IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

FDA's 2011 Process Validation Guidance: A Blueprint for Modern Pharmaceutical Manufacturing

By **John Hyde**, **Andrew Hyde**, **Paul L. Pluta**

Nov 24, 2013 2:31 pm EST

Peer Reviewed: Process Validation

Abstract

FDA issued *Process Validation: General Principles and Practices* in January 2011. The guidance integrates strategy and approaches to provide a comprehensive approach to validation. Three stages in the lifecycle approach are identified. The lifecycle concept links development, validation performance, and product/process maintenance in a state of control during routine commercial production. Understanding the sources of variation and control of variation commensurate with risk is a key component of the lifecycle approach. FDA has provided recommendations for the general lifecycle and Stages 1, 2, and 3. Specific expectations are discussed. The integration of development work, process conformance, and continued verification provides assurance the product/process will consistently remain in control throughout the entire product lifetime**.**

These approaches to pharmaceutical manufacturing science have been proposed prior to the release of the 2011 guidance document in various other FDA and international guidances and are entirely consistent with other current global harmonization initiatives.

Introduction

FDA issued *Process Validation: General Principles and Practices* in January 2011. This guidance has provided an integrated approach to pharmaceutical manufacturing—and it is truly a blueprint for the future. The guidance describes the lifecycle approach concept and transforms process validation from a single event to an ongoing continuum. The guidance document presents process validation itself as a process. This lifecycle-based concept is now being applied to many related areas of validation and qualification—including cleaning, equipment, facilities, utilities, computer systems, and others.

This paper provides an overview of the FDA *Process Validation Guidance*. Topics discussed include the historical basis for process validation, recognized gaps prompting the new guidance, the lifecycle approach that addresses these deficiencies, and the integration of process validation with other FDA initiatives.

Historical Bases of Pharmaceutical Process Validation

With the publication of good manufacturing practice (GMP) requirements for pharmaceutical manufacturing in the 1970s, practices and methodologies emerged for the validation of pharmaceutical processes. Pharmaceutical manufacturing methods were primarily manual at that time. The pharmaceutical industry focused on the codification of manufacturing procedures and the enforcement of adherence to standard operating procedures (SOPs) by production personnel rather than concentrating on

process development and understanding.

In 1987, FDA published *Guideline on General Principles of Process Validation* in response to requests from pharmaceutical manufacturers about agency expectations. The 1987 guidance document summarized regulatory requirements and defined process validation as follows:

> ***Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.***

In the time from the publication of the 1987 guidance to its revision in 2011, industry and regulators have generally viewed process validation requirements to include:

- Establishment of highly defined and controlled procedures for all phases of the manufacturing process.
- Verification of acceptable process performance at commercial scale through the production of a certain number of successful consecutive demonstrations or conformance lots. Three lots were typically manufactured.
- Assurance of the consistency of production by putting controls in place, most often procedurally based, that confirm that the methodologies used in the production of subsequent lots are identical to those used in the manufacture of the demonstration lots.
- Development and maintenance of comprehensive training programs to assure the adherence to manufacturing procedures by manufacturing staff
- Monitoring of process performance by periodic revalidation of the process, at pre-defined intervals, to show consistency of production operations over time. Monitoring also confirmed that critical process parameters and critical product quality attributes have not drifted from the values established during the production on the initial demonstration lots.

Process Validation Gaps

The methodologies described above for process validation have been used for at least 25 years. They have provided some assurance of manufacturing consistency and product quality. However, these approaches to process validation are based upon the ability of the manufacturer to consistently and identically reproduce the methodologies and process conditions that were used for the production of the demonstration lots without necessarily defining, understanding, or controlling critical process parameters or critical product quality attributes. One significant flaw in this strategy for process validation is that it does not account for inherent variability of process inputs. Even if any given production run is performed identically to the manufacturing process performed for the demonstration lots, product critical product quality attributes may be inconsistent with those measured during the production of the qualification batches; this could easily be undetected. Additionally, given the normal operating mode of most manufacturing facilities, it is often quite difficult to keep manufacturing personnel trained in executing production procedures identically to those performed for the manufacture of the production qualification lots.

The verification of process performance by the monitoring of critical process parameters and critical product quality attributes for a limited number of production runs and then placing complete confidence in procedural controls also has potential pitfalls. One major issue with this approach is the lack of statistical significance of the data collected. Coupled with limited ongoing monitoring of critical process parameters and critical product quality attributes, this can result in the manufacture, without detection, of product that does not meet the critical criteria established during process validation testing.

