Continued Process Verification

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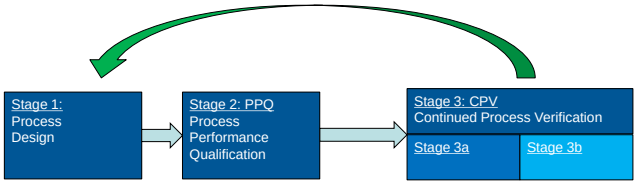
STRONGER PERFORMANCE AHEAD

Realizing the Full Value of Continued Process Verification

For nearly three decades the pharmaceutical industry has moved toward an increasingly comprehensive regulatory framework based on science and risk. A crucial part of that framework is continued process verification (CPV), detailed in *Process Validation: General Principles and Practices*, issued by the FDA in January 2011. To the first two stages of process validation—process design and process qualification—the new validation paradigm adds CPV as part of the product lifecycle approach manufacturers are expected to adopt.

Figure 1: The Three Stages of Process Validation



Subsequent legislation, as well as additional guidance from the agency, has made it clear that CPV is not optional. The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, requires the FDA to prioritize and schedule inspections based on the degree of risk a site poses. In October 2013 the FDA issued a strategic plan for addressing drug shortages. And in July of 2015 the agency issued its draft guidance on Quality Metrics, detailing how it plans to conduct risk-based inspections and predict or mitigate potential drug shortages.

Yet progress in implementing CPV remains uneven across the industry. Some companies have only just begun their CPV programs, while others stand at various stages of the journey. A few companies are far advanced. They have achieved compliance, used CPV as a platform to improve their scientific process understanding, and are building on CPV to attain the FDA's goal of ensuring reliable supply of products. Just as important, they are laying the foundation for routine reporting of Quality Metrics, which could significantly lighten regulatory burdens.

Converting Requirements to Opportunities

As manufacturers work to implement CPV they have a choice. They can aim for mere compliance, or they can aim much higher – at a strategic CPV program that integrates quality and compliance with science and technology to extract the full operational, regulatory, and business benefits from CPV requirements.

Operational benefits include:

- More focused process control strategy across the supply network
- Reduced out-of-specification results, deviations, discards, and rework
- Higher manufacturing throughput
- Avoidance of delays in the manufacturing and launch of pipeline products
- More reliable supply to the market.

Regulatory benefits of CPV, once Quality Metrics is phased in, include:

- More efficient scheduling and execution of reports, including both CPV reports and annual product reviews (APRs)
- Greater regulatory flexibility and reduced post-market change control burden
- Potential for reduced inspection frequency.

Together, these operational and regulatory advantages add up to significant business and financial benefits, including reduced cost of quality and higher margins. For example, inspections divert key personnel from their value-creating responsibilities, driving up the cost of quality, driving down margins, and interrupting revenue.

Discarded batches can also be costly. In biologics, the avoidance of one discarded batch can pay for an entire CPV program, including

enterprise-wide software. In small molecule manufacturing, where batch cycle times are much shorter, many bad batches may be produced before problems are detected and corrected. Avoiding a run of bad batches can add up to savings as significant as those for a single biologics batch. For example, a contract manufacturing organization (CMO), as part of its new CPV program, began to monitor temperature at a process step where it had not previously been monitored. Within the first two weeks, they caught a shift in temperature and were able to correct it after just one batch, before the campaign was finished. Without their new CPV program, they would have run 20 additional faulty batches before after-the-fact testing of the original bad batch revealed a problem.

Meeting the Three Major Challenges of CPV Implementation

Although CPV compliance is compulsory and its potential benefits are great, the challenges of designing and deploying it can be daunting. Those challenges appear in three major areas:

- Using *resources* efficiently, especially in data gathering
- Determining the right *scope* in monitoring
- Applying *statistics* to identify shifts and trends in process performance and bring previously invisible problems to light, without generating a high volume of distracting false alarms.

Companies that underestimate the difficulty of overcoming these obstacles or attempt to attack them with brute force are likely to find themselves risking non-compliance, not moving their program forward, and, most important, failing to realize the full operational and business benefits of CPV.

