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FDA Process Validation

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Working with the New 2011 Guidelines.

In January 2011, the FDA issued its newest guidance for Process Validation for industry and it is quite a departure from the previous guidance released in 1987. The old approach of developing products and hoping that testing would provide enough information to predict and control the process is no longer the order of the day. What does the new guidance contain and how does it differ from the 1987 version? Let's compare the two approaches to see where the changes lie and why they are important.

Back in 1987, the FDA defined process validation as a process of establishing documented evidence, with a high degree of assurance, that a specific process would consistently produce a product meeting predetermined specifications and quality characteristics. At that time, the industry's approach meant providing evidence from process development, from validating facilities, equipment, and cleaning, as well as process monitoring to support the process validation claim of having a stable and predictable process for manufacturing products. Proving quality through documentation and inspection has inherent deficiencies, however. Each part of the information pooled to make up the evidence for process stability constituted an operation that could be performed independently. Without the consistency of pulling together information from the entire process validation lifecycle in a concerted effort as a baseline for claims, the risk that key process variables could go unmonitored was liable to occur. And it often did. A case in point: how many times have we experienced failed acceptance criteria during the third run of a performance qualification or during a process validation run without immediately understanding why the failure occurred? In how many instances have we witnessed manufacturing runs slowly move out of specifications and finally exceed acceptance criteria so that we have to perform costly investigations to determine the cause of the issue?

The 2011 guidance provides a different approach to process validation, already revealed in the draft guidance introduced in 2008. This new approach caught the attention of the industry and spurred a huge response due to the drastic change from the 1987 guidance. More modern, the 2011 guidance aligns itself with many of the ideas in the FDA/International Conference on Harmonization (ICH) guidance for industry, Q8 (R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System. In essence, the FDA shifts its focus from proving quality through documentation and inspection to demonstrating it through sound scientific principles. Now, the FDA defines process validation as the *collection and evaluation of data*, from the process design stage to validation and throughout production. Scientific evidence is to be used to prove that the process is capable of delivering consistently manufactured quality products.

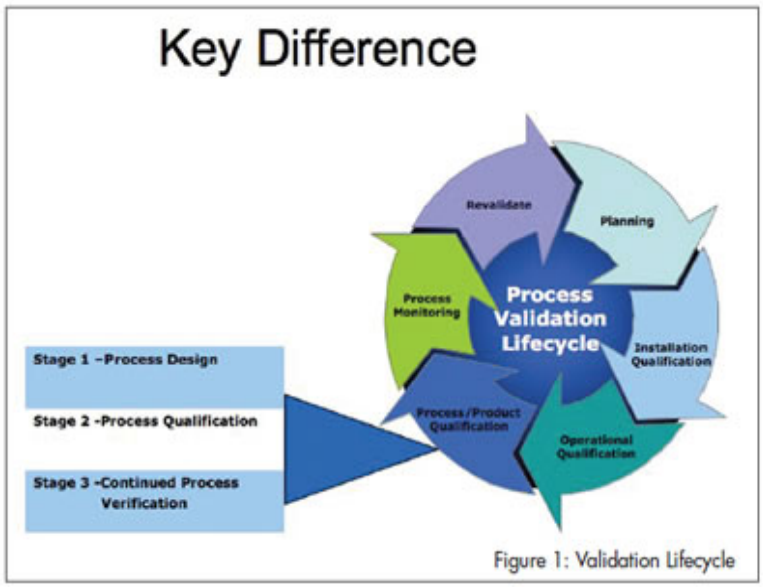

Figure 1: Validation Lifecycle

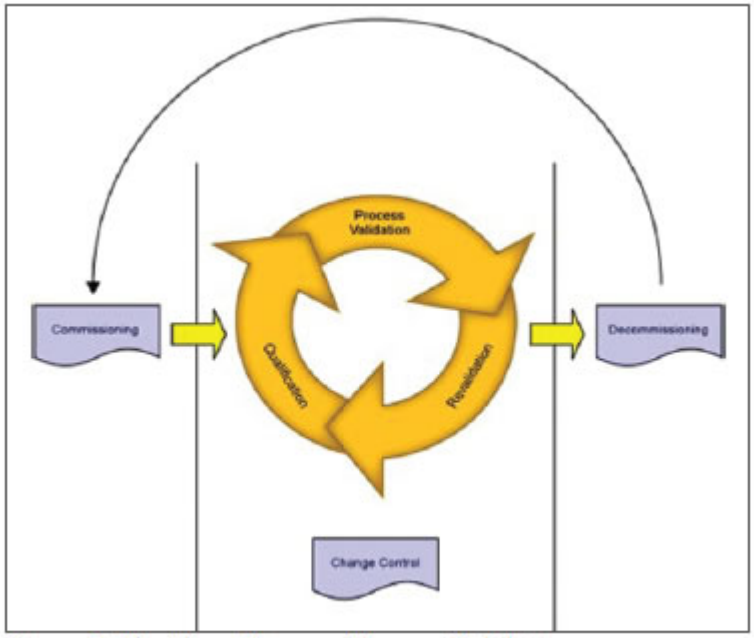

Figure 2: The Three Stages of Process Validation

Per the FDA, the new approach to process validation can be divided into three stages: Process Design, Process Qualification, and Continued Process Verification, described as follows:

“Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.”

The FDA now expects manufacturers to *understand the sources and impact of the variations* in the manufacturing process, to detect those variations reliably, and to control them in relation to the risk they represent to the process and product. Without this proof of understanding, manufacturers would not be able to justify to the FDA that they are in control of their process, and that they are not endangering the public to whom they distribute their product. Just focusing on validating equipment and processes for the sake of having documents on the shelf will not be sufficient anymore.

