Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

This document describes the documentation needed to support the use of Continuous Quality Verification (CQV) to demonstrate that a drug product (DP) or active pharmaceutical ingredient (API) process is in a validated state. It also describes some similarities and differences between CQV and traditional process validation using three discrete lots.

Process validation is used to provide assurance that the processes used to manufacture pharmaceutical products result in products which possess the required critical quality attributes (e.g. strength, identity, purity, safety, and efficacy).

Continuous Quality Verification (CQV) is an alternative approach to process validation. One of the primary differences for CQV compared to a conventional discrete, 3-batch process validation approach is that the process is continually monitored, evaluated, and adjusted (when necessary) to achieve defined Critical Quality Attributes (CQAs) using validated in-process measurements, tests, controls, and process end points.

CQV is applicable to all types of products and processes (e.g. Biopharmaceuticals, API, and drug product) and may be used with new, legacy, batch and continuous processes.

The principles may be applied during development of a new process or product, or for the improvement and/or redesign of an existing process. CQV may be applied to an entire process, or to defined critical manufacturing steps / unit operations.

Using CQV, processes are continuously verified as being capable of providing the desired product quality rather than the reliance on data generated from a few production lots.

Recommendations and Rationale
The CQV approach to process validation may be applied to both new and legacy processes when the necessary information is available. It requires a good understanding of the process and a process control strategy that ensures repeatable and robust performance of the process.

Differences between processes implementing CQV and those following a conventional approach:

The summary of the process understanding may also include enhanced understanding of material attributes, processing options and process parameters and be documented as Design Space (ref. *ICH Q8*).

Data supporting process understanding may be obtained from development and scale-up studies, experience from similar products and processes, or may include data from commercial scale manufacturing, depending on the stage of the product lifecycle.

The responsibility for providing the data will depend on the stage of the product lifecycle; for example, Research and Development (R&D) should provide documentation (for example, a Process Knowledge Report or Process Understanding Plan) for a new process, whereas for a legacy process, commercial batch data and any experimental data may be provided by the site Technical Services or Production Support groups.

b) *Documented Review of revised Risk Assessment review*

A review of the Risk Assessment defining the final CPPs and CQAs should be conducted once the specific site and equipment where the process will be performed are identified. In addition to accepting the risk assessment justifying the CPPs and CQAs, the review should include consideration of:

- The level of process knowledge available to support the proposed commercial scale (e.g. scalability studies or data at full scale)

- The impact of equipment capabilities on the CPPs that have been identified (e.g. comparison of expected normal operating ranges with proven acceptable ranges)

This revised risk assessment is recommended for any process, whether using CQV or a conventional process validation approach. This revised risk assessment is site-oriented, and therefore, where practical, personnel from the assigned manufacturing site(s) (for example, site technical services, site production support) should be involved in the preparation. It should be finalized before the approval of the Process Control Strategy as it is a key input to the strategy.

c) *Process Capability Studies*

It is recommended that CQV is only applied to processes that have been demonstrated to be both capable and stable. The data for this evaluation may also be used for the Preliminary Performance Evaluation (see below). Right-First-Time[8] (RFT) tools should be used to evaluate the process; the type of tool used may depend on the amount of data available.

For legacy processes where implementation of CQV is being considered, the Right First Time initiative on Product Based Process Capability may provide an indication of the process performance and therefore its suitability for CQV implementation.

2. Continuous Quality Monitoring & Control.

- A review of the manufacturing data for CPPs and CQAs against the acceptance criteria
- An evaluation of the process performance, including analysis of process capability. It is recommended that statistical process capability analysis, if used, be modelled on practices recommended by the Right First Time program and should include assessment of attributes that are critical to product quality.

- A conclusion whether the process is considered validated and recommendations for any modifications to the process understanding (e.g., CPPs, Design Space) or control strategy based on the increased process understanding acquired during the performance evaluation.

- A recommendation on the appropriate frequency for routine process performance evaluation, the data to be reviewed and how the data will be analysed

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b) Ongoing process monitoring and analysis

Process monitoring documentation typically includes manufacturing records and other process measurement data, as defined by the process control strategy.
When using a conventional process validation approach, individual batch release is based on confirming that the fixed process established during process validation has been repeated and that relevant in-process and end-product test specifications have been met.

For a process using CQV, individual batch **Acceptance and Release** is based on evaluation of the process data and process performance at a pre-defined stage of the process. The implementation of CQV may provide a level of confidence that each batch conforms to established quality attributes to enable the real time release of the final product, or to justify reduced end-product testing.

The acceptance criteria for release should include confirmation of the validity of the manufacturing process for the specific batch. The validity of the process is based on confirming that the process remained within the acceptance criteria defined in the control strategy and that this level of process control delivered the required product quality attributes.

In addition to the review of process performance that takes place as part of the release of an individual batch, there should also be ongoing monitoring and evaluation of the process over multiple, commercial batches. Ongoing monitoring of process performance can be achieved through a periodic documented evaluation. This periodic evaluation may be conducted as part of the Annual Product Review, or may be more frequent to verify the continued performance capability of the process.

4. Continuous Process Improvement

All processes should be reviewed to identify opportunities for continuous improvement, such as product quality improvements, process improvements, variability reduction,

