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

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Abstract

Continued Process Verification (CPV) is the third stage of the FDA Process Validation guideline and is a critical component of modern pharmaceutical manufacturing, ensuring that processes remain in a state of control throughout the product lifecycle. However, CPV has historically been overlooked, with many companies unaware of the need for CPV program implementation as a regulatory requirement. 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.
- ✓ **Establish a steady-state CPV program** using insights from data analysis to optimize processes and enhance product quality.

Continued (or Ongoing) Process Verification is Obligatory

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 and EMA guidelines to establish a clear framework for compliance. In FDA terminology, this process is referred to as Continued Process Verification, while the EMA defines it as Ongoing Process Verification. By analyzing these regulatory requirements, we identify key steps for successful implementation, ensuring 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.

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. Historically, manufacturers have concentrated on Stage 1 (Process Design) and Stage 2 (PPQ); however, the guidance emphasizes the importance of Stage 3 (CPV) as an integral and equal component of the validation framework.

2011 FDA Process Validation Guidance

1. **Stage 1: Process Design**
   - Execute Risk Assessments and Characterization Studies (DOEs)
   - Identify CPPs and Material Attributes
   - Establish Process Control Strategy
2. **Stage 2: Process Qualification**
   - Equipment/Utility/Facility Qualification
   - PPQ
3. **Stage 3: CPV**
   - Monitoring of CPPs, Critical Material Attributes (CMAs), and CQAs
   - Evaluate Statistical Control of Process

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.

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

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. Core QbD principles—such as process performance, capability index (CpK), and process robustness—align closely with CPV, reinforcing the importance of ongoing monitoring and data-driven decision making. Additionally, process understanding and continuous improvement, fundamental to QbD, play a critical role in CPV implementation, ensuring that manufacturing processes remain controlled, predictable, and capable of consistently producing high-quality products.

APQR vs. CPV

Annual Product Quality Reviews (APQRs) are a regulatory requirement with which manufacturers are well-acquainted with. While APQR trending plays a role in demonstrating a state of control, it does not, on its own, constitute CPV. APQR is retroactive, often taking up to a year to identify trends or shifts that require correction, whereas CPV is real-time and applies Statistical Process Control (SPC) for trend detection.

APQRs require the inclusion of CQAs for a given product, a task that can be time and resource intensive, especially when reliant on manual data transcription. A CPV program that automates the collection and interpretation of process data could offer significant value, particularly in streamlining the assembly of such reports.

Data trending in both APQR and CPV typically involves summarizing and plotting process data on a run chart. In CPV, this data is assessed against statistical control limits, providing valuable insights into process stability and potential deviations. This input is crucial for justifying the state of process control and ensuring that product quality remains consistent.

By integrating APQR and CPV databases, organizations can realize substantial time- and resource-saving benefits particularly in the generation of APQRs, enhancing overall efficiency and compliance with regulatory standards.

Regulatory Expectations

CPV, as defined by the FDA and the EMA, focuses on maintaining a "state of control" throughout the manufacturing process. The FDA's CPV guidance outlines several critical expectations for an effective program.

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 **stabiliy 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 a System for Detecting Unplanned Departures from the Process

- ✓ Evaluate the **performance** of the process
- ✓ **Identify process control issues**
- ✓ Determine if **corrective action** is necessary
- ✓ **Anticipate and prevent** problems to ensure control

A Business Case for CPV

While regulatory guidelines provide a strong incentive for implementing CPV, the benefits extend far beyond compliance. 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

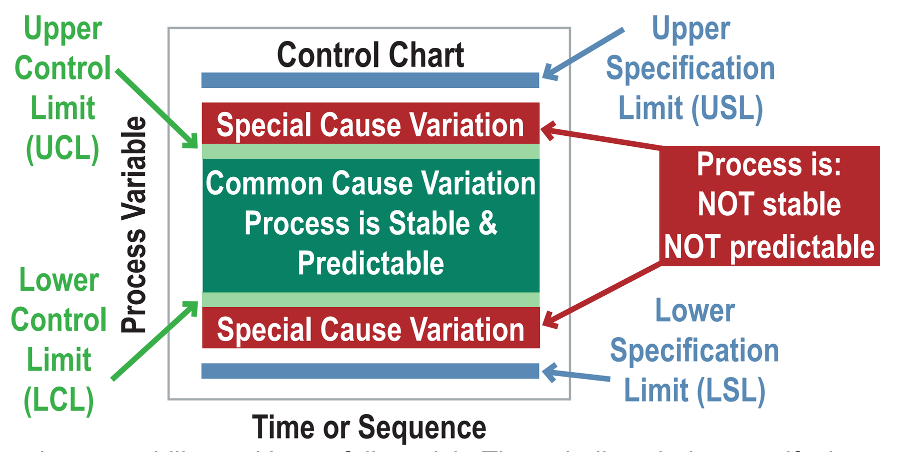
By integrating CPV as a proactive business strategy, manufacturers can achieve regulatory compliance while driving long-term business success through improved efficiency and cost savings.

