



White paper:

FDA Guidance for Industry Update – Process Validation

In January 2011, the FDA released the final version of its long-awaited update to its Process Validation Guidance for Industry. Since then, the guidance has fueled international debate by suggesting significant changes to process validation strategy, urging the implementation of a continuous improvement process, as opposed to strict adherence to previously established operating procedures.



This document was prepared in February 2016, any content including links and quoted regulation may be out of date. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net.

©2016 PharmOut. This document has been prepared solely for the use of PharmOut and its clients. Copying is prohibited.

MKT_TMP200_01_r06

Introduction

The United States Food and Drug Administration (FDA) is responsible for assuring the safety, efficacy, and security of products sold in the USA in the categories of human and veterinary drugs, biological products, medical devices, cosmetics, and products that emit radiation. To facilitate this purpose, the FDA issues guidance documents for auditors and industry to help define the practical expectations of meeting the US GMP regulations.

In January 2011, the FDA published an updated guidance entitled *Guidance for Industry - Process Validation: General Principles and Practices*. This document replaces the FDA's 1987 guidance document, *Guideline on General Principles of Process Validation*.

The 1987 document was written when process validation was a relatively new concept to the industry, which has now evolved in the 20+ years between the publications. The new version brings the guidance document into the 21st century by including evolutionary developments, as well as introducing the newest concepts in process validation.

Unlike the Codes of Federal Regulations (CFR), FDA guidance documents are not legally binding, and alternative approaches are acceptable provided they satisfy the requirements of the applicable regulations. They do, however, provide the best information on the current thinking of the regulator, and following them goes a long way to ensuring compliance.

Who is affected by the changes?

Manufacturers will be directly affected by the changes if they sell products into FDA regulated markets in the following categories:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Drug constituent of a combination drug/device

Both finished product and active pharmaceutical ingredient (API) manufacturers are affected.

While not directly affected, manufacturers of products in the above categories who are not currently regulated by the FDA can still benefit from this new guidance, which represents up-to-date thinking from one of the world's key regulators.

Manufacturers of the following product types are specifically excluded from the scope of the guidance. Where alternative guidance or regulation is used by the FDA, it has been specified:

Product Type	Relevant Guidance/Regulations
Type A medicated products (articles and feed) for animal use	NA
Medical devices	Global Harmonisation Task Force SG3/N99-10: Quality Management Systems – Process Validation Guidance ed. 2 (2004)
Dietary supplements	NA
Human tissue	FDA Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation (March 2002)

What are the key changes in the new guidance?

The updated guidance is virtually a complete rewrite of the 1987 document. There is very little retained wording from the original, although the general intent of the documents is similar. In saying this, there are several key points of difference, from the formal definition of process validation, to emphasis on product life cycle and risk management concepts. The key differences are explained below.

Process Validation Definition

For years, many in the industry have been able to recite the FDA's 1987 definition of process validation. The 2011 guidance has updated the definition and shifted the focus from documentation to "scientific evidence" throughout the product life cycle.

1987 Definition	2011 Definition
<i>"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"</i>	<i>"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"</i>

In the past, process validation emphasis has been on collecting large quantities of data from validation batches, leading to a perception of process validation as largely a documentation exercise.

The updated approach requires the manufacturer to collect data throughout the product life cycle and evaluate it scientifically and assess if it supports a quality process.

Focus on alignment with ‘product lifecycle’

The FDA is a party to the International Conference on Harmonisation (ICH) for human pharmaceuticals. The ICH publishes guidelines on quality, safety, efficacy and multidisciplinary topics. Quality guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) are directly referenced in the new FDA guideline.

The FDA has also referenced the ASTM E25001, where the focus has shifted from validation of individual parts of a process, to a collective ‘process validation’ effort that takes a more holistic view of process, highlights the GxP critical parts of the process and focuses efforts and resources on the most critical aspects.

Of specific importance to the validation guidance is the concept, detailed in these quality guidelines, of ‘product lifecycle’. The new guidance has been aligned with this concept, giving the following three-stage approach to process validation:

- Stage 1 – Process Design
- Stage 2 – Process Qualification
- Stage 3 – Continued Process Verification.

