

# Validating Automated Systems

George Koroneos



PHOTODISC, INC.



ROCKWELL AUTOMATION

As newer and more elaborate hardware and software systems are installed in automated manufacturing environments, companies are further incorporating good practices into their validation process.

**I**n an industry with scant room for error, flawless validation systems are vital to successful manufacturing plants. According to industry experts, however, companies vary greatly in both their awareness of the US Food and Drug Administration's current regulations on good manufacturing practices (CGMPs) and their ability to properly implement CGMPs into custom-tailored manufacturing systems. Thanks to additional resources such as the recently updated *Good Automated Manufacturing Practice (GAMP) Guide*, published by the International Society for Pharmaceutical Engineering (ISPE, Tampa, FL, [www.ispe.org](http://www.ispe.org)), pharmaceutical companies better understand how to ensure that pharmaceutical production achieves the same end result every time.

"[Validation] is something manufacturers are required to do to show that their systems will perform as they are intended to perform in their environment," says Stephanie McKiernan, senior validation specialist at Pilgrim Software (Tampa, FL, [42 \*Pharmaceutical Technology\* MARCH 2005](http://www.pilgrim-</a></p></div><div data-bbox=)

“If they are working on a big system, companies need a master plan to detail how they intend to do their commissioning, qualification, and validation.”

software.com). “How to get there is the hard part. If you don’t have a product with an off-the-shelf [validation component] that goes hand in hand with the application, you are going to have to build it from scratch, which could take years.”

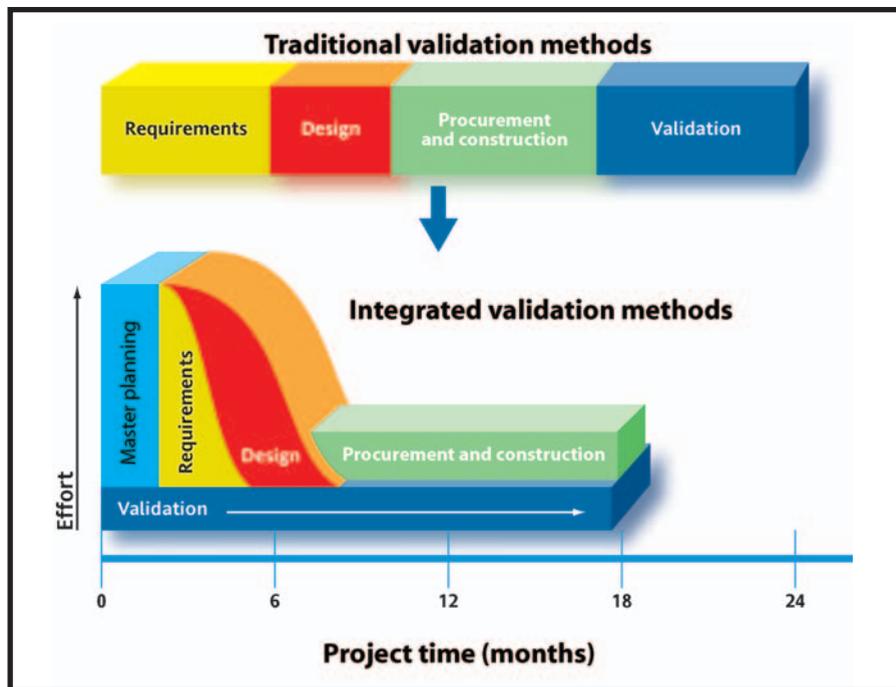
In addition, manufacturers need to take in account FDA’s regulations of electronic records and signatures, which appear in part 11 of Title 21 of the *Code of Federal Regulations*. Experts explain that 21 *CFR* Part 11 should not be viewed as another hurdle, but as a part of the overall validation process.

“CFR Part 11 today really shouldn’t be looked at independently,” says Michael Wyrick, senior director at Washington Group International (Fairfax, VA, [www.washingtongroup.com](http://www.washingtongroup.com)). “Companies need to build their compliance component into the validation program, because many of the things that have to do with 21 *CFR* Part 11 are really just pieces of the validation program.” For example, security, change control, and audit trails can be built into the validation program, thereby providing compliance to both the validation and *CFR* Part 11 requirements.

### The master plan

Experts recommend that companies with large numbers of automated systems take the time and effort to write up a master validation plan detailing the entire installation process from qualification to completion.

VTS consultant Ken Christie (Westborough, MA, [www.vtsconsultants.com](http://www.vtsconsultants.com)) says that “If FDA [inspects] a company and they see that it is highly automated, rather than start looking through mounds of



Early integration of master planning, requirements, design, and validation can reduce time-to-validation substantially.

