

Is Three-Batch Validation Obsolete?

Where is the new process validation guidance leading us?

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THE NOVEMBER 2008 PUBLICATION of FDA's draft guidance, *Process Validation: General Principles and Practices*, begs the question: is last century's process validation modus operandi — with its reliance upon three successful batches or test runs to declare valid any given process — still applicable?

"No," is the short answer from FDA officials.

So what are you to do? Simply toss aside decades of industry best practice? A look at the logic behind FDA's response can provide direction. In addition, a review of the draft document and its references can also provide something even more helpful: specifics as to what the agency — and its counterparts in the International Conference on Harmonization (ICH) — want to see when it comes to proof of compliance.

Validation by Design

Neither the FDA's current good manufacturing practice (cGMP) regulations for the 21st century, nor the ICH's Q7 guidance, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, require any particular number of test runs to prove process validity. In fact, the FDA now considers that distilling

all the factors that go into ensuring process validation into just three confirmatory runs is too simple.

By and large, processes today are becoming more and more complex. Complexity does not lend itself to after-the-fact validation by post-process testing.

In a March 2010 warning letter, the FDA cited Pierre Fabre for inadequate process validation procedures. The letter reads, "Your firm has not established written procedures that describe the in-process controls, tests, or examinations to be conducted on appropriate samples of in-process materials to monitor the output and validate the performance of manufacturing processes. . . ."¹

For FDA and other ICH members, today's process validation must rely upon the same philosophy that underpins quality by design: validation must be built into a complex process, not tackled after the fact. Indeed, as I point out in my book *Get to Market Now!*:

Over the past 20 years, our scientific and technical knowledge has dramatically increased, from decoding the human genome to mastering the building of nanoscale materials. As a result, professional expertise has dealt with this revolution of knowledge and technical ability through an increase in specialization, sub-specialization, and even sub-sub-specialization. Toxicologists have begat neurotoxicologists who have begat protoxic-neurotoxicologists.

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Specialization adds two significant problems in any organization:

1. Each specialized professional vies for his or her share of limited company resources, thus reducing the amount for everyone else, and
2. Ever more narrowly focused information makes it more difficult to see patterns and linkages.”²

It is this latter point especially that makes the old three-batch validation methodology increasingly risky.

Today’s process validation needs to be determined based on process knowledge. The more intimate your knowledge of a process — including its potential risks and limitations — the greater your ability to implement controls throughout the process. Thus, the greater your ability to guarantee process outcome.

Learning Lessons from a Short-Supply Situation

In 2004, the FDA staked out this precise point in its Compliance Policy Guide, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. This FDA Compliance Policy Guide outlines a process by which the agency will approve a “validation by design” approach to address short supply situations.

Under this scenario, as long as the firm had pre-defined enhanced tests and sampling in their validation plans, as well as the testing or control of additional attributes, the agency would approve the validation *even if the early batches were already distributed to the market*. Careful reading of this guide reveals very similar phrasing and language between this concept of short supply situation process validation and many of the later quality by design documents published by ICH.

Proof of Process Validation

Given this lifecycle, QbD-esque approach to process validation, what records do you need to have? Effective process validation can be shown through records, such as:

- Risk evaluations, identifying which processes are critical and why,
- A specific validation plan for each product or critical process,
- Sampling plans for each process (make sure to include both in-process as well as periodic sampling),
- Investigations of unexpected process control nonconformances,
- Pre-defined periodic process verifications that a process is still operating in a state of control, and
- Reviews of completed validations.

Depending on the process being validated, testing methods might also require their own validation. In other words, to rely upon an analytical test result to help prove a production process is valid, the analytical test method must itself be valid.

To provide more help in defining the right records, let us further examine the last bullet point: “reviews of completed validations.” Sounds simple enough, but there is a subtlety to be aware of: reviews of a completed validation — and presumably the original validation plan — should be done by an independent expert. *This does not mean you need to hire an outside consultant*. Rather, you must simply identify qualified individuals who do not have conflicts of interest with the process or its intended validation results or its executors, and have those individuals review the plans and the summary results. Thus, if you are outsourcing your manufacturing to a contract manufacturing organization (CMO), and expect that CMO to validate the processes, then make sure that at least your internal quality department reviews the CMO’s validation plans and validation results. In talking with several colleagues at the agency, there is one additional consensus recommendation if you are using a CMO to validate the manufacturing process: as part of the initial validation plan, your internal quality department should be providing the CMO’s validation team the minimum specifications to target. In other words, the validation plan should refer back to your drug development history file (if you are unfamiliar with a “drug history file,” look to the device industry’s design history file to get an idea of what might go into a good drug history file).

There should be no question in your mind: the new process validation complements the FDA and ICH emphasis on quality by design. As I note in my book, the more your firm, and your suppliers, have embraced QbD — from preclinical and early stage clinical trial pilot production through postmarket surveillance and manufacturing improvements — the better your results in the new compliance landscape of the 21st century. If you are still trying to get your arms around QbD, and its impact on drug development, clinical trials, manufacturing, and commercialization, the new process validation will add yet another layer of complexity. The risks of getting this wrong will jeopardize patient safety, product efficacy, quality system compliance, and your company’s future.

To avoid confusion and unnecessary expense of monies, time, and effort, consider bringing in an outside expert to help you simplify your strategy and your processes. As I’ve noted above, the new process validation requires a more holistic, subtle approach. A good consultant should be able to show you how best to work with what you already have in-house, how to take advantage of other processes and controls in your compliance infrastructure, and how to inadvertently avoid falling into traps that will raise questions in the mind of FDA reviewers. With the expert’s advice, you can minimize mistakes, costs, and risks when it comes to process validation in the 21st century.

Are you ready? ■

References

- 1 FDA Warning Letter dated March 26, 2010, at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm211391.htm>, accessed on 23 June 2010.
- 2 Avellanet, John (2010) *Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine*, Logos Press: Washington, D.C., p. 11.