PharmaSys

Compliance & Validation

# FDA Guidance for Industry

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# Process Validation: General Principles and Practices

**A PharmaSys, Inc. White Paper**

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## 1. Introduction:

The recent publication of the FDA's 2008 draft guidance on process validation demonstrates the agency's forward thinking regarding the lifecycle approach to product and process development and validation, as well as their recent emphasis on the use of risk assessment and quantitative statistics. This guidance is intended to replace the guidance published in 1987 and will provide the pharmaceutical industry the ability to create their own validation programs that are better tailored to their specific area of manufacture. Some other significant change in the draft guidance is that medical devices are no longer included, and the revised guidance is more specifically geared toward process validation only since process automation and computer system validation are now covered under a different FDA guidance documents.

To view FDA's draft guidance titled, ***Guidance for Industry: Process Validation: General Principles and Practices***, select the following webpage: http://www.fda.gov/CDER/GUIDANCE/8019dft.htm.

## 2. What is Validation

The 1987 guidance on process validation described validation as a qualification activity which should take place at the conclusion of product development and at the beginning of commercial production. This guidance required revalidation if there was a change encountered in either the raw materials, process, equipment, or packaging. This guidance also made allowances for the prospective and retrospective validation. The definition in the 1987 guidance states that 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 attributes (FDA, CDER, CBER, CDRH, 1987)."

The 2008 guidance defines validation as "The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products (FDA, CDER, CBER, CVM, 2008)." Although the general definition of validation remains the same, the general approach to obtaining a validated status has significantly changed. This draft guidance views validation as a lifecycle process in which commences in product development or the design phase, is heightened in the documentation and CGMP requirements during the qualification phase, and never has a defined endpoint as continued process verification must be considered in the evaluation of the process maintaining a validated state. The terminology of retrospective validation has been completely removed from the guidance.

## 3. Worst-Case

The 1987 guidance states that all equipment and process validation studies should consider and use worst-case conditions to challenge the operating ranges. Worst-Case is defined as "A set of conditions encompassing upper and lower limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure (FDA, CDER, CBER, CDRH, 1987)." There is also some references that the variability within and between batches should be evaluated to determine the inter and intra-batch variability. This has classically been a topic of debate in the industry. In order to quantitatively determine the variability of a process, statistical techniques must be employed. If the inputs to the process are continually changing, the statistical analysis of inter-batch variability cannot be accurately performed. In order to create a valuable quantitative statistical analysis of the variability of a process, the known variables in the process must be controlled as much as possible.

The term "worst-case" was removed from the new draft guidance and line 464 states that "PQ lots should be manufactured under normal operating conditions (FDA, CDER, CBER, CVM, 2008)." This change in thinking is also supported by the statement "It is not a regulatory expectation that the process be developed and tested until it fails, but rather that a process be controlled within commercial manufacturing conditions. Including those combinations of conditions posing a risk of process failure (FDA, CDER, CBER, CVM, 2008)." .This change in approach allows quantitative statistics to be more functionally deployed in the development and execution of validation efforts. The 2008 draft guidance makes specific reference that the impact of certain variables in the process should be supported with development documents or other process studies. These inputs to the process should be identified through process risk analysis, then tested and effects quantified as much as possible through Design of Experiments or other sound scientific studies. The qualification stage of the validation is designed to verify that the process can be maintained in a controlled state, rather than verify that the process can be stressed to certain limits.

## 4. Process Analysis

The 1987 guidance states that "In most cases, end product testing plays a major role in assuring the quality assurance goals are met, i.e. validation and end product testing are not mutually exclusive (FDA, CDER, CBER, CDRH, 1987)." The 2008 draft guidance states "Quality cannot be adequately assured merely by in-process and finished product inspection or testing (FDA, CDER, CBER, CVM, 2008)." This updated thinking is further supported by the statement "we strongly recommend the firms employ objective measures (e.g. statistical metrics) wherever feasible and meaningful to achieve adequate assurance (FDA, CDER, CBER, CVM, 2008)" and "PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance (FDA, CDER, CBER, CVM, 2008)." These quotations highlight the FDA's expectation that more than just in-process and final product testing will be required

to validate a process. Many in-process and final product testing procedures already incorporate statistical measures and replicate testing, but there will be an expectation moving forward to provide enough data to demonstrate the capability of the process and not merely the acceptability of the end product. There is also a stronger emphasis on the development and deployment of process controls. Since 1987 there have been significant improvements in process automation and the ability to control process variables through Process Analytical Technology (PAT) and automated PID control loops on process equipment. Process control strategies should be developed early in the design phase such that process equipment can be purchased which can adequately control critical process variables through automation and that automation should be a major focal point in the equipment and utility qualifications.

