validation

The four pillars of pharmaceutical validation

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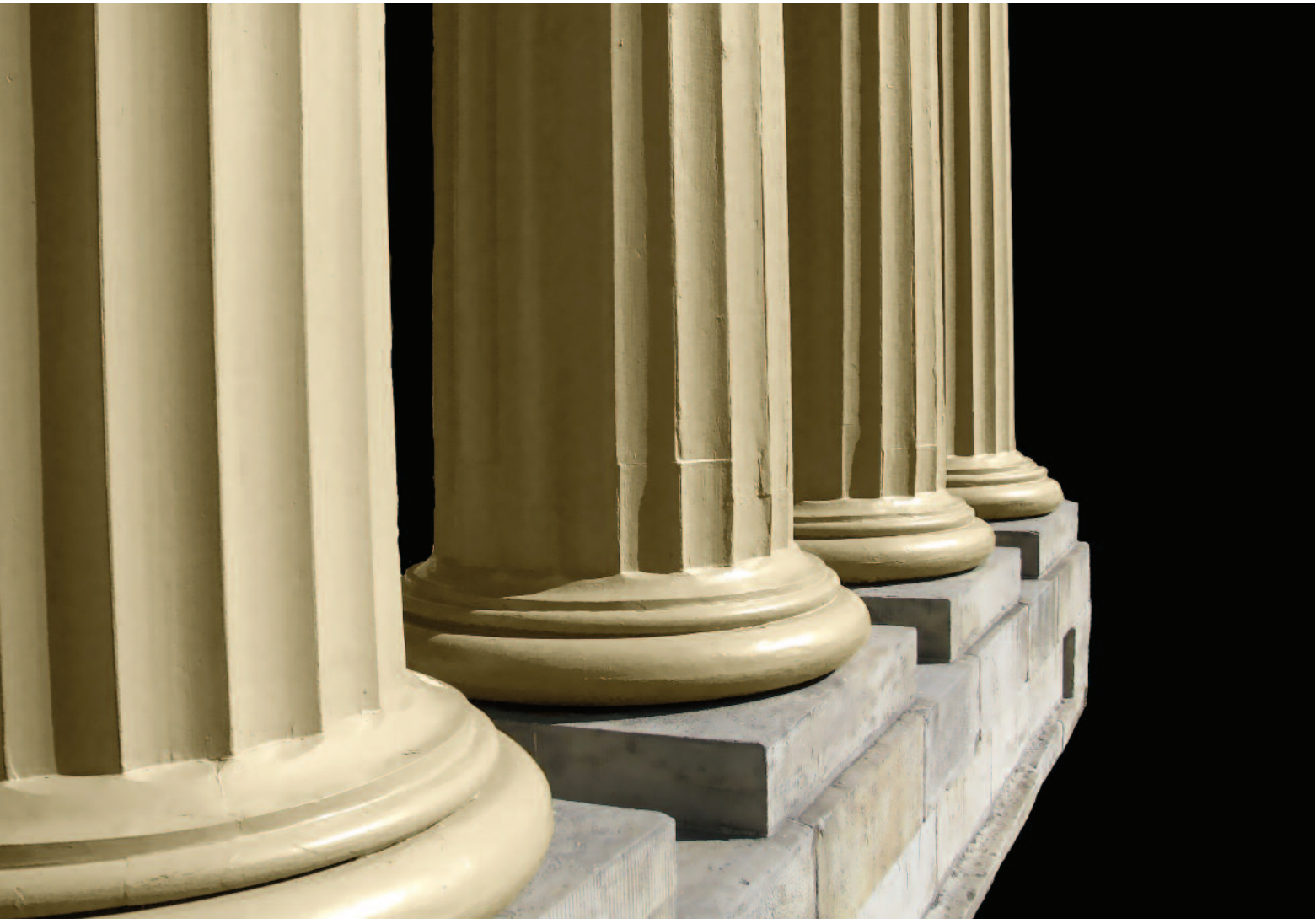

This article explains the four fundamental principles of validation: product and process understanding; data-driven and statistically supported action; multidisciplinary and broad-based methodology; and a holistic approach. With these universally applicable principles, you can develop compliant, effective, and efficient validation programs that suit any situation and that will comply with regulatory expectations.

Validation is an integral part of the quality systems used in the life-science industry. Though the basic principles of validation haven't changed, how we approach validation and the regulatory expectations have evolved over the years, especially since the FDA published "Guidance for Industry—Process Validation: General Principles and Practices" in January 2011 [1].

While people at many companies are still struggling to align their validation programs with this process validation (PV) Guidance, others are formally incorporating its core concept: "process improvement and innovation through sound science."