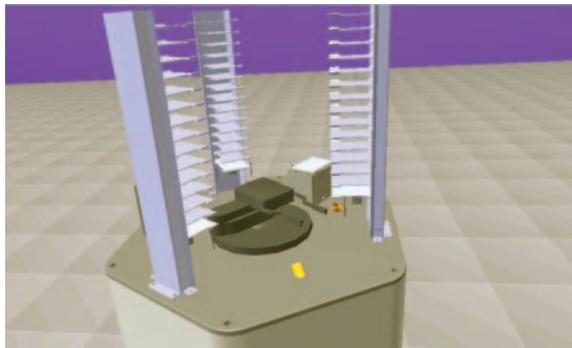
documents, their first question is, ‘What can you show me that tells me what your approach is to the qualification of these items?’” If the company has clearly defined the validation methodology for the system, inspectors might pick one or two items to focus on rather than evaluate the entire operation. “This is not meant to be a cover-up attempt, but a method of showing officials the efficiency of the company,” Christie continues.

“Many investigators have been trained to ask for either a master plan or validation plan if it’s for a specific system or piece of equipment,” says Wyrick. “If they are working on a big system, companies need a master plan to detail how they intend to do their commissioning and qualification and validation. They also have to include computers and distributive control systems. The agency also holds companies accountable to those plans—did they execute those plans?”

According to industry experts, one of the biggest challenges facing companies constructing a new automated system is that they have not allocated enough time to complete the master validation plan in the

rush to get the product to market. “It’s tough to go back to management and say that a drug has to be kept off the market for X months to complete the work,” says Justin Neway, chief science officer and executive vice-president at Aegis Analytical (Lafayette, CO, [www.aegiscorp.com](http://www.aegiscorp.com)). “The normal comeback to that is, ‘Find a way to do it faster.’ But when you start taking shortcuts, that’s when you run the risk of things turning up in an inspection.”

Another common challenge is incorporating traceability into existing systems, explains Mark Cupryk, vice-president and general manager of North American operations at Invensys Validation Technologies (Foxboro, MA, [www.invensys-vt.com](http://www.invensys-vt.com)). “Companies will come to us looking to reduce the cost of testing, but they have already built a lot of infrastructure up front. The expectation is that we will be able to massage everything miraculously to show complete traceability of every test that they perform without having any rework on the front. One of the major issues that we see is in the planning process. A lot of the major multinationals are not keeping the end in mind.”



### Qualification

With a master validation plan complete, a company can contract a vendor to construct the equipment based on its specifications. The manufacturer cannot, however, assume that the vendor is qualifying the machine during the build process. At Pfizer's (New York, NY, [www.pfizer.com](http://www.pfizer.com)) research group manufacturing facility, engineers conduct a battery of site acceptance tests (SATs) at the vendor's location and then a second series of SATs after the machine is brought to the manufacturing plant. If the system passes, local engineers install the equipment and the official qualification process is initiated.

Jose Soto, manager of the technical support group at Pfizer, explains that all equipment goes through three qualification steps: installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ). IQ refers to the process of checking the installation to make sure that all the parts purchased are indeed what were ordered. OQ is more specific: each individual function is tested page by page to make sure that every component on the machine works to specification. Finally, Pfizer engineers run a PQ, which entails a demonstration of the entire machine as it would perform in a live environment.

### Simplifying validation

To help manufacturers qualify and validate their systems more quickly, software vendors such as Pilgrim have begun including validation scripts that standardize acceptance testing. These scripts are step-by-step instructions, such as "if you do X the result must be Y" to pass the val-

idation test. Vendors also can develop and distribute scripts for future updates to an application.

Mark Cupryk of Invensys identifies another trend that takes validation scripts a step further: libraries of previously validated software modules that can control systems on a larger scale. Although he acknowledges that

some companies view the process as costly, Cupryk sees advantages in it. "We do see the library offering a lot more potential for consistency and fewer defects in the long run."

Even with these new methods of simplifying the validation process, pharmaceutical manufacturers and consultants still say that one of the biggest challenges

**The ultimate goal is to reduce the regulatory burden, because there is going to be less rework on product, less changes and an overall smoother operation.**

in validation is understanding what FDA considers to be "good practices." Many involved in validation would like to see decisive rules about how to properly validate their automated systems.

"If FDA was more specific in what they were looking for it would be a big help," Soto says. "Some of the recommendations are open regulations. Each company can comply differently to the rules. I understand that it's good to be flexible, but it would be easier to be compliant with a more definitive set of rules."

