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Meeting the Mandate

Pharmaceutical companies team with vendors and gear up to comply with 21 CFR Part 11.

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In 1990, pharmaceutical companies re-requested that the FDA look into accepting electronic signatures. In 1997, the FDA issued a regulation permitting the agency to accept electronic records, electronic signatures, and handwritten signatures. And last year, the FDA met with pharmaceutical companies and began to enforce the rule.

Rule 21 CFR Part 11 makes electronic records equivalent to paper records and handwritten signatures. The rule applies to all industry segments regulated by the FDA that include good laboratory practice (GLP), good clinical practice (GCP), and current good manufacturing practice (cGMP).

The regulation establishes requirements to ensure that electronic records and signatures are trustworthy, reliable, and generally equivalent substitutes for paper records and traditional handwritten signatures. In addition to electronic records submitted to the FDA, the concept in-cludes output from instrumentation.

As defined by the FDA: "Electronic record means 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, according to the FDA, is a "computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature."

Certain signatures are required by predicate rules. If these signatures are executed electronically, then Part 11 compliance is required. Part 11 also covers non-required signatures if they are executed against required electronic records.

No legacy systems

Part 11 applies to all electronic record and signature systems, even those developed before the ruling was issued. The FDA states, "Certain older electronic systems may not have been in full compliance with Part 11 by Aug. 20, 1997, and modification to those so called 'legacy systems' may take more time. As explained in the preamble to the final rule, Part 11 does not grandfather legacy systems and FDA expects that firms using legacy systems will begin taking steps to achieve full compliance."

"The use of electronic records is expected to be more cost effective for the industry

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and the FDA,” says Ludwig Huber, worldwide product manager at Agilent Technologies, Waldbronn, Germany. “The approval process is expected to be shorter and enable quicker access to documentation.

“Even though an audit trail in itself is nothing new for FDA-regulated environments, it is the most frequently discussed requirement of Part 11,” says Huber. “There are two reasons for this: software unavailable to meet the new requirements to generate the audit trail by the computer independently from the operator, and uncertainty as to when the audit trail should start and what it should include.”

Starting points

What are pharmaceutical companies doing to comply with the regulation? Most are looking into all laboratory systems producing electronic output.

“The key to compliance with electronic signatures and records requirements is to start with an assessment plan,” says Vincent Walshe, validation engineer at Janssen Pharmaceuticals Ireland Ltd., Dublin. “System security is the key to compliance for all Part 11 systems.”

Peter Miller, corporate senior manager/QC/QA information at Knoll Pharmaceutical Co., Mount Olive, N.J., adds, “Security is essential to the reliability of the functions and data in any computerized system. Reputability of the functions and data in a system is the basis of the regulation for electronic records and signatures. Regulators recognize the significance of this principle and cite these issues in their critiques of pharmaceutical companies.”

“We have a corporate project team that has given a mandate to all sites worldwide to achieve compliance with 21 CFR Part 11,” says David Hardy, QA manager at AstraZeneca in Mississauga, Ontario. “Each site has a local ambassador responsible for training the staff and for ensuring that the site conducts gap analysis to identify the specific targets for compliance.

AstraZeneca’s program entails taking in-ventory of all of the systems that can be affected by the regulation, performing gap analysis, and developing an action report to close the gaps and meet the requirements. Then each local site monitors and documents progress and communicates with the corporate project team on a quarterly basis, according to Hardy. The Ontario site alone has 75 systems that create electronic data.

The first workshop for the local site ambassadors started in January 2000. Subsequent workshops were held in June 2000 and January 2001. The workshops provide forums for discussing issues, reporting success, and sharing information.

“Our site is now in the monitoring and tracking phase,” says Hardy. “We expect the process of compliance to take 2 or 3 years because of deficiencies in the software. We have to do all we can in the short term to show the FDA that we’re working on it.”

Partnering with vendors

According to Wayne Ziegler, senior manager/automation validation at CENTOCOR, Inc., Malvern, Pa., a Johnson & Johnson company, “The key for the pharmaceutical industry is working with technology suppliers to develop compliant computing solutions. Suppliers and integrators that are successfully working at this will have a huge advantage over their competition. The FDA holds pharmaceutical firms re-sponsible for compliance.”