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 Process Capability Index (Ppk), 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:** 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.

Beyond documentation, controls 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), exhibiting only inherent, random variation that is naturally part of the process. However, when data points fall outside control limits, it signals the presence of special cause variation–an external, non-random factor effecting process performance. Since such occurances are statistically unlikely, their presence suggests process instability, requiring investigation and corrective action to restore control.



Capability indices (Ppk, Cpk) measure process performance, with Ppk preferred for assessing long-term intra- and inter-batch variation. A Ppk below 1.00 suggests poor process capability, while values above 1.00 indicate better stability and lower failure risk. These indices help quantify the likelihood of meeting specifications consistently.

A well-designed CPV system proactively detects process drift before deviations occur. Since CPV functions at a supervisory level, it does not inactive historical batch releases but helps ensure ongoing process control. The system should differentiate between signals requiring immediate escalation and those that inform continuous improvement. Alarms, alerts, In-Process Controls (IPCs), and release testing serve as frontline quality measures, while CPV enables long-term stability and optimization without overwhelming the Quality Management System (QMS) with unnecessary investigations.

Implementation of a CPV Program

Implementation Goal

A phased rollout that can balance the need to become compliant relatively rapidly while providing a learning environment necessary to design a sustainable system.

Phase 1:

- Minimize the initial data collection infrastructure investment to critical process outputs.
- Increase the effort to perform data verification, review, and analysis.
- Properly design critical CPV program components.
- Ensure the CPV program is sustainable and ready for the increased volume of data.

Phase 2:

- Expand the program to include process inputs (e.g., CPPs, KPPs).
- Enable efficient data collection.
- Establish steady-state CPV program.

Legend A

Document | Activity | Data

Legend B

Green:

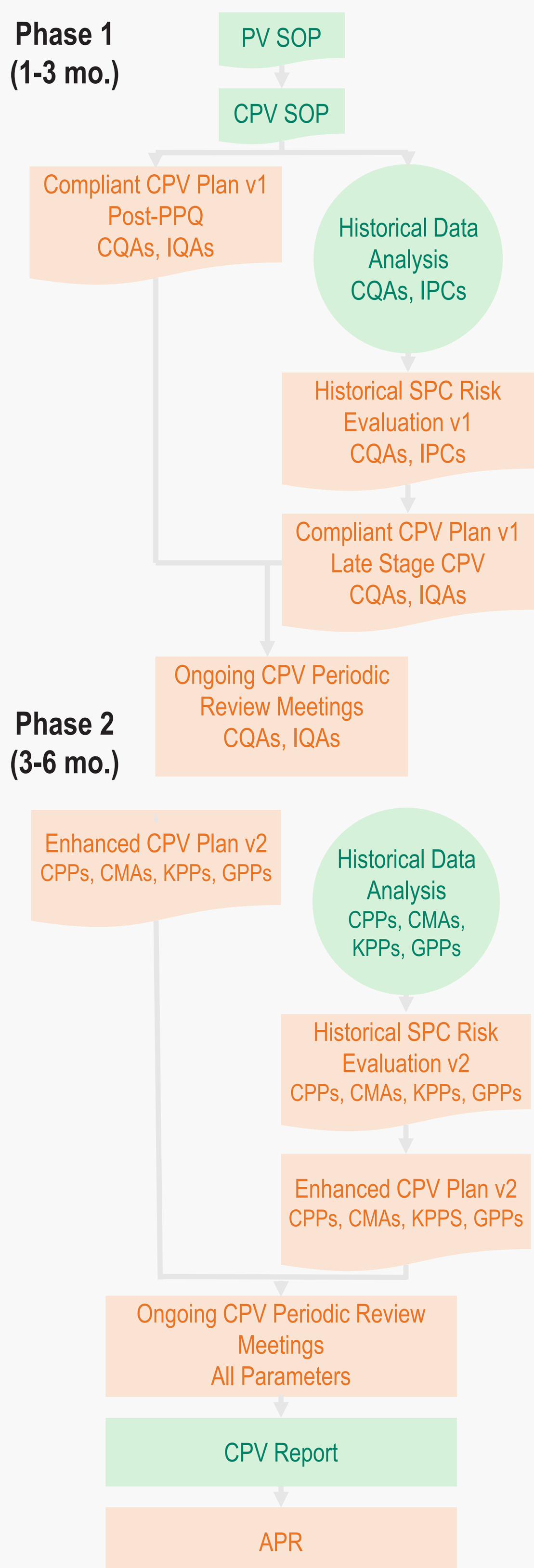
- *Kymanox has access to all relevant data, know-how, tools, resources, templates to draft & execute the document or activity.*
- *No or minimal input required from client.*