## 5. Revalidation vs. Continued Process Verification.

Revalidation was a term used in the 1987 guidance to define qualification activities that were performed following changes in a process, equipment, or raw material. The new draft guidance covers all of these types of changes through ongoing process verification. Process knowledge gained during process development or scientific studies performed prior to implementing a change to a process can support the implementation of a change without revalidation. The continued process verification should be designed such that data from in-process, final product, and critical equipment parameters are continually evaluated for process changes or process drift. Procedures must be in place which "guard against overreaction to individual events as well as against failure to detect process drift (FDA, CDER, CBER, CVM, 2008)."This process helps safeguard and process against sources of variation which may not have been identified during the original process development. As mentioned in the previous section, if these variables are identified early in the development, equipment can be designed such that critical data is automatically written to a database and analyzed by a qualified person or computer system. This data will then also be available in electronic format to be evaluated by statistical techniques for troubleshooting or investigations.

## 6. Special Circumstances

Many manufacturers have adopted the practice of matrix validation and concurrent release of product during validation activities. The new draft guidance specifically addresses each of these issues.

Matrix validation is the practice of using a combination of product presentations or equipment to simultaneously validate multiple processes or multiple pieces of equipment. The 1987 guidance warns that "There is an inherent danger in relying on what are perceived to be similarities between products, processes, and equipment without appropriate challenge (FDA, CDER, CBER, CDRH, 1987)." The new guidance has a revised thinking on this topic by stating"Previous credible experience with similar products and processes may also be considered [in determining the PQ approach] (FDA, CDER, CBER,

CVM, 2008)." The draft guidance allows for variation in the design of PQ protocols given that the manufacturer can supply documented evidence that there is enough process understanding to support a given approach to qualification.

The practice of concurrent release is often employed by manufacturers which have a critical supply level or need their initial batches for clinical supply. This practice has been accepted but often frowned upon by regulators. The draft guidance provides a clear FDA thinking on concurrent release during validation. The new guidance states "FDA expects that concurrent release will be used rarely. Concurrent release might be appropriate for processes used infrequently because of limited demand for the product (e.g., orphan drugs), processes with necessarily low production volume per batch (e.g., radiopharmaceuticals, including positron emission tomography drugs), and processes manufacturing *medically necessary* drugs to alleviate a short supply, which should be coordinated with the Agency (FDA, CDER, CBER, CVM, 2008)."

## 7. Conclusion:

Given that this regulatory guidance document has not been revised in 20 years, many of the changes are simple updates to what has become industry standard practice. With the revolution of process automation and company information systems in the last 20 years, most manufacturers have embraced the technology and are already using statistical analysis, for trending, statistical process control, sampling, and final product testing. There have also been multiple other initiatives prior to the release of this draft guidance such as the International Conferences on Harmonization (ICH), Quality by Design (QBD), Good Automation Manufacturing Practices (GAMP), and other FDA guidance documents released for topics such as software validation and PAT. This update was very much needed to baseline the FDA's thinking on how process validation has evolved with the technological revolution of the last 2 decades and how process validation can tie all of these elements together. The draft guidance captures how the industry has adopted a lifecycle approach to product development and validation, how modern risk analysis tools can be used to document a groups thinking on critical process parameters, and how many companies have incorporated six sigma philosophies of process control. The agency has done a very good job of capturing their expectations in this document without overburdening manufacturers with requirements which may not apply to all products. They have also opened the door so that companies can create a new standard of industry best practice by embracing the ability to abandon traditional validation practices and utilize new statistical tools to qualify a process.