REVIEW ARTICLE

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

The New Paradigm of Pharmaceutical Process Validation - Continuous Process Verification

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Received: 13.06.2018 Revised: 17.06.2018 Accepted: 25.06.2018 Published: 30.06.2018

ABSTRACT: Modern regulatory requirement about the pharmaceutical process validation is the process should remain in the state of control throughout the product life cycle. To achieve that state of control of the process, a thoughtful process design should be incorporated from the process during initiation and scale-up till the product life cycle. Thus the new pharmaceutical process validation concept came in the picture. Now expectation of the regulatory agencies is to follow this new concept. Continuous Process Verification during the product lifecycle is a new mandatory requirement and according to the new EMA draft is applied regardless of the approach that you have selected to process validation. "Subsequent to Process Validation and during commercial manufacture, companies should monitor the product quality to ensure a state of control is maintained throughout the commercial part of the product lifecycle". Continuous Quality Verification (CQV) as an approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted (as necessary). The continued Process Verification –Third stage process validation lifecycle after design and qualification. The goal is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture. FDA recommends continued monitoring and sampling of process parameters and quality attributes at the level established during PPQ until sufficient data is available to generate variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level.

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Keywords: Continuous process verification, CPV, Life cycle approach, Verification of an established process, On-going process verification.

INTRODUCTIONS:

FDA issued a guidance document Process Validation: General Principles and Practices, which emphasized the principles of 'continued process verification' (CPV) as a crucial element in the lifecycle management of a product. Similar guidance followed later from the European Medicines Agency. Since then, the expectation has been that validation should be an ongoing effort.

Through regular reporting over multiple batches, CPV encourages the collection of more data, linked to process knowledge, providing a vast amount of information about the process [1].

This information enables necessary changes to the process to be made without significantly impacting production of commercial supply and bestows a high level of confidence in the consistency of the process and, by extension, the product, ensuring that every aspect of the process remains in a constant state of control. Both industry and regulators seem to agree that CPV is necessary for ongoing quality assurance, and the industry is aware that regulators expect manufacturers to implement CPV in order to be in compliance. Understanding how to implement CPV is another matter. Regulatory guidance documents—out of necessity—lack detail, providing scope for companies to implement their own strategies that work for their operations. If every biopharmaceutical company forges ahead with its own interpretation of the guidance, however, no one benefits. Inspections would be time-consuming, possibly resulting in numerous observations, and manufacturers would feel like they were taking random stabs in the dark trying to guess what inspectors might be thinking [1].

To enable continuous process verification, companies should perform, as extensive inline, online or atline controls and monitor process performance and product quality on each batch. Relevant data on quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end points, and assessment of CQA and critical process parameter (CPP) trends. Process analytical technology (PAT) applications i.e. NIR spectroscopy with or without feedback loop (e.g. end point determination of blend homogeneity, determination of granules surface area, determination of content uniformity with large sample size) and Multivariate Statistical Process Control (MSPC) can be viewed as enablers for continuous process verification [2].

Sufficient knowledge and understanding of the process is required in order to support continuous process verification. However, the scope and extent of continuous process verification will be influenced by a number of factors including:

- Prior development and manufacturing knowledge from similar products and/or processes.
- The extent of process understanding gained from development studies and commercial manufacturing experience.
- The complexity of the product and/or manufacturing process.
- The level of process automation and analytical technologies used.

The data generated during continuous process verification at production scale should be available at the site for inspection. The applicant should define the stage at which the process is considered to be under control and the validation exercise completed prior to release of the product to the market, and the basis on which that decision will be made. The discussion should include a justification for the number of batches to be used based on the complexity and expected variability of the process and existing manufacturing experience of the manufacturing site. Continuous process verification would be considered the most appropriate method for validating continuous processes. Continuous process verification can be introduced at any time in the lifecycle of the product. It can be used for the initial commercial production, to re-validate commercialized products as part of process changes or to support continual improvement [1,2].

REGULATORY CHALLENGES:

Process validation for drugs is a legally enforceable requirement under section 501(a)(2)(B). Process validation is required by GMP regulations in parts 210 and 211. Regulatory requirements require manufacturers to design a process, including operations and controls, which results in a product meeting its Critical Quality Attributes. 211.110(a), Sampling and testing of in-process materials and drug products, requires that control procedures " be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in process material and the drug product [3].

