it.

Streamlining Authorization

Beyond quick-fixes (often introduced as an afterthought) for the paper-based process, there is a far more important aspect of an electronic workflow that must be considered. It has received much less attention, and yet we consider it crucial if organizations are to harvest the benefits of a fully electronic workflow. Any electronic authentication must be seamlessly integrated into the workflow. Only then will communication be easier than in the paper domain and bring productivity gains.

Hybrid document management systems. Why is this point so important? Consider for a moment the practical consequences of failing to integrate authorization into the process. Consider a manufacturer whose organizational infrastructures already use PCs and email to prepare and communicate batch records where there is no official mechanism for electronic identification and authorization. We can call such implementation a "hybrid" because it positions the process between the electronic and paper domains. The key problem with such hybrid implementations is that any electronic piece of information still requires a paper-based authorization. Hybrid processes include the cost of both electronic and paper-based document management systems.

Undoubtedly, hybrid implementations save some of the cost of paper trafficking during the development of documents, such as the presignature versions of a batch record or a spreadsheet containing process data for analysis. But they fail to eliminate the use of paper altogether, because for the authorization of the final version a paper copy of the document must circulate to capture and document the signatures of all contributors. This final authorization becomes the rate-limiting step of the process. Such hybrid systems incur a double cost of operating and maintaining two systems and deliver only the benefits of the lesser of the two.

What is the practical importance of that insight for pharmaceutical production environments? It is the recognition that pharmaceutical production has very little use for document development entailing successive versions. The task of batch reporting is to document the derivation of a product and the history of the production process.

For example, it is not unusual for production batches to remain in quarantine until results from the quality check have arrived and until the quality control group has approved the records. If, in this example, quality control is done in-house, document approval becomes the rate-limiting step. Accelerating this step can save a company thousands of dollars by allowing it to implement smarter inventory management as part of an optimized workflow around batch-release procedures.

Production environments using hybrid implementations limit the effective distribution speed of the production record to the speed of paper delivery. That is because each subsequent step can proceed only after the arrival of the authorized papers of the previous step. Thus, although there is some value in the use of a hybrid implementation in office settings, hybrid implementations are of limited use in pharmaceutical production.

Not surprisingly, for many companies the key to productivity gains from Part 11 implementation is a fully electronic workflow. Only an electronic process that integrates authorization will minimize the

bottleneck that exists in paper environments (Figure 1).

Manage Your Formats

Because production reports are routinely circulated internally, each pharmaceutical organization must choose a standard internal data format. In addition to being necessary internally, production reports regularly must be shared with external institutions. For this reason, pharmaceutical organizations producing a drug — and their respective regulatory bodies — must agree on data-exchange formats and on ways to verify each other's authorizations. Today, however, many control software products generate their reports and documents in proprietary formats. Others provide reports in commonly accessible but open formats (such as Word or Excel documents) that are unprotected against modification after the original creator stored them. Equipment using such control products must comply with Part 11 with respect to generating electronic records.

If such a system is considered by itself, the compliance claims of the instrument and its computers are all a customer needs to minimally meet Part 11 requirements. However, for effective and beneficial implementation of Part 11 compliance across a pharmaceutical organization, the process does not end with the instrument or computer; it begins there.

Technological advances. The technical challenges entailed in providing durable data formats and media over the retention periods of records have been discussed elsewhere (1–3). The ability to move files across networks with ever-increasing ease continually diminishes the importance of durable media. If a particular computer with important data on its hard disk nears retirement, just copy the files to the successor's hard disk. The advent of file servers and ubiquitous bandwidths, together with the falling prices of storage space, allows almost eternal life for electronic files. For these reasons, the best response to the traditional "media question" is instead to create network-based repositories. Recent guidance has been published to help the file migration process (4).

However, the issue of data formatting prevails, and no single valid answer satisfies all requirements. To illustrate this point, try

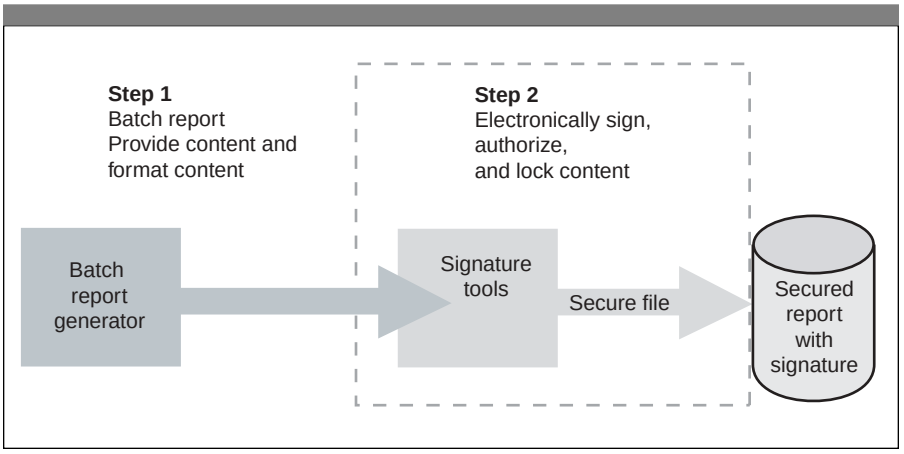

Figure 1. 21 CFR Part 11 compliant systems must provide tools to electronically lock and sign data.

to remember the names of some word processor software and computer hardware that were popular 10 years ago. Microsoft Word for DOS was then in wide use, but so were programs that have become rare, such as the Ventura Publisher, FrameMaker, Digital's All-in-One, and various text programs associated with extinct or marginalized hardware platforms.

IBM mainframes and others incorporated the now largely unused EBCDIC coding. Binary and even plain-text files stored on mainframes in such codes must be converted when moved to machines running under the ASCII code widely used today.