According to Neway, FDA is moving towards becoming more of a coach than a policeman. "It's true that a lot of their role is as an enforcement agency, but they are shifting much more towards encouraging innovation and providing a regulatory framework and other capabilities needed to introduce innovation in pharmaceutical manufacturing."

Another answer is the *Good Automated Manufacturing Practice Guide*.

### GAMP ground

Initially a European initiative, the *GAMP Guide* is a voluntary set of guidelines created by industry leaders to help companies understand and meet CGMP regulations for automated systems. Produced by the GAMP Forum, a technical subcommittee of ISPE, the *GAMP Guide* has been revised several times to accommodate changes to regulatory policies and is now in its fourth edition, *GAMP 4*.

"I've seen a lot of companies suffer from very wordy procedural validation practices," a member of the European GAMP advisory board says. "Somewhere along the line I think we lost track of where the actual value of validation was. And I think [the GAMP Forum] was a reaction to that."

Many companies have found the *GAMP Guide* useful. "The corporate guidelines that we use to set policies at our site have lineage back to the ISPE GAMP 4 guideline," says Mike Doenlen, manager of manufacturing process engineering at Roche Colorado Corporation (Boulder, CO, [www.rochecolorado.com](http://www.rochecolorado.com)). "The format that we follow is pretty well adopted throughout the industry."

### A risk-based approach

As part of its recent initiative, "CGMPs for the Twenty-First Century: A Risk-Based Approach," FDA has begun applying risk analysis to inspections, including validation inspections.

"FDA has been a lot more open, in the last few years, to using risk analysis techniques to allow manufacturers to make a conscious decision about where to put their time and effort in validation," explains Christie Deitz, senior principal engineer at Emerson Process Management (St. Louis, MO, [www.emersonprocess.com](http://www.emersonprocess.com)). For example, if a company has a system that tracks the quantity of active ingredient that goes into a batch, and another system in place that monitors the cooling water

temperature, the system that measures the active ingredient amount is much more critical than the cooling water temperature. It would be more important to spend additional time and effort to verify that the active ingredient system is working properly than the less-critical cooling water system.

“By using this risk-based approach, companies can determine which of their systems needs the most validation,” Wyrick says. “Because manufacturers have limited resources, it is important to utilize those resources effectively and efficiently. We are finding that high-risk systems are being validated at a higher level than medium-or minimum-risk systems. Most companies today are not validating all systems the same way—it’s a waste of resources.”

It’s not just the manufacturer’s validation resources that have been taxed. According to an FDA report, *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model*, the number of registered human drug establishments has increased by more than 400 percent in the last 25 years. “Over the same time period,” the report states, “the number of human drug CGMP inspections conducted has decreased by more than 60 percent. As a result, it is impossible for FDA to achieve uniformly intensive CGMP inspectional coverage for all registered drug facilities.”(1)

In a presentation to the FDA Science Board entitled, *CDER Risk-based Site Selection Model: An FDA Risk Management Tool*, Kate Morgan, of the FDA’s Office of Planning/Office of the Commissioner explains the risk model the agency planned to use to judge site risk potential (SRP). FDA has assessed an SRP score to every manufacturing site in the United States, and sites that scored higher will be more prone to inspection. Sites were ranked on a product factor, a facility factor, and a process factor.

As explained in the presentation, a site will be less frequently selected for inspection if:

- It has been inspected recently and has

few or no previous violations of GMPs and a smaller volume of product (facility weight)

- It makes nonsterile, OTC drugs, and/or other product types that are not associated with a high frequency of recalls and/or serious defects (product weight)
- It makes products judged to be relatively straightforward to manufacture with consistent quality, and not vulnerable to contamination (process weight). (2)

Plants earmarked for priority inspections include those that produce sterile drug products, those that produce other prescription drugs, and new registrants that had not been inspected previously.

“I don’t think that the industry has really grasped that this is taking place,” says Neway. “The FDA is piloting their risk model, which they published, and they are using it to rank manufacturing site inspections in 2005.”

### On the audit trail

Part 11 requires drug makers to maintain an audit trail. If a company is keeping a record electronically, and the primary source is electronic, then they are required by law to document changes: who changed it, why they changed it, and when they changed it. Additionally, that audit trail has to be linked to that record.