211.180(e) requires that information and data about product quality and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. 211.180(e) evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate and prevent problems so that the process remains in control. An ongoing program to

collect and analyze product and process data that relate to product quality must be established [3,4].

The definitions of the continuous process verification as per the regulatory.

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.(ICH Q8)3.

Continued Process Verification:

A stage (Stage 3) of the Process Lifecycle, after Performance Qualification (Draft FDA Guide).

Continuous Quality Verification (CQV):

It is described as an approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary" (ASTM).

cGMP requirements:

The collection and evaluation of information and data about the performance of the process will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180 (e).

PROCESS APPROACH:

Process Validation (As per FDA):

The Process validation 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 products [5].

Process Validation (As per Europe):

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes. The goal of CPV is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause [5,6].

The continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. We recommend that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or undesirable process variation, and coordinate any correction or follow-up actions by production [7].

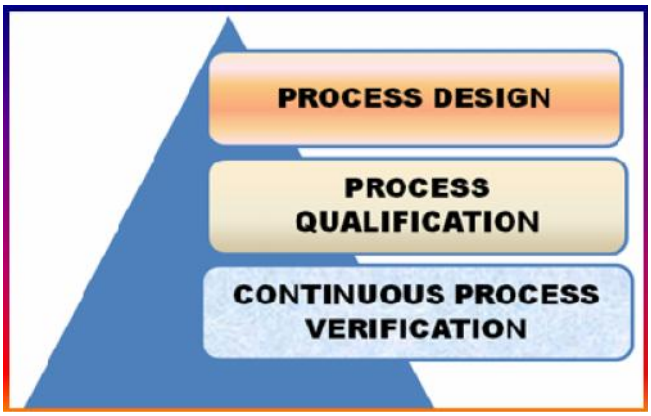

Fig 1. Product life management.

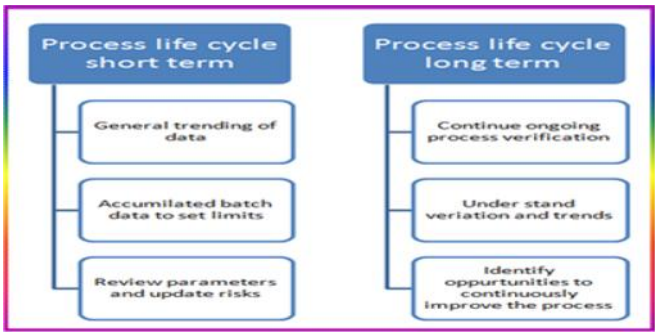

Fig 3. Product life cycle (Short term and Long term strategies).

Requirement of Continued Process Verification [7,8]:

- System or systems for detecting unplanned departures from the process (CPP's/CQA's?) as designed.
- Adherence to GMP requirements.
- Data collection plan and procedures.
- Procedures that describe the process for measuring and evaluating process stability and capability.
- Quality oversight.

The current regulatory requirement for the process validation approach categorized in three stages such are Process Design, Process Qualification and Continued process verification.

Stage 1 - Process Design:

The commercial manufacturing process is evaluated to stage based on knowledge gained through development and scale-up activities.

Stage 2 - Process Qualification:

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 - Continued process verification:

Ongoing assurance is gained during routine production that the process remains in a state of control.

Ongoing program to collect and analyze product and process data that relate to product quality.

The entire process is intended to accomplish the following [9,10]:

- Allow detection of undesired process variability.
- Identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems.
- Collect and analyze product and process data that relate to product quality.
- Data collected should include process trends, quality of incoming materials or components, in-process material, and finished products.
- Information collected should verify that the quality attributes are being appropriately controlled throughout the process.
- Procedures should describe how trending and calculations are to be performed.
- Procedures should be capable to guard against overreaction to individual events.
- Procedures should be capable to prevent failure to detect unintended process variability.
- Data collected should include the following: Relevant process trends, Quality of incoming materials or components, in-process material, and finished products.
- Data should be statistically trended and reviewed by trained personnel.
- Continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates.
- Variation can be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Quality unit should meet periodically with production staff to evaluate data, discuss possible trends or undesirable process variation, and coordinate any corrective actions.
- Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control.
- Equipment and facility qualification data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification.
- Maintenance and calibration frequency should be adjusted based on feedback from these activities Process variability should be periodically assessed and monitoring adjusted accordingly.
- Production line operators and quality unit staff should be encouraged to provide feedback on process performance. Process variability should be periodically assessed and monitoring adjusted accordingly.
- Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield

variations, batch records, incoming raw material records, and adverse event reports.