On the other hand, portable document format (PDF) software such as Adobe Acrobat was yet to be invented. The general use of HTML as a standard for text formatting across computer platforms was unheard of. Even the Internet was in its infancy and considered a curiosity without any real application.

Data format choices. Technological progress has simplified things: For records with substantial retention requirements, the choice of data format is simpler today than it was 10 years ago. The universe of computer hardware choices is considerably smaller, as is the range of available word processors. Meanwhile, an entire industry of conversion software has emerged, dedicated to the faithful conversion of text and formatting among diverse word processor platforms. Many organizations now choose Adobe Acrobat, which offers WYSIWYG ("What you see is what you get") capabilities across screen displays and printers.

Among other features, Adobe's PDF software allows document creators to enable a built-in tamper guard that indicates whether the content of a file was modified after the file was locked. Readers can add their annotations and comments, which remain distinct and identified by author. PDF also is the only document format mentioned by FDA as acceptable for document transmission (5). It is for these reasons that Millipore has included functionality to create and sign PDF files into its Common Control Platform v5 (CCPv5) software for the control of process systems.

Implementation Makes a Difference

The provision that PDF makes for document security goes far beyond these measures, including fully developed mechanisms for electronic authorization and signatures that meet requirements both of workflow in large organizations and of communication with their regulatory bodies. PDF is free of the limitation of localized authorization concepts, an implementation still widely used by many software packages. Localized authorization employs a proprietary concept that identifies individuals in databases that are only available on one computer. To verify a signer's identity on an electronic document, localized authorization forces users to return, sometimes physically, to the issuing computer to verify the authenticity of a signature or authorization.

PDF has implemented a provision for the remote verification of authorizations and signatures on computers different from the one issuing the authorization. The exchange of "key files" between individual computers

allows any recipient of a signed document to verify the signatures in the file against a reference. More sophisticated implementations may use so-called key servers. Such servers are corporate-wide resources on the network that transparently verify the authenticity of all documents as users handle them.

The Benefactors of Compliance

Who are the benefactors of 21 CFR Part 11? In the short term, the companies who are poised to benefit the most are the large, international, or progressive manufacturers, many of whom began to redesign their communication processes and workflows some time ago. Today they are eager to complete implementations and run fully compliant, paperless production facilities. Their reengineered workflows integrate electronic records and signatures, often through a central database, and with fully electronic trafficking of documents and authorization in a global context.

But what about those who have elected to "engineer away" and minimize all possible exposure to Part 11's requirements from their processes and equipment? Many of the managers in these companies are skeptical about the promises of productivity enhancement and prefer to "play it safe" — keeping it all in paper.

The stage seems set for a productivity gap that is opening up between companies that fully embrace 21 CFR Part 11 as an opportunity to improve their processes and those that react to it as if to protect themselves from a perceived threat.

The cost of compliance. Let's size the cost gap between those two camps. Novartis recently introduced a new, completely paperless production process that covers the entirety of a pill-production plant from "dock-to-stock" (6). For validation purposes, Novartis plans to keep paper records in parallel with electronic records, thereby increasing the production cost by an estimated 5% for a limited time. By project end they intend to completely eliminate the paper-based system and therefore realize an estimated plant-wide, permanent cost reduction of 10 to 15%.

If we use Novartis' estimates as a guideline, the hybrid process comes at an extra 5%, while a fully electronic implementation could save as much as 15%. This sizes the gap between the two concepts at about 23%, a potential for cost savings that no commercial organization can actually afford to ignore (7).

In the longer term, the entire industry will benefit from these few who boldly go forth to take advantage of Part 11. Vendors who serve these pioneers will develop robust solutions. Technology and competition will drive the cost of these solutions down. This is precisely where a supplier's in-depth knowledge of the workflow of its customers — built into production equipment — becomes part of the value proposition around a proposed sale.

Any electronic authentication must seamlessly integrate into the workflow.

A Fully-Integrated System

Part 11 compliance applies to and includes the whole manufacturing organization. This requires nothing less than the reengineering of the production workflow. In passing this regulation, FDA emphasizes the unique role of fully integrated, fully electronic document generation and transmission. Only the seamless management of documents within and among organizations, together with integrated authorization and authentication schemes, will provide the productivity gains that pharmaceutical organizations expect from Part 11.

In order to make future-proof investments in production equipment, pharmaceutical producers seek to acquire production units that have reporting functions capable of catering to the new needs discussed in this article. One way or another, production reports must easily become part of an organization-wide workflow that embraces and integrates electronic authorization by design, rather than as an afterthought.

In a production environment, hybrid implementations that combine electronic document management with paper-based authorization schemes are of little use. Such hybrid solutions add the cost of electronic document handling to that of managing paper-based documents. Hybrid implementations fail to speed up the process as a whole and do not deliver the benefits intended in 21 CFR Part 11. Those hybrid installations can increase manufacturing costs over the current paper systems and are in excess of 20% more expensive to run than a paperless system.

Suppliers of pharmaceutical and biopharmaceutical production equipment must produce systems that are not only world-class but also capable of integrating with their customers' workflows and information infrastructures. To maximize the productivity gains in pharmaceutical production environments, companies must choose suppliers that are intimate with the new communication paradigms in the coming age of electronic workflows. *BPI*

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(6) Information given is about the MES Project "Ulysses," which is currently implemented at the Novartis site in Suffern, NJ. The project was the focus of an all-day "open-house" for the ISPE New England Meeting, May 2002.

(7) 23% is the relative surcharge of 100%+5%=105% for the hybrid workflow over 100%-15%=85% for an implemented fully electronic workflow, using the fully electronic process as cost basis.