



White Paper

FDA Guidance for Industry Update - Process Validation

The changing face of Validation; are IQ, OQ and PQ really dead and buried?

In November 2008, the FDA released a draft version of its long-awaited update to its Process Validation Guidance for Industry. The new draft is currently undergoing finalization after public comment and is expected to come into force before the end of 2009.

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In November 2008, the FDA published a draft guidance entitled “Guidance for Industry - Process Validation: General Principles and Practices”. This document, issued for public comment, is intended upon finalization, to replace the FDA’s 1987 guidance document entitled “Guideline on General Principles of Process Validation”. The FDA has indicated an intention for the final document to be published before the end of 2009¹, although a publication date is yet to be formally announced.

The 1987 document was written when process validation was a relatively new concept to the industry and it’s fair to say that the concept has evolved in the 21 years between the publications. The new guidance 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.

¹ Pharmaceutical Engineering, Volume 29, No, 3, May/June 2009

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 2008 draft guidance has updated the definition and shifted the focus from documentation to "scientific evidence" throughout the product life cycle.

1987 Definition	2008 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 for evidence that 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 more 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:

¹ ASTM E2500 – 07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

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

* 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”.

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 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 2008 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

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, was expressly discouraged in the 1987 guidance.

Conversely, the 2008 guidance provides specific acceptance of the practice, stating “Previous credible experience with sufficiently similar products and processes can also be considered”.

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 manufacture (e.g. radiopharmaceuticals) and manufacture of medically necessary products in short supply.

Additional expectations for customer feedback and stability are stated for concurrent validation batches

Retrospective validation is not mentioned in the guidance and is no longer considered acceptable.

Other Changes

Also of note is 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

Draft Status

It is important to note that the November 2008 guidance is currently in draft form and is not yet implemented. A lengthy process of industry feedback and consultation has been underway since the publication and there may yet be significant changes to the final published guidance.

It is reasonable to assume, however, that the key concepts discussed in this white paper will remain in philosophy, if not the specific detail.

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

Title
FDA Guidance for Industry – Process Validation: General Principles and Practices (Draft Guidance) November 2008
FDA Guideline on General Principles of Process Validation – May 1987.

About PharmOut

PharmOut is a boutique consultancy to the Pharmaceutical, Medical Device, and Veterinary drug industries.

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