The guidance provides specific examples of what sort of validation activities are expected at each stage. Each stage is briefly summarized in the table below.

Stage	Intent	Typical Activities
Process Design	<p>To define the commercial process on knowledge gained through development and scale up activities</p> <p>The outcome is the design of a process suitable for routine manufacture that will consistently deliver product that meets its critical quality attributes</p>	<p>A combination of product and process design (Quality by Design)</p> <p>Product development activities</p> <p>Experiments to determine process parameters, variability and necessary controls</p> <p>Risk assessments</p> <p>Other activities required to define the commercial process</p> <p>Design of Experiment testing</p>
Process Qualification	<p>To confirm the process design as capable of reproducible commercial manufacturing</p>	<p>Facility design</p> <p>Equipment & utilities qualification</p> <p>Performance qualification (PQ)*</p> <p>Strong emphasis on the use of statistical analysis of process data to understand process consistency and performance</p>

Stage	Intent	Typical Activities
Continued Process Verification	To provide ongoing assurance that the process remains in a state of control during routine production through quality procedures and continuous improvement initiatives.	Proceduralised data collection from every batch. Data trending and statistical analysis Product review Equipment and facility maintenance Calibration Management review and production staff feedback Improvement initiatives through process experience

* The term “Performance Qualification” or PQ in the new guidance equates to the term “Process Performance Qualification” from the 1987 guidance . This term is analogous with the traditional concept of “process validation”, as multiple batches of product made at commercial scale under commercial manufacturing conditions. It is not the same as the concept of “equipment performance qualification”.

Ramifications of the validation product lifecycle

The life cycle approach to validation has significant impact on manufacturers who previously have seen validation as a discreet effort at the commencement of product commercialization.

For many companies, core validation activities have been IQ, OQ, PQ and 3 process validation batches. The FDA is keen to move firms away from this thinking. Indeed the guidance states:

“Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality.”

Verifying adequate assurance of quality will involve assessment of all three stages described in the guidance. This will significantly increase emphasis on pre- qualification activities such as product development, as well as assessment of procedures for, and results of ongoing process verification.

What has happened to the concept of IQ, OQ and PQ for equipment?

It has widely been recognized that there is no mention of the terms installation, operational or (equipment) performance qualification in the new guidance. Does this mean that equipment IQ, OQ and PQ are no longer required?

The answer is both yes and no! Yes, in that there is no expectation expressed in the guidance for the preparation of three stages of qualification documents for critical equipment. No, in that there is a clear expectation that equipment will be qualified, and that the qualification will include all the aspects that have traditionally fallen into the IQ/OQ/PQ categorization.

The new guidance shifts the focus from completing a suite of qualification documents, to ensuring that equipment and utility qualification activities are appropriate and complete.

While there is now less focus on what equipment qualification activities are called, there is little difference between the requirements of the old and new guides, as illustrated in the table below.

1987 guide	2008 guide
Describes “Installation Qualification” which, in practical terms, refers to IQ, OQ and arguably equipment PQ. The 1987 guide does not mention OQ or equipment PQ.	Describes “Equipment Qualification” which, in practical terms, refers to IQ, OQ and equipment PQ.
Describes “Process Performance Qualification” which, in practical terms, refers to equipment PQ (if not previously covered) and prospective process validation batches.	Describes “Process Performance Qualification” which, in practical terms, refers to prospective process validation batches.

The golden three batches

Although not expressly stated in the old guidance, manufacture of three batches for process validation has become industry standard. For some time now, the FDA has been trying to steer manufacturers away from this thinking, and to be more critical in determining how many batches are required for effective process validation.

The new guidance makes it clear that it is the manufacturer’s responsibility to provide assurance that the process is adequately qualified. The use of statistical methods to provide objective evidence of this is strongly recommended.

In practice, this may mean that 3 batches is sufficient to provide the necessary data, or it may be that more are required (it is unlikely to be less). The manufacturer needs to assess, justify and clearly state those requirements during the preparation of the PQ protocol.

Revision of worst-case concept

The concept of worst-case conditions for process validation was a key theme of the 1987 guidance. The 1987 guidance defines worst-case 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.”