According to the updated 21 CFR Part 11 guidance, companies are required to “use time-stamped audit trails to document record changes, all write-to-file operations, and to independently record the date and time of operator entries and actions. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as required for the subject

electronic documents and shall be available for agency review and copying.” (3)

The audit trail is part of the change control program. If an operator or administrator wants to change the steps of an application, or change set values, the system will not allow the change unless security measures are met. The program will also automatically stamp the date of entry, the identity of the person who made entry, and capture the change made. So if an auditor wants to see changes that have been made to the system, the program can print out an audit trail to show when changes were made and who made them. If a manufacturing problem occurs and the follow-up investigation goes back to the software, the audit trail becomes a piece of information that is reviewed as part of the investigation.

“A lot of products are being sold with the logo ‘Designed for 21 CFR Part 11,’ which really means that the product was designed with components such as electronic signature and audit trail capabil-

ity—things that were not only designed toward 21 CFR, but also help maintain validated systems,” says Bart Reitter, market development manager for life sciences at GE Fanuc (Charlottesville, VA, [www.geindustrial.com](http://www.geindustrial.com)). “A lot of those

tools are built into products to help with the validation process.”

Once a system is validated and put into production, maintenance becomes a priority to make sure that the product is never modified beyond its intended form. Experts

suggest that a change-control system be installed to assess the impact of any system modifications. Change-control procedures call for a written or electronic signature to be recorded every time a system is adjusted. This provides both a history of who has used the unit, and a security measure to make sure only authorized personnel have had access to the machine.

### Re-evaluation

After a validated system has been in use for some time, companies re-evaluate it. “Over time, companies need to take a look at the overall impact of changes,” Wyrick says. “That’s what we call periodic review.” The onus is on each company to decide, based on the criticality of the system, how frequently the periodic review must be done. “Typically, you find it to be every 24 months, but if it’s a very critical system, they might review it every 12 months,” Wyrick continues.

During the periodic review, a company will look at the number and character of changes to the system, and decide if it is still operating as effectively and efficiently as it was designed. Administrators should also look at documentation and training records to make sure that they are up to date.

Soto explains that at Pfizer, engineers re-evaluate a machine every three years after the initial qualification. They check for any deviations and view the entire history of the machine. A demonstration batch is also run to make sure that the machine works properly. “The most challenging part is that you have to protect the computer from viruses and make sure that every patch added to the software has been verified. We need to go back and reevaluate that those patches don’t affect the computer system,” Soto says. “That has to be done almost every month. The computer is also run through a network system and maintaining that network can be difficult.”

Risk analysis can be used to determine if a patch needs to be validated. Patches to operating systems need not be validated, but product-manufacturing software should be validated through change control. Based upon the impact of that change,



administrators can determine whether the software upgrade has altered the end product. “What a lot of companies will do is batch the individual patches up into one patch,” Wyrick says. “A company also has to have the right processes in place, like change control, to evaluate the impact of those changes and decide whether the patches should be installed or not.”

#### PAT and beyond

So what does the future hold for new validation methods?

Normand DuBuc, senior director of automation at Invensys Validation Technologies, says that the much-discussed process analytical technology (PAT) framework will continue to mold control-system implementation and validation. “There is now a push by the regulatory bodies to encourage the manufacturing companies to better understand their processes, to better control their processes, and in turn to provide a better product in the end. The ultimate goal is to reduce the regulatory burden, because there is going to be less rework on product, fewer changes, and an overall smoother operation.”

The PAT initiative is designed specifically to try to get product through the manufacturing process more quickly and reduce the time it takes for laboratory testing and cycle time. “[Manufacturers] are mov-

ing towards real-time release,” says Jimmi Filice, product-marketing manager at GE Fanuc. “They want to get it to where a powder goes into one end and out the other end comes a bunch of pills, without ever stopping along the way—that’s a far cry from where pharma manufacturing is today.”

#### References

1. Food and Drug Administration, *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model*, (FDA, Rockville, MD, 2004), [www.fda.gov/cder/gmp/gmp2004/risk\\_based\\_method.htm](http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm) (accessed 23 February 2005).
2. Food and Drug Administration, *CDER Risk-based Site Selection Model: An FDA Risk Management Tool*, (FDA, Rockville, MD, 2004), [www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4080b1\\_07\\_Kara%20Morgan.ppt](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4080b1_07_Kara%20Morgan.ppt) (accessed 23 February 2005).
3. *Code of Federal Regulations, Title 21, Food and Drugs, Subchapter A—General Part 11 Electronic Records; Electronic Signatures* (General Services Administration, Washington DC, 1 April 1973). **PT**

#### Please rate this article.

On the Reader Service Card, circle a number:  
**339 Very useful and informative**  
**340 Somewhat useful and informative**  
**341 Not useful or informative**  
*Your feedback is important to us.*