- Production line operators and quality unit staff should be encouraged to provide feedback on process performance.

PARAMETERS TO BE INCLUDED IN CONTINUOUS PROCESS VERIFICATION:

Principles outlined in the ICH guidelines Q8, Q9, Q10 and Q11 **[7-9, 22]** provide the basis for the methodology used for this case study, even though Q11 was published after the A-Mab case study. All types of parameters should be considered for inclusion in CPV. Typically those included will be weighted more in favor of CPPs and WC-CPPs because of their importance to the control strategy. Parameters to be included should be based on the current understanding of the manufacturing process and may be subject to change over time. Parameter types described in A-Mab study are as follows [11,12]:

Critical and well controlled Process Parameter (CPP and WC-CPP):

CPPs and WC-CPPs are process parameters whose variability impact a critical quality attribute and should be monitored or controlled to ensure the process achieves the required product quality.

- A WC-CPP has a lower risk of falling outside the specified limits.
- A CPP has a higher risk of falling outside the specified limits.

The assessment of risk is based on a combination of factors that include severity of impact to quality, equipment design considerations, process control capability and complexity, the size and reliability of the proven acceptable range and/or design space, ability to detect/measure a parameter deviation, etc.

Key Process Parameter (KPP):

An adjustable parameter (variable) of the process that ensures operational reliability when maintained within a narrow range. A key process parameter does not affect critical product quality attributes but rather impacts process consistency.

General Process Parameter (GPP):

An adjustable parameter (variable) of the process that does not have a meaningful impact on product quality or process performance.

Establishing strategy of process control:

Control Strategy – A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

Fig 4. Control Strategy for Continuous process verification.

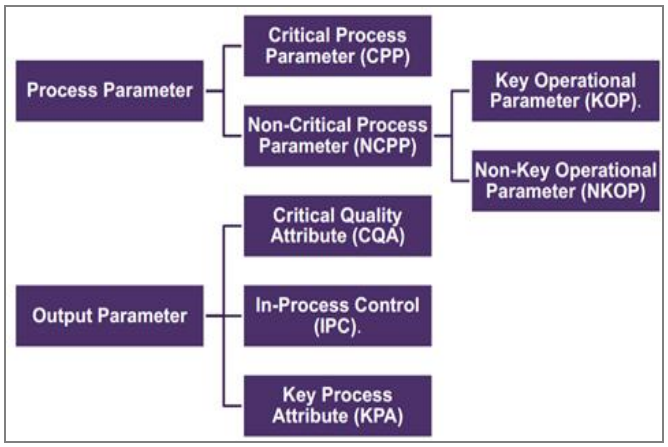

Fig 5. Control strategy – Input and output parameters.

The controls can include parameters and attributes related Effective process validation contributes significantly to assuring drug quality. The basic principle of Quality Assurance is that a drug product should be produced that is fit for its intended use. The principle incorporates the understanding that the following conditions exist [13].

1) Quality, Safety and efficacy are designed or built in to the product.

2) Quality cannot be adequately assured merely by in-process and finished product inspection and testing.

- Process and product monitoring.
- Selection of Attributes and Parameters to be monitored.
- Data Analysis and Review.
- Control Charts.

Manufacturing processes that are stable and capable over time can be expected to to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls,

finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10) consistently produce product that is within specifications and thereby cause no harm to patients due to nonconforming product. A stable manufacturing process is a process that is in a state of statistical control as each batch of tablets is being produced and as batches of tablets are produced over time.

A process in a state of statistical control consistently produces product that varies within the process control limits; typically set at the process average (X-Bar) plus and minus three standard deviations (SD) of the process variation for the parameter of interest. Separate control limits are set for each parameter (e.g., tablet thickness and hardness). Any sample value that falls outside of these limits indicates that the process may not be in a state of statistical control [13,14].