Another significant issue with these process validation methodologies is the utilization of time-based revalidation to provide assurance of process consistency over time. Time-based process revalidation is problematic because it is based on an assumption that manufacturing methodologies tested during the production of qualification lots have been strictly performed between initial commercial scale validation and the time of revalidation. Another problematic issue with time-based process revalidation is the premise that there is no significant process input variability that would cause unacceptable changes to process critical control parameters or product critical product quality attributes. This is very risky because if critical failures result from process revalidation testing, product quality and patient safety for an entire time frame of production may be called into question.

New Approaches Afforded by the 2011 FDA *Process Validation Guidance*

While the 2011 *Process Validation Guidance* states that FDA's current thinking on process validation is consistent with the principles first introduced in the 1987 guidance document, the 2011 guidance document redefines process validation as follows:

> ***Process validation is defined as the collection and evaluation of data, from the process design stage through production, which establishes scientific evidence that a process is capable of consistently delivering quality products.***

This new approach defines process validation as a lifecycle rather than a discrete event, as implied in the 1987 guidance document. The new guidance document goes on to say that "process validation involves a series of activities taking place over the lifecycle of the product and process." The new guidance describes process validation activities in three stages including process design, process qualification, and continued process verification. Stated another way, process validation may be defined as:

> **Process Validation = Lab Studies + Development History + Commercial Scale Manufacturing at Target Values + Continuous Process Verification**

The process development, risk management, and quality systems strategies and tactics outlined in International Conference for Harmonisation (ICH) Q8 *Pharmaceutical Development*, Q9 *Quality Risk Management*, and Q10 *Pharmaceutical Quality System* provide additional bases for the concepts outlined in the 2011 guidance document.

Three Stages of Process Validation

The following briefly summarizes each stage of the lifecycle approach to process validation as described in the 2011 *Process Validation Guidance*. Typical expected activities are described.

Stage 1: Process Design

The scientific bases for characterization of the commercial process are developed during this stage of process validation. Process knowledge is gained, documented, and defined through laboratory and pilot scale studies. Sources of variability are identified and understood with respect to product quality and patient safety. Risk assessments are conducted to determine the degree of management and control reasonably required for the sources of variability. Critical process parameters and critical product quality attributes are identified and evaluated through multivariate analyses. The effects of scale are assessed. Design of experiment (DOE) methodologies are used to perform mechanistic modeling to establish process design and operating spaces that confirm acceptable operating ranges for process critical control parameters. Process controls are established to manage critical process parameters and variability of process inputs. As a part of the establishment of design and operating spaces, "worst-case" conditions and parameters are evaluated. The Stage 1 work defines the process in enough detail such that the control of critical parameters and sources of variability is effective at commercial scale. The resulting design and operating spaces are as outlined in ICH Q8 *Pharmaceutical Development*.

Stage 2: Process Qualification

The testing performed in this process validation stage confirms that the process design is capable of manufacturing drug product at commercial scale in accordance with the process critical control parameters and product critical quality attributes developed in Stage 1. Prerequisites to this work include completion of activities in Stage 1, qualification of the facility and critical utilities, qualification of process systems and equipment, validation of sampling and analytical methods, and performance of manufacturing operations by trained staff using approved manufacturing instructions and records.

The process qualification work is documented in a protocol that defines manufacturing conditions, operating parameters, processing limits, and raw material inputs. The protocol also defines the data to be collected and how it will be evaluated, the tests to be performed for each significant process step, acceptance criteria for those tests, a sampling plan including sampling points and numbers of samples, and the frequency of sampling based upon statistical rationale. The criteria that provide rationale to conclude that the process produces a consistent product, including statistical methods to be used in the evaluation of the data and a pre-established plan for addressing deviations and non-conformances, is also included in the protocol. The work is documented in a report summarizing the testing along with the results and their conformance with expectations that confirm consistence of the manufacturing operations. Additional in-process material and product testing beyond for-routine manufacturing operations is expected.

The bases of requirements for the process qualification testing in Stage 2 with regards to process controls and in-process specifications can be found in *Code of Federal Regulations (CFR) Title 21 Part 211.100(a)* and *211.110(b*), respectively.