Resources: Automate 'Data Wrangling'

In CPV an enormous amount of effort can go into gathering, contextualizing, and verifying the process data on which effective monitoring depends. Why does this "data wrangling" entail so much work? Four reasons:

- Gathering data – on batches, dates of manufacture, critical quality attributes (CQAs), parameter values, and more – can be tedious and time consuming. Often this mountain of data must be pulled from many disparate sources: the enterprise resource planning (ERP) system, the laboratory information management system (LIMS), and batch records. Pharmaceutical manufacturers have been slow to adopt electronic data systems, perhaps because of the regulatory hurdle for implementation of any new system. As a result, much of process data exists in paper records and must be transferred manually to software for analysis.
- Process data must be put in context of its genealogy. For example, each batch of raw materials must be matched with the batch or production materials it goes into.
- Once data has been gathered and contextualized, it must be verified – checked to make sure no errors have been introduced. Surprisingly, verification often takes even longer than the initial data gathering and contextualization.
- The data must then be analyzed. This is the least time consuming aspect of the process and for most personnel the most interesting of these four activities.

To reduce the magnitude, inefficiency, and cost of the effort, data gathering and automation can be standardized and streamlined where appropriate. Contextualization, which is critical for Right-First-Time manufacturing, must also be reliably automated. Verification, too, must be built into the system – it can't be an

afterthought. Reducing data effort in this way can yield big benefits – companies that have set up efficient data systems have dramatically reduced the amount of staff time required, realizing savings of 40-70 percent typically.

Scope: Monitor the Right Things, Not the Most Things

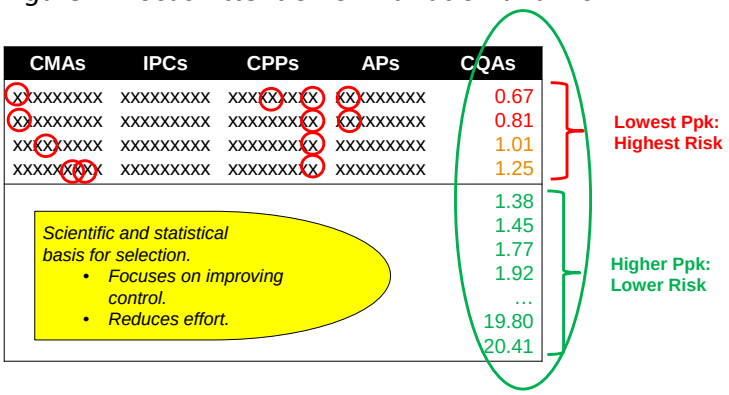
An effective CPV strategy both improves control of the process and reduces the effort required to maintain and demonstrate that control. Achieving both of those objectives requires careful scoping of the process parameters to be monitored. Consider, for example, the large number of parameters for a typical biologic product:

- 13 critical material attributes (CMAs)
- 14 in-process controls (IPCs)
- 32 critical process parameters (CPPs)
- 15 assay parameters (APs)
- 22 critical quality attributes (CQAs)

That adds up to 96 parameters. At a rate of four CPV reports annually, you would need 384 control charts per product per year. Faced with so many charts, your personnel are likely to suffer attention fatigue, lose focus, and miss important cues.

The far better option is to use knowledge of the product and apply statistical techniques to focus attention where the highest risk exists. So, for example, with the typical biologic above, you might begin by calculating the process capability (Ppk) of all 22 CQAs. Suppose you find that 18 of those 22 CQAs are at 1.3 or above, a well-accepted threshold for risk, which means that they are well controlled. Based on statistical analysis and your knowledge of the process, you can then select the parameters that are most likely to cause problems in the four high-risk CQAs that remain.

Figure 2: Focus Attention on Variation and Risk



From this work, a sound control strategy emerges: monitor all 22 CQAs and the 12 parameters likely to create issues in higher-risk CQAs. Instead of monitoring 96 parameters, you are now monitoring 34, dramatically reducing effort while sharply focusing the organization's attention on the parameters that matter most.

