IMPLEMENTATION OF A CONTINUED PROCESS VERIFICATION PROGRAM FOR POST-MARKET COMPLIANCE & PRODUCT SUCCESS

Anthony Stewart, Senior Process Engineer, Biologics & ATMP & Ryan Doxey, Vice President, Technical Services

Abstract

Continued Process Verification (CPV) is the third stage of the FDA Process Validation guideline and is a critical component of modern pharmaceutical manufacturing. This poster uses a case study to describe the key steps for successful CPV program implementation using a phased-approach for both legacy and approved products, as well as products entering process validation.

Objectives

- ✓ **Achieve compliance immediately** through the efficient deployment of a CPV program.
- ✓ **Collect, evaluate, and visualize data** from Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) across historical product lots.
- ✓ **Score and rank product and process-related risks** to allow for efficient and effective monitoring of high-risk CQAs and CPPs.
- ✓ **Employ advanced statistical tools** to analyze data, identify trends, and detect deviations related to the high-risk CQAs and CPPs.

Continued (or Ongoing) Process Verification is Obligatory

FDA GMP Requirements

In this case study, we explore a structured approach to implementing CPV in alignment with regulatory expectations. Recognizing the importance of a practical application, we first examine relevant FDA (Continued Process Verification) and EMA (Ongoing Process Verification) guidelines to establish a clear framework for compliance and ensure robust monitoring and control throughout the implementation lifecycle. This approach facilitates data-driven decision making, enhances process understanding, and supports regulatory compliance in pharmaceutical manufacturing.

Nasr MM. Implementation of QbD: Status, Challenges and Next Steps. Advisory Committee for Pharmaceutical Science (ACPS), 5 October 2006

Core QbD principles—such as process understanding, robustness and performance, capability index (CpK), and continuous improvement—align closely with CPV, ensuring that manufacturing processes remain controlled, predictable, and capable of consistently producing high-quality products.

FDA Process Validation

The 2011 FDA Guidance on Process Validation (PV) establishes PV as a continuous lifecycle that extends beyond Process Performance Qualification (PPQ) (Stage 2) into commercial production.

Stage 1: **Process Design -** Execute Risk Assessments and Characterization Studies (DOEs), Identify CPPs and Material Attributes, and Establish Process Control Strategy

Stage 2: **Process Qualification -** Equipment/Utility/Facility Qualification, and PPQ

Stage 3: **CPV -** Monitoring of CPPs, Critical Material Attributes (CMAs), and CQAs, and Evaluate Statistical Control of Process

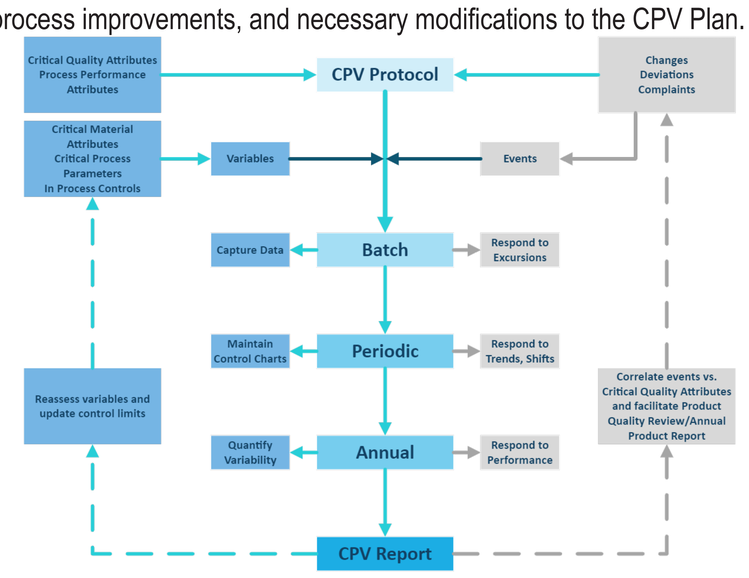
CPV was first introduced as part of the Quality by Design (QbD) framework in the early 2000s, emphasizing a proactive approach to process control and product quality.

By positioning CPV as a fundamental element of ongoing process control, the guidance effectively underscores its role as a Good Manufacturing Practice (GMP) requirement, reinforcing the need for continuous monitoring and improvement throughout the product lifecycle.

CPV Toolkit

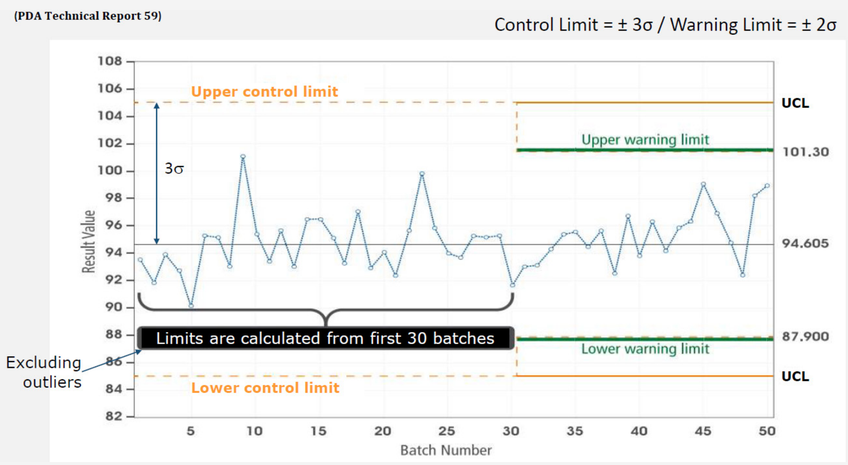
Regulatory guidelines define four (4) essential documents that structure and guide CPV:

1. **CPV Standard Operating Procedure (SOP):** Establishes methods, responsibilities, and operational workflow, outlining CPV stages, default or recommended Capability Index (PpK, CpK), and responses to process signals.
2. **Risk Assessment (RA):** Evaluates process risks using historical data and past discards for legacy products or Stage 1 & 2 risk assessments for new products. Updated post-PPQ to define monitoring parameters.
3. **CPV Plan (protocol):** A product-specific strategy detailing the data collection approach, trending methodologies, and specific monitoring parameters.
4. **CPV Report:** A periodic review of observed process signals, responses, process improvements, and necessary modifications to the CPV Plan.

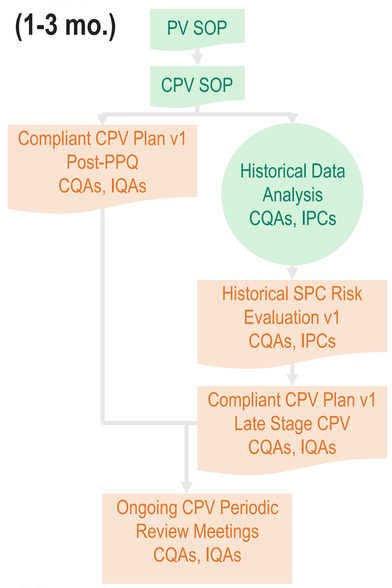


Control Charts

Beyond documentation, control charts play a critical role in CPV by monitoring process stability and detecting variations. A stable and predictable process remains within statistical control limits (e.g., Nelson Rules) and capability indices (pPk, Cpk), exhibiting only inherent, random variation that is naturally part of the process. Data points that fall outside control limits signals process instability, requiring investigation and corrective action to restore control. A well-designed CPV program should differentiate between signals requiring immediate escalation (e.g., alarms, IPCs, and release testing) as front line quality measures and those that inform long-term stability and optimization.



Implementation of a CPV Program



The objective of our program was to implement a comprehensive CPV strategy. Like many CPV programs, we divided the process into two (2) distinct phases.

In Phase 1, the primary goal was to achieve rapid compliance by focusing on key components such as data review, analysis, CPV planning, trend reporting, and responding to potential signals. By minimizing initial data collection, we ensured that all necessary elements were in place for the program's readiness.

In Phase 2, the focus shifted from compliance to adding value. The aim was to expand the scope of CPV, enhance the program itself, and enable its full benefits.

To illustrate the practical application, we gathered data from all manufactured batches, excluding those batches with rejections to ensure accurate representation within CPV scope. A critical subset of parameters and attributes was selected for trending, focusing on release specifications and IPCs, with an eye on additional CMAs for future analysis.

The data collection process involved approximately 600 data points, including CQA data and select IPCs. This was a manageable amount, allowing for thorough analysis. Each parameter and attribute was assessed using a risk ranking methodology, which considered individual risk factors to determine an overall risk ranking, from highest to lowest. The statistical analysis performed helped further refine our approach and solidify our path forward in CPV implementation.

Regulatory Expectation

CPV, as defined by the FDA and the EMA, focuses on maintaining a "state of control" throughout the manufacturing process.

An Ongoing Program for Collecting and Analyzing Product & Process Data that Relate to Product Quality

- ✓ Procedures for **data collection and trending**
- ✓ Data collected to **verify the quality attributes**
- ✓ **Analysis of intra-batch and inter-batch** variation
- ✓ Data collected to evaluate process **stability and capability**
- ✓ Data collected is **statistically trended**
- ✓ It is recommended that a statistician or person with adequate statistical training develop the data collection plans and methods for analysis

Must have system for detecting unplanned departures from the process

Evaluate the performance | Identify control issues | Determine if corrective action is necessary | Anticipate & prevent problems

Business Case for CPV

A well-executed CPV program enhances efficiency, product quality, and overall business performance, making it a strategic investment rather than just a regulatory obligation.

- Regulatory Compliance & Inspection Readiness
- Minimized Out-of-Specification (OOS) Events
- Enhanced Process Robustness & Yield
- Improved Schedule Adherence
- Lower Operating Costs
- More Efficient Process Improvements
- Reduction in Lost Batches

References

- FDA–Guideline for Industry–Process Validation: General Principles and Practices (2011)
- EMA/CHMP/BWP/187338/2014
- ICH Q8(R2) Pharmaceutical Development, November 2009
- ICH Q11 Development and Manufacture of Drug Substances, May 2012
- ICH Q10 Pharmaceutical Quality System, April 2009
- PDA TR59, Utilization of Statistical Methods for Production Monitoring
- PDA TR60, Process Validation: A Lifecycle Approach
- ISO 7870-1:2007, Control Charts–Part 1: General Guidelines
- ISO 8285:1991, Shewhart Control Charts

Kymanox®