Ziegler adds, “It may be in the interest of the firm to partner with a supplier to help ensure that the requirements for 21 CFR Part 11 are understood, properly interpreted, and correctly implemented. A vendor evaluation process and vendor audit are key components to selecting a qualified vendor.”

Automsoft International, Dublin, Ireland, which developed the real-time access plant information database (RAPID), has introduced a new package for pharmaceutical and FDA-regulated companies needing to comply with 21 CFR Part 11. Automsoft's RAPID-Pharma module offers out-of-the-box compliance with the specification, enabling companies to keep complete audit trails of their electronic records in a highly secure system.

RAPID-Pharma stores all process and batch records in its high-performance, secure database systems. The system maintains a complete audit trail of all human interactions with batch production records in a separate audit database. "The ability to run two independent databases is a big security advantage for this type of solution, as the audit database can be completely isolated from the process and batch database," says Ian Pepper, Automsoft's chief technology officer.

Pharmaceutical companies cite data integrity and security as key requirements. RAPID-Pharma's security features support the management of identification codes and passwords. Any attempt to access the system or edit data is recorded in the audit trail. RAPID-Pharma enforces the user ID codes and electronic signatures through appropriate controls and a complete user history. This is particularly important, because the audit trail could be the only evidence that an electronic record has been modified or deleted.

Data loss and archiving

A core aspect of 21 CFR Part 11 compliance concerns the issue of data loss. "The FDA stipulates that although data may be deleted from the database, you must still be able to recover from the electronic records. This presented us with an interesting technical challenge," says Pepper. "RAPID-Pharma already offers this functionality as standard within the product, demonstrated by its use of zero-loss data compression technology."

"Archiving of system data is one of the least discussed topics in the industry, but could prove to be a huge stumbling block," says Graham Rhys, computer validation project leader at Hoffmann-LaRoche, Nutley, N.J. "Due to large amounts of data stored on systems these days, it is not possible or cost effective to maintain all data in the live environment. When systems become too large, their response times slow, and administering the system becomes a nightmare. Archiving data to online storage is a typical solution because of complex business issues and regulations that govern data archiving."

The FDA's rule states that data created in an electronic format must remain in that format. Scientists can no longer print a report, jot down a note, paste in a graphic, and expect such a record to be acceptable to the FDA. NuGenesis Technologies Corp. (formerly Mantra Software), Westborough, Mass., has developed a scientific data management system that enables pharmaceutical companies to streamline data management and comply with the rule.

NuGenesis UNIFY software captures data as an enhanced Windows Metafile page description and stores it as a compressed, encrypted object within a central database. Users can view reports in the database using NuGenesis VISION software that also lets scientists select elements of the image for use in other applications. This combination provides flexibility in preparing reports and presentations, for sharing work across the company, and producing this data at a moment's notice.

NuGenesis' ARCHIVE software captures raw data at the time of creation and stores it to stable media. It is designed to meet GLP/GMP guidelines in high-throughput analytical laboratories. Data files are automatically archived to secure media and periodically removed from the acquisition computer's hard drive at user-specified time intervals.

"During the last 5 years, there has been a significant change in laboratory

automation and computing in the pharmaceutical analysis laboratory, from custom robotic solutions to off-the-shelf platforms from the major vendors,” says Bill Howard, analytical scientist/pharmaceutical developments at Glaxo Wellcome Inc., Research Triangle Park, N.C.

Howard adds, “While the technology vendors are providing more comprehensive solutions for sample preparation, much remains in the area of realizing a complete integrated package—from sample handling, to sample preparation, to sample measurements, to data handling. Some vendors have collaborated to produce an integrated solution of sample preparation, sample measurement, and data handling.”

Reaching compliance

These technology changes will enable pharmaceutical companies with worldwide R&D and QC laboratories to transfer analytical methods in a more straightforward and timely manner, according to Howard. He cites the need for vendors to provide solutions that comply with the latest regulatory trends, such as 21 CFR Part 11.