Statistics: Separate the Signals from the Noise

Improving control of a process requires signals that reliably indicate when it is in danger of slipping out of control. These signals should have three characteristics. First, they must be true. Otherwise, you waste time, effort, and money investigating false alarms. Second, signals must be timely – leading indicators, not lagging indicators. Learning about a variation months after the fact is not good enough. Third, the signals must be actionable. Your system may generate a great number of signals that are both true and timely, but those signals might be useless for improving process control.

True signals: reducing the number of false alarms

Much of the wasted effort in process monitoring stems from false alarms. If your standard operating procedures (SOPs) require a response to each alarm, the cost can mount up quickly. Depending on the level of quality oversight required, investigating those false alarms can cost $1,000 to $10,000. They not only drain

resources and distract attention from true alarms but also seriously diminish the credibility of statistics.

In fact, many such false alarms result not from inherent flaws in statistics but from the misapplication of basic statistical methods. For example, a process you are monitoring might generate only three or four distinct values. Such data sets are "low resolution," and will never follow a normal distribution. Yet most basic statistical methods require normally distributed data. If you plug low-resolution data into the software and apply commonly recommended methods, you are likely to generate numerous false alarms, especially with processes that are already well controlled. Instead, the review of process data by a qualified statistician, with input to your CPV program design and standard operating procedures, can reduce the number of false alarms right up front.

Making the invisible visible

Once the distraction of false alarms has been eliminated, statistical methods can shine a spotlight on high-value signals that surface problems that were previously invisible. This opens up opportunities to better control a process and remediate it in a timely way.

How do you identify signals that are true, timely, and actionable? By applying statistical techniques efficiently and in a more sophisticated way than simply looking at one parameter at a time. Consider the case of a vaccine maker. The company monitored nearly 40 different parameters for the performance of a bioreactor. No single parameter indicated any significant trends in bioreactor performance, but the critical quality attributes (CQAs) had shifted dramatically. No one knew why. Three years of investigating the causes turned up nothing and the product had to be pulled from the market – precisely the kind of interruption of supply the FDA is now determined to prevent through CPV.

But when the company embarked on serious process monitoring, experienced statisticians examined the nearly 40 parameters of bioreactor performance in a multivariate model. Unlike univariate models, this multivariate model was able to uncover the complex interactions of multiple variables that were the root of the problem. The company was also able to model the possible combinations of the critical process parameters that would keep the resulting product within specification. They now monitor accordingly: routinely tracking these true, timely, and actionable signals of bioreactor performance. As a result, the company was able to establish a track record of reliable, consistent supply for the product. The financial benefits were measured in millions of dollars.

Full Lifecycle Management

With streamlined data management, focused monitoring, and rigorous statistical methods in place, you are positioned to complete the feedback loop that full lifecycle management entails. Consider, for example, the case of another vaccine process. Prior to establishing a rigorous CPV program, the ratio of actual to expected yield of the manufacturing process appeared to show the kind of high, but acceptable, variability that is typical of vaccines. However, in implementing a statistically sound CPV program, the company discovered an alarming trend in the process: the ratio of expected to actual yield had dropped without detection by some 20 percent. The manufacturer had made no changes to the process. Had the organization not implemented CPV, this deterioration could have continued without remediation. Most importantly, the signals of variation found in stage 3b of the CPV framework, enabled the manufacturer to return to stage 1 – process design. Improvements to the process design reversed the yield decrease and now support stronger scientific evidence that the process continues to be in control. Thus, though CPV is the last stage of three-stage

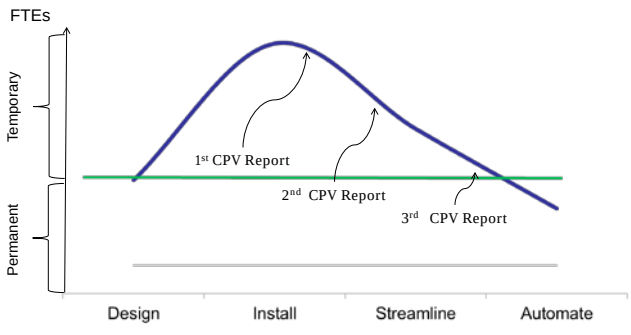
validation, it is not the end; it is the engine – of ever greater process understanding in a comprehensive control strategy.

