Process Validation Vs Process Qualification - An Overview

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***Abstract* —** *Process qualification is the qualification of manufacturing and production processes to confirm they are able to operate at a certain standard during sustained commercial manufacturing. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Validation studies are conducted in accordance with pre-defined protocols. Written reports summarizing recorded results and conclusions are prepared, evaluated, approved and maintained. Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. Validation is the art of designing and practicing the designed steps alongside with the documentation.*

Keywords — *Validation, Qualification, Process, Quality.*

INTRODUCTION

PROCESS VALIDATION:

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

PROCESS QUALIFICATION:

New FDA (2011) guidance effective from Oct 15, focused on product quality through process understanding & control:

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

Process qualification is the qualification of manufacturing and production processes to confirm they are able to operate at a pre-determined specification during sustained commercial manufacturing.

Data of CPP (Critical process parameters) must be recorded and ensure CQA (critical quality attributes) throughout production. This may include testing equipment at maximum operating capacity to show quantity demands can be met. Once all processes have been qualified the manufacturer should have a complete understanding of the process design and have a framework in place to routinely monitor operations. Only after process qualification has been completed can the manufacturing process begin production for commercial use. It should be noted that equally important as qualifying processes and equipment is qualifying software and personnel. A well trained staff and accurate, thorough records helps ensure ongoing protection from process faults and quick recovery from otherwise costly process malfunctions.

Process qualification should cover the following aspects of manufacturing:

Facility
Utilities
Equipment
Personnel
End-to-end manufacturing
Control protocols and monitoring software.

"Process qualification is the second stage of Process Validation."

PROCESS VALIDATION APPROACHES.

- **Prospective:** Validation to be completed prior to distribution of a finished product. (Three consecutive successful production batches considered before commercial distribution)
- **Concurrent:** Validation of the processes during routine production.*(normally Three batches considered but batches produced infrequently &batches can be released based on thorough monitoring & testing of Drug substance or Drug Product)*
- **Retrospective:** Validation of processes that are stable and in routine use, which have not undergone a formally documented validation process. For which historical data may be utilized to provide necessary documentary evidence that the process is validated considering

a) Critical Quality Attributes (CQA) & Critical Process Parameters have been identified (CPP)
b) Appropriate in-process acceptance criteria & controls have been established
c) These have not been significant process / product failure attributes to causes other than Operator error or equipment failure unrelated to equipment suitability
d) Impurity profile have been established for existing process
(*Normally 10 to 30 batches)*

- **Revalidation:**
  - ❖ A periodic revalidation is must (Once in a 5 years) – VMP
  - ❖ Due to Key Changes, can Impact on Product Quality & Patient safety such as but not limited to
    - i) changes in CQA / CPP / Manufacturing Process
    - ii) changes in Manufacturing formula or in Specifications
    - iii) changes in manufacturing equipment's (principle of operations)
    - iv) changes / modification in facility
    - v) Others

PROCESS VALIDATION APPROACHES (AS PER USFDA GUIDELINE).

Three stages as mentioned below.

Stage 1: Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development

Stage 2: process qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial

Stage 3: Continued Process Verification Ongoing assurance is gained during routine production that the process remains in a state of control

STAGE 1 – PROCESS DESIGN:

The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

- "Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities" (QbD)(lab, engineering, pilot, small scale & commercial scale studies.)

- Design a process suitable for routine commercial manufacturing.

a) Building and Capturing Process Knowledge and Understanding

- Define quality attributes (Risk Assessment, selecting parameters, and environment? – CPP)
- General manufacturing pathway - Modelling (predicting and confirming the process/ parameter behaviour – (CQA)
- Documentation & Reviews (Shall reflects basis of design)

b) Establishing a Strategy for Process Control

- To reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.
- Use of PAT (Process Analytical Tool)
- The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.
- Regulatory constrains

STAGE 2 – PROCESS QUALIFICATION

During this stage, the process design is evaluated to determine if the process design is capable of reproducible commercial manufacturing. Including qualification of the facility, utilities & equipment's Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing" (for CPP & CQA)

This stage has two elements:

a) Design of the facility and qualification of the equipment and utilities (DQ/IQ/OQ/PQ)

- Proper design of a manufacturing facility is required under cGMP regulations on *Buildings and Facilities*. (URS/DQ/IQ/OQ/PQ/Requalification strategy & respective SOPs)

- *Qualification* of utilities and equipment are suitable for their intended use and perform properly. (including Specifications)

- Shall be completed satisfactorily before manufacturing of product at the commercial scale. (completion of Report)

b) Process Performance Qualification (PPQ) (including protocols & Report)

Successful completion of this stage 2 is necessary before commercial distribution. For all activities during the Process Qualification – cGMP procedures must be followed.

This is second element of stage 2

- The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches.

- Successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

- A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug substance or product

- PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production.

- The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch

STAGE 3 – CONTINUED PROCESS VERIFICATION:

Maintenance continuous verification & process improvement ongoing assurance that routine production process remains in a state of control Assessed by collecting & monitoring information during commercialization.

Many activities occur in more than one stage (think lifecycle...)

"**Continued Process Verification – Assurance**

- The goal of this stage is to continually assure that the process remain in a state of control during commercial manufacture.
- In 1987 it was called Revalidation or Requalification.
- In 2011 a more broad focus should be applied.
- An ongoing program must be established to collect and analyse *product and process data*.
- The information collected should verify that the Critical Quality Attributes are being controlled throughout the process.
- Once established, the equipment qualification status must be maintained through:
  - Routine monitoring
  - Maintenance
  - Assessed periodically to determine whether re-qualification should be performed.
- On-going Sampling is part of the program:

- **In the first phase of commercial production.** Continued monitoring and/or sampling at the level established during the process qualification stage.
- **In the second phase of commercial production.** When sufficient data is available to generate significant variability estimates and the variability is known. - Sampling and/or monitoring should be adjusted to a statistically appropriate and representative level.

DEFINITION OF CPV/CPP/CQA

- **Continued process verification (CPV) :**
  Documented scientific evidence that the process remains in a state of control during commercial manufacture.

- **Critical process parameter (CPP)** :
  A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces desired quality.

- **Critical quality attribute (CQA)** :
  A physical, chemical, biological or microbiological property or characteristic of materials or

products that should be within an appropriate limit, range or distribution to ensure the desired product quality

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CONCLUSIONS

Data covering critical process parameters must be recorded and analyzed to ensure critical quality attributes can be guaranteed throughout production. This may include testing equipment at maximum operating capacity to show quantity demands can be met. Once all processes have been qualified the manufacturer should have a complete understanding of the process design and have a framework in place to routinely monitor operations. Only after process qualification has been completed can the manufacturing process begin production for commercial use. It should be noted that equally important as qualifying processes and equipment is qualifying software and personnel. A well trained staff and accurate, thorough records helps ensure ongoing protection from process faults and quick recovery from otherwise costly process malfunctions. In many countries qualification measures are also required, especially in the pharmaceutical manufacturing field. Process qualification should cover the following aspects of manufacturing: Facility, Utilities, Equipment, Personnel, end-to-end manufacturing And Control protocols and monitoring software. Process qualification is the second stage of Process Validation. A vital component of process qualification is Process Performance Qualification Protocol. PPQ Protocol is essential in defining and maintaining production standards within an organization.

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