The Guidance shows that the FDA has clearly shifted from a rigid view of validation to a flexible and innovative lifecycle approach, which is consistent with the approach outlined by recent FDA-ICH guidances, including "Q8 (R2) Pharmaceutical Development" [2], "Q9 Quality Risk Management" [3], and "Q10 Pharmaceutical Quality System" [4]. The FDA's PV Guidance expects each manufacturer to develop product and process understanding and to continue to do so throughout the product's lifecycle in order to improve product quality, safety, and efficacy.

All elements of validation are interdependent, so avoid a piecemeal approach that can lead to noncompliant and/or ineffective programs.

In short, basic compliance isn't good enough anymore. Instead, continuous improvement and technical innovation and excellence must be integrated into your validation programs for them to meet current regulatory expectations. Although the extent and complexity of validation vary according to the nature of the site, manufacturing operation, and products (sterile/non-sterile, solids/liquids/pastes, and single/multiple products), the principles of validation remain the same.

Product and process understanding

The basic objective of validation is to provide assurance that a commercial manufacturing process is capable of consistently making products of acceptable quality under commercial manufacturing conditions. Can anyone imagine meeting this objective without fully understanding the goal (product) and the path (manufacturing process) to reach that goal? Meeting this objective requires understanding the complete profile of the finished product(s) in terms of the identity, strength, quality, and purity that you claim they possess. You must also understand the nature, source, extent, and impact of process variability on product quality. Granted, some degree of variability is inherent to any manufacturing process. Even so, you must develop a strategy to control it in a way that ensures the process remains consistent and reproducible during routine commercial manufacturing.

The FDA's current PV Guidance is based on the lifecycle approach, which comprises three stages: Process design, process qualification, and continued process verification.

Stage 1: Process design. This stage entails gathering information to obtain product and process understanding.

Stage 2: Process qualification. During this stage, you select and verify the design of the process equipment, utilities, and facility. Next, you test the manufacturing process, commonly referred to as process performance qualification.

Stage 3: Continued process verification. The last stage requires monitoring the critical process parameters and the critical quality attributes during routine commercial production to provide ongoing assurance that the manufacturing process remains in a state of control.

Although the product and process understanding efforts begin in Stage 1, they do not stop there. In fact, they never stop! You must continue to hone your understanding through stages 2 and 3 and during routine commercial production throughout each product's lifecycle.

Even if you're not directly involved in validation, you've likely encountered examples of failed, ineffective validation caused by insufficient product and process knowledge. Indeed, the lack of product and process knowledge is likely the largest contributor to validation failures. The reason is simple: It is almost impossible to fully understand all of a product's characteristics or how a process performs during the initial phase of that process. That's why the journey toward product and process understanding must continue throughout the product's lifecycle. Normally, the opportunities to enhance product and process understanding increase with the passage of time as the volume of commercial-scale process data grows and becomes available for review and analysis. But there is no finish line in the race to enhance product and process understanding.

Consider, for example, tablet hardness. Without sufficient product knowledge, a manufacturer may fail to fully understand the mechanism of how the hardness of some tabletted products can change over time. That could lead to cases where tablet samples fail to meet the hardness specification during stability testing, even though they met that specification during in-process and initial product testing. Or perhaps problems arise during dry powder blending, where product characteristics such as particle size distribution, bulk density, tap density, and moisture content play crucial roles in process performance. It's impossible to validate a blending process without fully understanding how variation in these characteristics affects the performance of the manufacturing process.

At the same time, it's possible that the specifications for some critical raw materials are not fully supported by the process design data. Maybe the specifications have wide ranges for parameters like particle size distribution, bulk density, etc. If so, you may observe significant variation in process performance even when all the raw materials meet those specifications.

Furthermore, some aspects of product and process understanding may seem trivial. But be careful because these seemingly insignificant characteristics can lead to unexpected and undesirable results. For example, if the bottom curvature of a container that holds finished products is uneven, the container may rock or even fall over during packaging. No detail is trivial when you seek full understanding.

Data-driven, statistically supported validation

The current Guidance defines PV thus: "The collection

and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products."

Note how the definition starts with "collection and evaluation of data," which clearly indicates their significance in PV. Furthermore, the Agency expects you to evaluate the collected data statistically. (The term "data" is used 31 times in the Guidance's 19 pages, and the term "statistics" appears 15 times.)

If raw material specifications have a wide range, you may observe significant variation in process performance even when the materials are on-spec.

Indeed, even GMP regulations require manufacturers to develop a data-driven and statistically supported control strategy for their processes. Examples include §211.165(c) and (d) regarding a sampling plan; §211.110(b) regarding in-process specifications, and §211.180(e) regarding product and process analysis. If you look at the results of FDA inspections, you'll find that many, if not most, of the common observations related to GMP regulations fall into the categories of product sampling, process capability, statistical process control, and analysis of variance.