Attempting to cover worst-case conditions in process validation would often mean that parameters applied to validation batches bore little resemblance to the standard conditions. As a result, it has been more common that the worst-case concept is given scant consideration within process validation exercises.

The 2011 guidance has not only removed the concept of worst-case conditions, it has redefined the expectation as follows:

“The commercial manufacturing process and routine procedures must be followed. The PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process.”

The new guidance shifts the responsibility for addressing processing variability to the Process Design stage of validation activities. It is intended that product development studies and risk analysis should address process variability and quantify the effects on the product where possible.

Revision of the revalidation concept

The 1987 guidance included the concept of revalidation of processes when changes to a process are introduced (e.g. changes in formulation, raw material, equipment), or when process variation is detected.

The 2008 guidance has revised this concept with the introduction of Continued Process Verification. This involves the ongoing assessment of process data (in-process, finished product, equipment parameters, etc) against variability limits established during the first two stages of process validation.

The sorts of changes which previously required revalidation may now be adequately addressed through a company's Continued Process Verification procedure, incorporating the use of statistical and qualitative methods, as well as risk assessment. The use of these methods may also provide impetus to re-perform all or parts of stage 2 of validation.

Matrix approach

The 1987 guidance expressly discouraged matrix approaches to process validation, where multiple similar products, presentations or equipment are grouped together within the one validation exercise to reduce the overall testing requirements.

Conversely, the 2011 guidance provides specific acceptance of the practice, stating:

“Previous credible experience with sufficiently similar products and processes can also be considered”.

This methodology will assist firms to obtain sufficient data for statistical analysis, while minimizing the total number of PPQ batches required.

Concurrent & Retrospective validation

The concept of concurrent validation was not included in the 1987 guidance. The new guidance provides information on the precise circumstances under which concurrent release of validation batches is acceptable. These include infrequent product manufacture, necessarily low volume or short shelf-life manufacture (e.g. radiopharmaceuticals) and manufacture of medically necessary products in short supply.

The FDA expects that concurrent validation approaches will be used rarely. If used, the approach must be fully justified and additional expectations for customer feedback and stability are required.

It is clear that the FDA expects that, in normal circumstances, Stage 2 validation (PPQ batches) will be complete and fully assessed before commercialization of product. It can be inferred that business imperatives will not be considered acceptable justification for concurrent validation.

Retrospective validation is not mentioned in the guidance and should not be considered an acceptable approach for planned validation.

Other Changes

Other minor changes include the acknowledgement of some concepts which have gained wide acceptance in industry including:

- Integrated team approach – the guidance strongly recommends input in the validation process from a wide range of disciplines, as well as the full support of senior management
- Process Analytical Technologies (PAT) – the guidance introduces PAT concepts and gives guidance on the role it can play in process validation.

What should you do?

You should review your current validation policies and procedures against the new regulations to determine what extent of change is required. It is likely you will need to consider policy and procedure revision, resourcing and training in order to begin the road to compliance.

As leading compliance experts within Australasia, PharmOut can significantly reduce this effort and allow you to focus on your everyday business operations of making and selling quality products.

References

FDA Guidance for Industry – Process Validation: General Principles and Practices January 2011

FDA Guideline on General Principles of Process Validation – May 1987

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net



PharmOut is an international GMP consultancy serving the Pharmaceutical, Medical Device and Veterinary industries. PharmOut specialises in PIC/S, WHO, United States FDA, European EMA, and Australian TGA GMP consulting, engineering, project management, training, validation, continuous improvement and regulatory services.

Our team includes international GMP experts who have previously held leadership roles within regulatory bodies.

For more information please visit www.pharmout.net or contact us at info@pharmout.net.

PharmOut Pty Ltd, ABN: 85 117 673 766, Unit 10, 24 Lakeside Drive, Burwood East, Victoria 3151.

Ph: +61 3 9887 6412, Fax: +61 3 8610 0169, Email: info@pharmout.net Web: www.pharmout.net

©2016 PharmOut. This document has been prepared solely for the use of PharmOut and its clients. Copying is prohibited.