Orange:

- *Kymanox may not have access to all relevant data or have ready-made templates.*
- *The document or activity is low complexity but requires significant time commitment.*
- *Some client support is required.*

Red:

- *Kymanox may not have access to all relevant data or have ready-made templates.*
- *The document or activity is complex and requires a high degree of critical thinking.*
- *Significant client (and potentially CMO) support is required.*



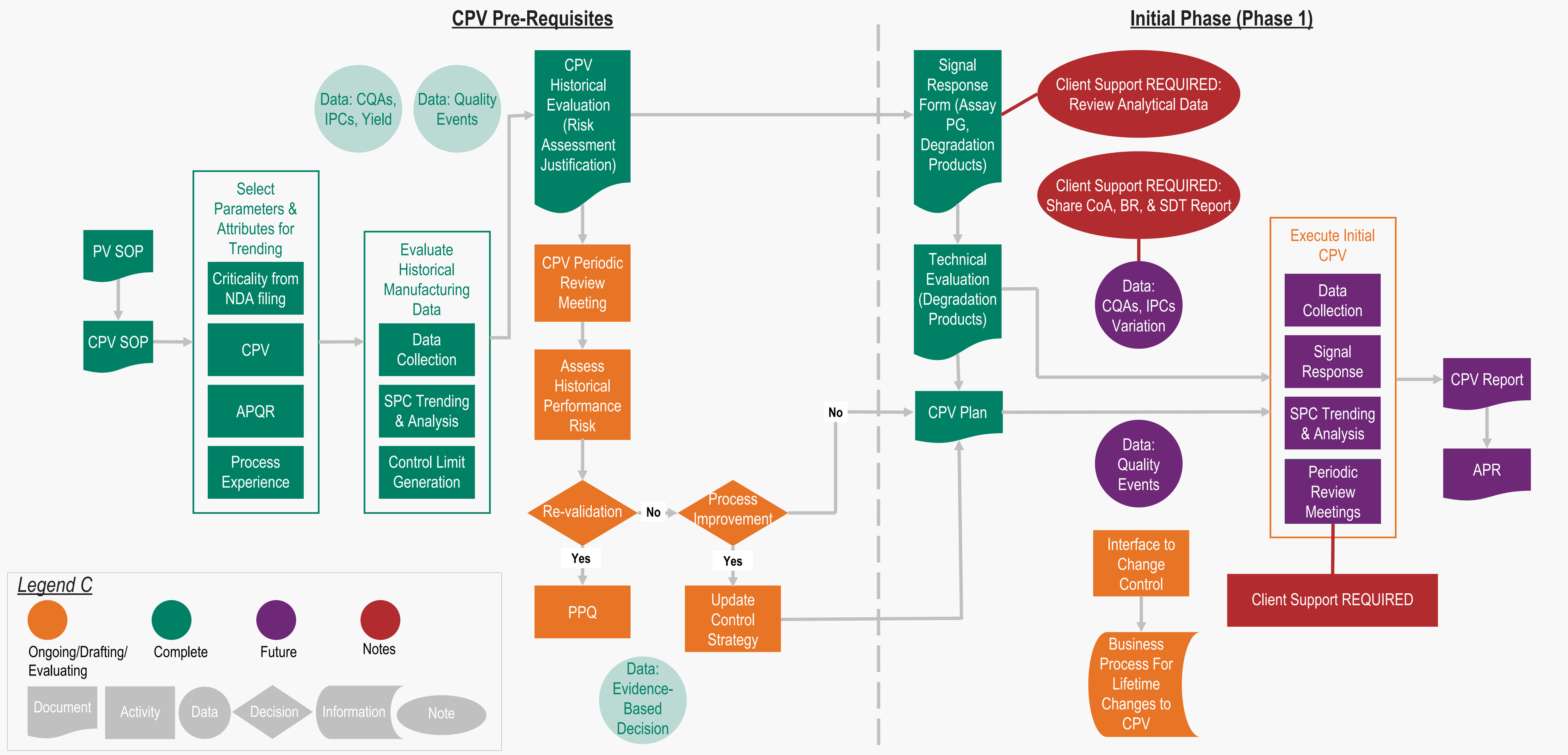
The objective of our program was to implement a comprehensive CPV strategy. Like many CPV programs, we divided the process into two (2) distinct phases. In Phase 1, the primary goal was to achieve rapid compliance by focusing on key components such as data review, analysis, CPV planning, trend reporting, 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 track progress, we created a flowchart to visualize our readiness for CPV, outlining the prerequisites for Phase 1.

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.



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 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

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