So, as industry professionals and leaders in our field, how do we adjust to the new guidance yet still manufacture products that are safe and efficacious but also maintain the integrity, potency, and purity that we had intended?

Let's look at the three stages starting with Stage 1: Process Design. This stage takes much of its approach from ICH Q8 and Q9. ICH Q8 describes the strategies involved in developing your process from a small to a large scale by identifying and understanding the main critical-to-quality attributes. Then, with these attributes in mind, it describes how to proceed to designing your process, so that it is operationally reliable and away from the edges of failure. Although the early stages of process development may not be in a cGMP environment, the same sound practices should be followed to specifically document the key decisions taken in developing the product. Product development now plays an even more critical role in this process design stage. Even generics manufacturers who, typically, have poor levels of process development, have to conform to the new guidance by better understanding the key process variables.

The practice of using risk analysis tools as described in ICH Q9 is very useful in the process design stage. This is the stage where many critical parameters are identified, verified, and/or thrown out of consideration on the road to scale-up, validation, and manufacturing. Risk analysis studies results and experiment designs are then used to justify ranges of critical-to-quality attributes for the process, whether they are equipment operational ranges or specific product quality attributes.

In Stage 2—Process Qualification—the guidance shifts our qualification process by steering away from the classic model of performing three runs to show the manufacturing process is stable. Traditionally, validation has been the practice of documenting and testing every function of a piece of equipment. In recent years, we have improved our ability to reduce the amount of testing by generating User Requirements Specifications that whittle down testing to only those functions that are specific to what we need. Even so, the age-old threerun method is still the accepted and most common practice. The new guidance steers away from the threerun method, requiring as many validation runs as needed to demonstrate the process is stable and capable. In other words, if the case can be made that fewer than three lots are necessary to demonstrate process capability and stability, then it is up to us to prove it and to provide data to support the claim.

Nomenclature in the 2008 draft guidance was a hot button in the industry due to terms introduced by the FDA that were not well defined. While the 2011 guidance either addressed or omitted most of those terms, the term Process Qualification remains. Process qualification is a new term that is not well understood. We've been accustomed to using the terms Performance Qualification and Process Validation to demonstrate process stability and capability. Under the new guidance, we decipher Process Qualification as an enhanced form of Process Validation where the responsibility of proving process stability

and capability through sound science and data is mandatory. Process Qualification still requires that supporting validations be completed prior to demonstrating process capability and stability of the process. The strategy for supporting validations should be laid out in a validation master plan and include the facility, equipment, in-process/release testing methods, and cleaning. Also to be included before process capability and stability runs are raw material specifications and supplier qualification analysis.

Once the equipment, facility, utilities, and raw materials have been qualified, the performance qualification of the process can begin. Again, the rationale behind the new FDA guidance steers toward sound science and our understanding of how we make our product, including the key input and output variables important to our process. Characterization, using risk management tools, should be performed to prove that we know which variables are important versus ones that are non-critical to the process. This means we will have to prove that we have the proper tools to measure, control, and evaluate these key process variables and that we understand how fluctuations in the process affect product performance. The process qualification protocol will need to simulate manufacturing conditions and testing of critical quality and process attributes. The data collected from the process qualification runs should include operating parameters, processing limits, and component inputs to evaluate according to the specifications we have established as important to our process.

Stage 2 “combines the actual facility, utilities, equipment, and the trained personnel with the commercial manufacturing process, control procedures, and components to product commercial batches.”[1] It confirms that the commercial manufacturing process performs as expected. The successful completion of this stage signifies that the drug product is approved for commercial distribution to the public.

Now with the drug product on the market and commercial manufacturing underway, the third stage of process validation begins. Stage 3—Continued Process Verification—demonstrates to the FDA that the manufacturing process remains in a state of control over time. How many times have we seen a process deviate over time and then eventually slide out of specification? Product recall is usually the next step for such out-of-control processes, and it can cause serious damage to a company’s bottom line. The high-profile recalls related to quality issues at Johnson & Johnson are a key example of how a company’s reputation may be damaged from these types of manufacturing process deviations.

The key to demonstrating continued process stability and control lies at the beginning of the process validation cycle, when key process variables are determined and process characterization takes place. A well-designed process includes a control plan that clearly defines critical-to-quality attributes and process variables that are well measured and understood throughout the commercial manufacturing phase. The use of the control plan and summaries of the manufacturing process will help anticipate process fluctuations and variability. Appropriate mitigation plans should be in place, if necessary, so that if we perform our upfront tasks in Stage 1 correctly, we will know how to steer the process back because we already know why the process drifted and how to bring it back into control.

In summary, while the FDA’s roadmap has evolved substantially from the 1987 guidance, it also plays to our scientific competencies. Sound science and a well thought-out framework for approaching process validation is now the norm, and the industry must shift

its way of thinking to conform to the new standards of the January 2011 guidance. Risk management tools, when properly applied; represent an opportunity for continuous improvement and monitoring that can lead to quicker product approval to market, less uncertainty about decisions made in the development process, and continued successful commercial manufacturing with fewer failures.

Reference

1. Guidance for Industry, Process Validation: General Principles and Practices, U.S. Department of Health and Human Services Food and Drug Administration, CDER, CBER, CVM, Current Good Manufacturing Practices (CGMP), Revision 1, January 2011

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