“As many companies began to employ document-management systems across the enterprise in the later 1990s, 21 CFR Part 11 became essential for all new development,” says Valarie King-Bailey, VP/marketing at Qumas, Cork, Ireland. “Most commercial off-the-shelf systems today focus on controlling the documents, lifecycle workflows, and integration of various electronic signature technologies. The impact of a sound, long-term electronic records strategy has been largely ignored.”

Qumas develops, markets, and supports a suite of integrated document and compliance management products designed to help FDA-regulated companies ensure compliance. Using advanced technology and regulatory domain expertise, the Qumas solution delivers FDA- and ISO-related best practices for the automation of controlled documentation and submissions. Qumas products are designed for rapid deployment and include validation, training, and technical support. Qumas serves a global customer base that includes pharmaceutical companies, such as Pfizer, Warner-Lambert, Novartis, Roche, C.R. Bard, Monsanto, Becton-Dickinson, and Pharmacia & Upjohn.

“Compliance with 21 CFR Part 11 is a timely and difficult goal for quality assurance and manufacturing staff in the US pharmaceutical industry,” says Betzy Castilla, VP/quality assurance at Block Drug Co. Inc., Jersey City, N.J. “The task was made even more difficult when the computer system studied had been designed before Part 11 considerations were known. The term usually used to describe such systems is legacy.

“We have developed and implemented an effective correction plan for legacy systems,” says Castilla. “Our approach is consistent with interpretation of current regulatory practice, which also recognizes the limitations of legacy systems and minimizes the risks incurred in their continued use.”

Applying gap analysis

Block Drug Co. uses gap analysis to identify the weaknesses and strengths of the system. The company prioritizes legacy systems based on GMP impact and non-compliance areas. It has developed a remedial action master plan, with strategy, plan, and timetable.

Rockwell Automation, Milwaukee, has addressed Part 11 rules through a gap analysis methodology, according to William Murrey, pharmaceutical industry marketing manager. Gap analysis, he says, should include the relationship between system and component contexts, the specific definition of Part 11 compliance for each product, the need for a Part 11 support infrastructure, the role of computer security, and the role of open technology.

Rockwell's RSView32 is an integrated, component-based software package that monitors and controls factory automation, which is a critical component of a 21 CFR Part 11-compliant system. "As the FDA steps up its enforcement of these regulations, we need to ensure that our customers are readily equipped to comply," says Joe Bartolomeo, marketing manager of Rockwell's HMI business unit.

Devising validation plans

Stephen Dobro, Zymark Corp., Hopkinton, Mass., manager/product testing and validation, developed an exercise to research 21 CFR Part 11 and evaluate two of Zymark's products for compliance with the regulation. This exercise created the process that Zymark now uses to ensure compliance for all its products covered by the requirements of the new standard.

"We set up very specific goals for the project," says Dobro. "The first goal was to create a standard validation plan that could be used to evaluate existing products, as well as new products. It had to be generic enough so that it could easily be adapted for any Zymark product. A second goal was to create a resulting package that would be of value to Zymark customers, who are directly answerable to the FDA."

First, it was necessary to create a requirements traceability matrix—a table in which the first column lists all of the requirements, and the second column lists one or more test cases for each requirement. Dobro then developed the validation plan, listing generic test cases that could be used for any product and using this template to be specific for the actual product tested.

The first product tested was the Tablet Processing Workstation II, a legacy product used in pharmaceutical quality-control labs. Its software had been up-graded recently and incorporated a new security module. Months later, Dobro adapted the plan to apply to the Prelude, a new product that listed the regulation as a product requirement.

Dobro drafted a validation, including detailed procedures for each test case. Then he asked a pharmaceutical industry consulting group to analyze the results. The consultants told him to keep in mind the purposes of the regulation: First, make sure that electronic records and signatures are as credible as paper records and signatures, and second, make sure the FDA can access this information. "Zymark is now positioned to assure 21 CFR Part 11 compliance for all of its products," says Dobro.

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