

## USFDA Guidelines on Process Validation - A Review

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**Abstract:** Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110) and is considered as an enforceable element of Current Good Manufacturing Practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act. The basic principle of Quality Assurance is that a drug should be produced that is fit for its intended use. Process Validation is defined as the assortment and estimation of data, from the process design stage through marketable production, which establishes scientific evidence that a process is capable of consistently delivering quality product. USFDA process validation guideline published in 2011, suggest three stages of validation;

- Process design
- Process qualification
- Continued Process qualification

Before marketable delivery begins, a manufacturer is expected to have stored enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after adequate product and method development, scale-up studies, equipment and system requirement, and the effective accomplishment of the initial conformance batches. Conformance batches (sometimes referred to as "validation" batches and demonstration batches) are prepared to validate that, under standard conditions and defined ranges of effective parameters, the commercial scale process appears to make adequate product. Prior to the manufacture of the conformance batches the manufacturer should have identified and controlled all critical sources of changeability. A validated manufacturing process has a high level of precise assurance that it will constantly produce acceptable products.

**Keywords:** Commercial manufacturing process, Concurrent release, continued process verification, Performance indicators, Process design, Process qualification, Process validation.

### Introduction:

**2011 Definition:** "The collection and assessment of data, from the process design stage all the way through production, which establishes logical indication that a process is capable of consistently delivering quality products"<sup>[1]</sup>

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century - A Risk Based Method," particularly with regard to the use of industrial advances in pharmaceutical manufacturing, as well as implementation of new risk controlling and quality system tools and concepts.

## Approach to Process Validation:

**Stage 1: Process Design:** The marketable manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities<sup>[2]</sup>

**Stage 2: Process Qualification:** Throughout this stage, the method design is estimated to determine if the process is capable of reproducible marketable business.<sup>[3]</sup>

**Stage 3: Continued Process Verification:** Constant assertion is gained during routine production that the process remains in a state of control.<sup>[3]</sup>

### Stage1: Process Design:-

*Constructing and Apprehending Process Knowledge and Understanding:*

- The functionality and limits of commercial manufacturing equipment should be considered in the process design.
- Design of experiments (DOE) studies can help to develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs and the resulting outputs.
- Risk analysis tools can be used to display possible variables for DOE studies .

*Creating an Approach for Process Control:*

- Controls and consist of material analysis and equipment monitoring at significant.
- hese controlled records are established in the Master formula records and control processing points.
- Trecords.
- The calculated commercial production and control records should be carried forward to the next stage for confirmation.

### Stage 2: Process Qualification:-

**Element (1): Design of a facility and qualification of utilities and equipment**

- Ensure qualification of facility, utilities and equipment is completed & documented prior to initiate process qualification.

**Element (2): Process Performance Qualification (PPQ)**

- The PPQ combines the actual facility, utilities, equipment's and the trained personnel with the commercial manufacturing controls.
- A company must successfully complete PPQ before commencing commercial distribution of the drug product.
- To understand the marketing process adequately, the manufacturer will need to consider the effects of scale.
- Strongly recommend firms employ objective measure (e.g. Statistical Metrics) wherever feasible and meaningful to achieve adequate assurance.
- The increased level of inspection, testing, and sampling should continue through the process verification stage as correct, to establish levels and occurrence of routine sampling and checking for the particular product and process.
- Considerations for the duration of the intensified sampling & checking period could include (not limited to):
  - ✓ Volume of production
  - ✓ Process Complexity
  - ✓ Level of process understanding
  - ✓ Experience with similar products and process

**PPQ Protocol:**

**Some of key elements to be captured in validation protocol as detailed below;**

<b>Key Elements</b>	
➤ Manufacturing conditions, including operating parameters, processing limits, and raw material inputs	➤ Compression RPM (low, medium, target) is not recommended in protocol.
➤ Test to be performed and acceptance criteria for each significant processing step	➤ Batch records does not provide any detail about the RPM which are not worked
➤ Sampling plan (sampling points, number of samples, frequency of sampling)	➤ Currently followed
➤ No. of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches	➤ Sampling points not pictorially depicted (however SOP reference is mentioned)
➤ Status of the validation of analytical methods used is measuring the product	➤ Between the batches?
➤ Provision for addressing deviations	➤ Currently not followed
➤ Approval of the protocol by appropriate department	➤ Currently followed
	➤ Currently followed

- Validation shall be executed as per validation protocol duly approved by Quality unit.

**PPQ Report:**

- To state a clear conclusion as to whether the data indicates the process meets the conditions established in the protocol. If not the report should state what should be accomplished before such a conclusion can be reached.
- This conclusion should be based on entire compilation of knowledge and information gained from the design stage through the PPQ stage.

**Stage 3: Continued Process Verification:-<sup>[4]</sup>**

- To confirm that “the process remains in a state of control during commercial manufacture.”
- An ongoing process to collect and analyze product and process data that relate to product quality must be established.
- The results obtained should be statistically trended and reviewed by trained personnel.
- Recommend that a person with suitable training in statistical process control techniques develop the data collection plan and statistical methods.
- Good process design and development should anticipate significant sources of variability and establish appropriate detection, control and or qualification schemes, as well as suitable alert and action limits.
- Study of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program.
- Deviation can be detected by the timely assessment of
  - Defect complaints
  - OOS findings
  - Process deviation report
  - Process yield variations
  - Batch record & reports

- Manufacture line operatives and quality unit staff should be encouraged to provide feedback on process performance.
- Quality unit meet periodically with production staff to evaluate data, discuss possible trends and coordinate any correction or follow-up actions by product.
- Data collected during this stage might recommend ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions, process controls, etc.
- Well justified rationale for the change, implementation plan, quality unit approval before implementation.

#### **Concurrent Release of PPQ batches:**

- FDA expects that simultaneous release will be used rarely.
- Circumstances and reasoning for simultaneous release should be fully described in the PPQ protocol
- System of careful oversight of the distributed batch to facilitate rapid customer feedback.

#### **VI. Documentation:<sup>[5]</sup>**

Documentation at each stage of the process validation lifecycle is essential for effective statement in difficult, lengthy, and multidisciplinary projects. Documents is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle.

The degree and type of records required by CGMP vary during the validation lifecycle. Records requirements are greatest during Stage 2, process requirement, and Stage 3, continued process confirmation. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see §§ 211.22 and 211.100).

<b>1987 Definition</b>	<b>2011 Definition</b>
“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”	“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”

This table gives conventional and latest definition of process validation.

#### **Conclusion:**

By doing validation as per USFDA process validation guideline, product and process understanding will be improved and also reduction in waste, rejections, lead time and any other failures. This guideline also helps for continual improvement of validation process through the product life cycle.

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