In some cases the original process design may be unavailable. For example, that can happen with products made by CMOs or with products that have been so long in-market that the process design is buried in widely scattered, old paper records. In such cases, the manufacturer has to replicate the original process design and then improve and document it. Replicating the process design requires a lot more work, but with CPV in place and the greater process understanding it generates, the task is far more manageable.

Investing in the New Paradigm and Preparing for the Next Wave

Overcoming the challenges of CPV implementation requires investment up front, but it soon reaches the break-even point and thereafter generates significant return on investment.

Figure 3: Overcoming Challenges Requires Investment



Though the dollar benefit of ongoing CPV monitoring is hard to quantify precisely, it often produces big wins like the vaccine maker's avoidance of lost batches or the API producer's rescue of an entire campaign. Further, routine monitoring produces ongoing knowledge that leads to continual improvements in control strategy, reduced compliance and regulatory exposure and the costs associated with re-validations, manufacturing delays, and investigations – producing, over time, a many-fold return on investment.

The amount of that initial investment depends on your specific circumstances. There is no one-size-fits-all CPV solution. The solution you implement must be both comprehensive and customized to your product history, state of process knowledge, and state of internal resources, all of which help determine the cost of the program. In addition, part of that initial investment may go to a solution partner experienced in CPV implementation. To make the most of that investment you must be sure that your partner is able to do the following:

- Deploy the right mix of statisticians, process experts, and scientists to complement your team
- Coach and mentor your personnel
- Provide a uniquely efficient method of handling data
- Help develop policies and SOPs for CPV and processes for adhering to them
- Establish links to the design and PPQ (Process Performance Qualification) stages of validation where process knowledge is lacking
- Assess process capability (Ppk) baselines and updates, and develop risk mitigation strategies across your portfolio
- Provide basic and advanced training in statistical process control (SPC)
- Align CPV with annual product reviews in order to avoid duplication of effort
- Offer expertise in online, real-time monitoring

Along with the right partner, a comprehensive, customized approach ensures efficient progress from compliance to science to reliability—and the operating and competitive advantages of CPV and full lifecycle management.

Approaches to CPV that focus narrowly on mere compliance miss the full impact of the paradigm

shift to lifecycle management – a virtuous circle of compliance and deeper process understanding, supported by the right technology, that generates continual improvement. This strong science-based foundation is, in our experience, the fundamental principle that should guide your CPV efforts.

It also positions your organization to ride the next wave of regulation: Quality Metrics and its risk-based inspection program. The advent of Quality Metrics sends an unmistakable signal. The FDA is already looking past CPV to ensuring, in the agency's words, "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight." Organizations that have not yet achieved full CPV maturity are not just one step behind, but two steps. For those organizations, the CPV imperative is not only to do CPV right, but to do it now.

About the Author

Julia O'Neill, currently a Principal at Tunnell Consulting, has over 30 years of statistical engineering experience in the vaccines, biologics, pharmaceutical and chemical industries. She consults with a wide range of companies developing and manufacturing both traditional and novel biopharmaceutical products. Before joining Tunnell she worked at Merck & Co. as Senior Scientific Fellow – Statistics in Regulatory & Analytical Sciences; and Principal Engineer/Director in Global Technical Operations – Vaccines & Biologics. Her experience includes development of specifications; design and implementation of Continued Process Verification; development of metrics and monitoring for process and product robustness; and expert Design of Experiments support for a wide range of QbD programs in vaccines, biologics, and small molecules. She led the team that authored the manufacturing division guidance for SPC implementation at all Merck sites, and directed multiple teams that established a track record of successfully resolving complex investigations, driving sustained improvements, and representing solutions to regulators.
Her education bridges statistics and engineering, with an MS in Statistics from the University of Wisconsin, and a BS in Chemical Engineering from the University of Maine.