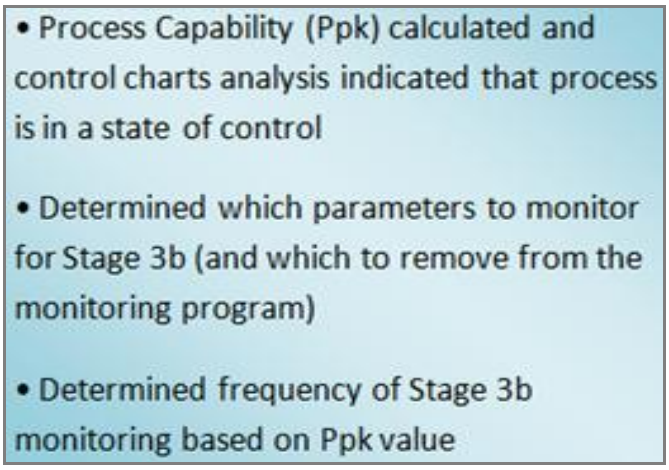

Fig 6. Revised approach to CPV for new products (The good).

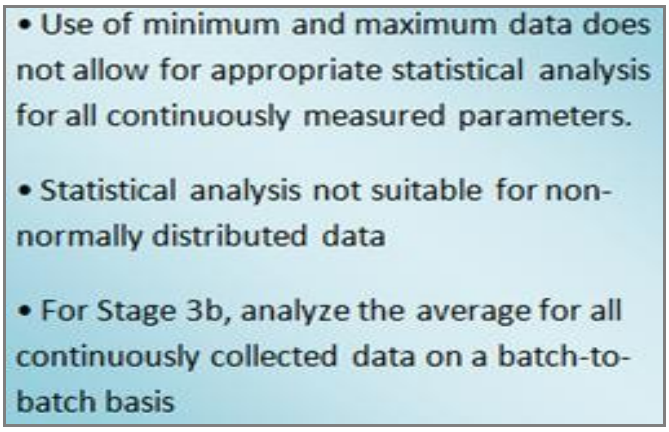

Fig 7. Revised approach to CPV for new products (The bad).

A capable process is one that consistently produces tablets that are within specifications for all tablet parameters (3, 4). A process-capability analysis compares the process variation to the lower and upper specification limits for the product. A broadly used measure of process capability is the Ppk index, or process performance index, which is discussed in greater detail later in this article [14,15].

A production process can include any one of the four combinations of stability and capability: stable and capable (desired state), stable and incapable, unstable and capable, and unstable and incapable (worst possible situation).Process stability and capability are typically evaluated twice:

A) During the production of each batch to ensure that the process is in control and to identify when process adjustments are needed. Some key questions that need to be addressed during this analysis include:

- Is the batch production process stable during the production of the batch with no trends, shifts, or cycles present?
- Is the process capable of meeting specifications (i.e., are the process-capability indices acceptable)?
- Is the within-batch sampling variation small, indicating a stable batch production process?

B) Monthly or quarterly to ensure batch-to-batch control throughout a given year and between years. Some important questions that should be addressed during this analysis include:

- Is the batch-to-batch variation stable from year to year and within years with no shifts, trends, or cycles present?
- Is the batch-to-batch variation small?

These two analyses also help to assess the robustness of the process.

CONCLUSION:

Thus in conclusion, it is recommended that robust systems and procedures are designed and developed in order to archive data and validate the accuracy of data retrieval in order to minimize errors during CPV. It is of course, the responsibility of each individual organization responsibility to fulfill the CPV requirements. Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The equipment and facility qualification data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification. Maintenance and calibration frequency should be

adjusted based on feedback from these activities. So continued/ongoing process verification is now a regulatory expectation, for both EU and US markets. Companies must have effective systems to capture the necessary data and perform the appropriate statistical analysis.

ACKNOWLEDGEMENT:

Authors wish to thanks Oman Pharmaceutical Products Co. LLC for providing library facility to carry out this review study.

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Conflict of Interest: None

Source of Funding: Nil

Paper Citation: Das P, Kumar SVR, Maity A. The New Paradigm of Pharmaceutical Process Validation - Continuous Process Verification. J Pharm Adv Res, 2018; 1(5): 261-267.