

# Continued Process Verification

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## Introduction

The main objective when implementing Continued Process Verification (CPV) is to provide information for the production process during manufacturing of commercial batches. This information is collected to be used as an evidence to prove that the manufacturing process of the product is the same as the validated process. CPV is very similar and connected with Product Performance Qualification (PPQ), in terms where it represents a documented plan to check and conform that the production process remains in its validated state during routine production, and the constant quality of the product is maintained (Gorsky, 2020). CPV represents an ongoing program where the main scope of the program is to collect and analyze product and process data that indicates the product quality status. The data collected during CPV needs to be in accordance with the cGMP requirements and it should be relevant, i.e. it can be easily concluded on the status of the quality of the product.

To detect the undesired process variability, precise process of data collection needs to be established, so the manufacturers can evaluate the performance of the process and to define if there is need for further action, in order to correct, remove, and prevent problems so that the process remains in control (FDA, 2011). Proper control strategy should be established, in accordance with change management system, in order to provide high quality drugs.

## Continued Process Verification (CPV)

CPV, which is the third stage of process verification, occurs perpetually in terms of that, CPV is performed for every commercial batch. The implementation of this

phase assures that the production process is constantly in a state of control (the validated state) during commercial production of batch. Creating an adequate procedure for this phase is an obligation for every pharmaceutical company, as well as standard operative procedure, monitoring program and a diligently created system, which can enable collection and evaluation of information about the performance of the process. Documentation is the backbone of CPV, it must be in accordance with the cGMP, and it has to be approved by the responsible person from the quality assurance unit and in lieu with the regulations. In order to perform continued process verification, manufacturers should collect data through expansive analysis with in-line, on-line or at-line test methods. CPV should be applied to every commercial batch, so the manufacturer can monitor process performance and product quality on each batch (EMA, 2021). Good understanding of the products properties and the technological procedure for production is a necessity for implementation of CPV. Few factors influence the scope and extent of continued process verification:

- gained knowledge form the early stage of product development
- the extent of process understanding gained from commercial manufacturing experience
- the dosage forms and characteristics of the product
- the equipment and technologies that are used during manufacturing

Documented monitoring and sampling plan needs to be created, and it should contain concise and clear instructions and responsibilities of how the monitoring process will be performed for CQA and CPP of every production phase. This document should contain sampling plan and data source, sampling frequency, quantities, test methods and the type of the equipment that should be used, quantities of the samples and methods of analysis. The monitoring level during the CPV program can be adjusted, depending of the data outputs. According to the

results, there can be triggers for increased or reduced monitoring. Triggers increased monitoring are: trends and signals shows sources of limited or unknown variability and process robustness not fully achieved during PPQ, new equipment, materials, suppliers, frequent deviations or out of specification results. Triggers for reduced monitoring are high process robustness, variability and impact of product quality well understood and controlled. The collected data for every product need to be sufficient to a statistically appropriate and representative level. The multidisciplinary team for CPV should analyze the collected data and evaluate undesirable process variation. Production line operators can participate and discuss process performance, possible trends or process variation. To evaluate the collected data software for statistical analysis to trend and to assist in the evaluation can be used. This software is used to calculate the process capability  $C_p$ , process capability index  $C_{pk}$  and to create control charts. Process capability  $CP$  in statistical tool to measure the ability of a process to produce results within the specification limits of the product and process capability index  $C_{pk}$  is used to give us information of how close the results are to the target values and how consistent the manufacturing process is. After finished evaluation of the data gathered during this stage, if there is necessary in the conclusion there might be suggested recommendations to improve and/or optimize the process by modifying some steps of the production process, such as sieving of the substances or more process controls during production.

In cases where the process needs to be optimized a request for change should be initiated. Well-justified reason for the change, an implementation plan, risk assessment and quality unit approval before implementation must be documented. Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted (FDA, 2011). Maintenance of the equipment, premises, has influence if one manufacturing process remains in a state of control. Once the qualification status is established, it must be maintained and proven by performing routine scheduled checks, preventive maintenance, and calibrations on the equipment. The frequency for preventive maintenance and calibration should be based on the Maintenance and calibration frequency should be based on the results from the routine scheduled checks (FDA, 2011).

## Conclusion

The final purpose is always the same: to demonstrate with a high level of certainty that the manufacturing process is able to consistently produce a quality product, within the acceptable and very well understood variability. It is a science based and a real-time approach to verify, confirm and demonstrate that the manufacturing

process is performed in within the predefined specified parameters limits and consistently produces final product, which meets its all predefined critical quality attributes (CQAs).

## References

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