Stage 3: Continued Process Verification

This stage may be simply described as “maintaining validation” or “maintaining the validated state.” Maintenance activities of Stage 3 should be commensurate with the risk identified for the product and process. Assuming good development of the process, identification of potential variation, and control of same, the manufacturer must maintain the process under control over the entire product lifetime. This control must accommodate expected changes in materials, equipment, personnel, and other changes throughout the commercial life of the product based on risk analysis. Expectations for this stage involve an ongoing program to collect and analyze process data, including process trends, incoming materials, in-process material, and finished products. Data should be analyzed using statistical principles by trained personnel. Procedures defining trending and calculations, evaluation of inter-batch and intra-batch variation, evaluation of parameters and attributes, adjustment of monitoring levels based on the above and timely assessment of defect complaints, out-of-specification (OOS) investigations, deviations, yield variations, and other information are expected. Process improvement changes are expected based on review of process data. Facilities, utilities, and equipment must be maintained to ensure process control.

The purpose of this process validation stage is to verify that the process is in a state of control and is performing consistently and in accordance with the process that was tested during the process qualification stage. Continuous process verification, or ongoing monitoring by means of process analytical technology (PAT), is desirable and highly recommended. Detection of deviations or excursions from the operation of the qualified process is essential to effectively perform continued process verification. This is done by collecting and analyzing process information in real-time, especially critical process parameter and critical product quality attribute data, to assess process performance and to make real-time process corrections, as required, to assure that a consistent product is produced from each manufacturing run. The 2004 FDA *Process Analytical Technologies Guidance* provides a basis for the strategies that support real-time adjustments to manufacturing processes to correct for input variability.

The bases for continued process verification with respect to monitoring production output, performance of statistical analyses on processes, and establishment of statistical quality control criteria can be found in 21 CFR 211.100(a), 21 CFR 211.110(b), and 21 CFR 211.165(b), respectively.

FDA Initiatives

These progressive approaches to pharmaceutical manufacturing science have been proposed prior to the release of the 2011 guidance document. For instance, FDA’s publication titled *Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach*, published in 2004, proposed initiatives to modernize the regulation of pharmaceutical manufacturing and product quality, summarized in the following objectives:

- Encouragement of the adoption of new technological advances by the pharmaceutical industry
- Facilitation of pharmaceutical industry application of quality management techniques, including implementation of quality systems approaches to all aspects of pharmaceutical production and quality assurance
- Encouragement of the implementation of risk-based approaches that focus both pharmaceutical industry and FDA attention on critical areas
- Assurance that regulatory review, compliance, and inspectional policies are based upon state-of-the-art pharmaceutical science
- Improvement of the coordination and consistency of FDA’s drug quality regulatory programs by further integrating

enhanced quality systems approaches into FDA's business processes and regulatory policies concerning review and inspection activities.

Additionally, there have been forward-looking comments from FDA officials regarding the modernization of pharmaceutical manufacturing and regulation. For example, Dr. Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research (CDER), in a statement about goals of pharmaceutical manufacturing, described her vision for pharmaceutical production as, "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight." Dr. Woodcock has also stated that FDA wants pharmaceutical manufacturers to "own quality" by establishing metrics for real-time monitoring and statistical analyses of process critical control parameters and critical product quality attributes. The pathway to these goals is embodied in the principles and practices discussed in the 2011 *Process Validation Guidance*.

Summary

The 2011 *Process Validation Guidance* modernizes concepts of process validation to encompass a lifecycle approach that is risk-based. The lifecycle approach encompasses process development, process verification at commercial scale, and continued process monitoring. Process development activities define the scientific bases for the process, characterize and evaluate sources of variability, establish design and operating spaces that can be scaled, and identify critical process control parameters and critical product quality attributes based upon DOE-based studies. The guidance document also addresses qualification of the process at commercial scale based upon process knowledge established during the process development stage. Additionally, the guidance document provides a pathway to consistent process performance through continued process verification by collection and statistical evaluation of critical process data coupled with trend analysis and real-time process correction.

The principles outlined in the new guidance document provide the bases for a much higher level of process consistency, product quality, and patient safety through better process development, more comprehensive process understanding and monitoring, and assurance of process operation within established design and operating spaces through continued process verification. These practices make good business sense as they will enable the operation of optimized processes that provide for lower costs of goods through more efficient resource allocation and fewer process deviations, excursions, and failures.

General References

Code of Federal Regulations, Title 21, Food and Drugs Office, Part 211.

FDA, *Guidance for Industry Process Validation: General Principles and Practices* (Rockville, MD, Jan. 2011).

FDA, *Guideline on General Principles of Process Validation* (Rockville, MD, Jan. 1987).

FDA, *Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach* (Rockville, MD, Sept. 2004).

FDA, *Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (Rockville, MD, Sept. 2004).