The main objective of collecting and evaluating data is to develop a science- and risk-based control strategy in order to keep the process in a continual state of control during routine commercial production. That requires employing specialists who are qualified to evaluate that state of control. Without these experts, there is a risk of misinterpreting the process data, which could lead you to make unnecessary changes and/or not to make changes that are warranted. Which statistical analysis tools you use is also important. Make sure they will truly help you maintain a continual state of control.

While statistics plays an important role in all three stages of PV, beware of developing statistical evaluation programs that are overly complex and/or aren't fully relevant to maintaining a continual state of control. Too often someone's enthusiasm or an immature approach has led companies to develop complex statistical monitoring systems that generate statistical parameters that are irrelevant to the end goal. Those systems are likely to pose serious problems during an FDA inspection. Keep in mind that validation programs must remain process-driven, and statistics is just a tool to make these programs more compliant, effective, and efficient. Be sure you have the right tools for the job.

Multidisciplinary, broad-based program

Validation programs should not be confined to validation departments, as they have been in the past. Rather, with so much emphasis on product and process understanding, manufacturers should develop broad-based validation programs that use the product knowledge and process understanding of other departments. No employee or department has complete knowledge of all aspects of the product and manufacturing process. So develop multidisciplinary validation programs. That will make complying with regulatory expectations easier. In fact, the current PV Guidance explicitly recommends following an integrated team approach by including experts from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance.

Not only should validation activities cross the boundaries of other departments, but they should also be spread across all levels in the organization. Get top managers involved and committed to the validation programs so that you get the necessary financial and human resources. In fact, regulators expect you to clearly outline the roles top management plays in validation programs within your company's high-level documents, such as validation policy and master plans.

It's especially beneficial to get operators involved in validation activities during all three stages of PV because they have hands-on experience, and their observations are often critical to process success. In fact, operators can make significant contributions to the validation documents as you develop them. There's no substitute for someone who can point out the discrepancies between real-life situations and the theoretical information that can sometimes appear in equipment manuals and other documents. I know of several instances in which first-hand information from operators led to significant process improvements. The operators who load powders or granulations into the tablet press hopper, for example, may have observations about their flow characteristics. This information can be very helpful in making your PV efforts successful.

Holistic approach

Validation is crucial to any FDA-regulated, life-science site because it affects nearly all aspects of operations covered by GMP regulations. So when you're developing validation programs, adopt a holistic approach that encompasses all aspects of the compliance and technical requirements. That means identifying and implementing all components of validation, including facility, utility, and equipment qualification; computer system validation; cleaning validation; and PV. A piecemeal approach will likely lead to noncompliant and/or ineffective validation because

all the elements of validation are inter-dependent and each can affect the effectiveness of the validation program. Can you imagine performing effective PV using poorly designed, inadequately qualified process equipment? Impossible.

A validation program should not only focus on the initial validation, but should include a mechanism to ensure that the validation state is maintained throughout commercial production. That's where change control comes in. Unfortunately, most change-control systems assess changes one by one before and after implementation to see how they affect the state of validation. A better approach is to perform periodic evaluations collectively so that all the changes implemented over a certain period are evaluated to gauge the effect of their interaction.

Last, never forget the human factor when developing validation programs. Some of the best processes, even when performed on the best equipment, can fail purely due to the human factor. Call it human error if you like, but the experience of operators and/or the level of care they show in performing their job are often a significant factor in the variation of process performance. Whether operators work a day or night shift can also influence the process, as can the length of their shift. Changes in their physical health and emotional state can also contribute to variation.

Conclusion

Validation is a legally enforceable regulatory requirement, so there's no option: You must implement compliant validation programs. But keep in mind that compliance is just the minimum requirement. If you want a competitive edge, the programs must also be effective and efficient. Effective means that the validation program meets most of the process goals. How much you invest initially and how much you spend operating the program, as well as the process cycle times, figure prominently in how efficient the validation program is. To be deemed a success, the validation program must be all three: compliant, effective, and efficient.

But the real benefit of validation comes from developing innovative and efficient manufacturing processes through continuous improvement, as noted in the FDA's 2011 PV Guidance. The lifecycle approach and general principles outlined in that Guidance are applicable not only to the validation of manufacturing processes, but also to other components of validation, including computer systems and cleaning methods.

Apply the four fundamental principles discussed in this article—which essentially recapitulate the FDA's current thinking from the Guidance—and you will have compliant, effective, and efficient validation programs. *T&C*

References

1. FDA. Process Validation: General Principles and Practices. Guidance for Industry, January 2011.

2. FDA-ICH. Q8 (R2) Pharmaceutical Development. FDA/ICH Guidance for Industry, November 2009.

3. FDA-ICH. Q9 Quality Risk Management. Guidance for Industry, June 2006.

4. FDA-ICH. Q10 Pharmaceutical Quality System. Guidance for Industry, May 2007.

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