Abstract

To ensure that a commercial biomanufacturing process is in a state of control, life science companies must create and successfully execute initiatives to meet continued process verification (CPV) and other monitoring guidelines. Management at pharmaceutical, biotech, and medical device companies commonly receive directives associated with data monitoring. Various challenges arise in the development and maintenance of a successful global monitoring program. Because of this, many companies develop data monitoring programs that are not scalable and sustainable. Company leaders struggle with how best to adopt, deploy, and scale monitoring systems to achieve defined quality monitoring goals.

The purpose of this article is to display a maturity model to help companies navigate the major steps of implementing a global monitoring plan for continued process verification.

Introduction

Life science companies have various motivations to successfully implement a monitoring program, including adhering to regulatory guidelines, increasing process understanding, reducing process variability, improving process consistency and predictability, and ultimately, increase profits and efficiency. However, limited literature exists regarding specific techniques to achieve a successful monitoring program in the ever-changing life science manufacturing environment. One outstanding reference work is Continued Process Verification: An Industry Position Paper With Example Plan, from Biophorum Operations Group.[1]

In my experience with helping life science manufacturing organizations develop and implement monitoring programs, I’ve seen companies advance through all phases of continued process verification (CPV) implementation. Each phase contains key elements and tasks necessary for successful implementation and continuous improvement. This article will highlight the specific phases for deploying continued process verification. These are best practices—an accumulation based on my experience in establishing CPV for various companies in the life science industry.

The Challenges of Maintaining a State of Control

Over the years, the FDA has created a variety of initiatives. One of the most recent is Guidance for Industry—Process Validation: General Principles and Practices.[2] The regulatory agencies and experts have been saying the same thing for a long time: Companies should know, understand, and monitor their manufacturing process. European authorities and the International Conference on Harmonization (ICH) also have guidelines. They all have similar themes: Know your process, be proactive, reduce variability, increase predictability, validate your tools, use statistically appropriate tools, and team collaboration is necessary. The monitoring guidelines are not prescriptive, which is good. This allows companies to develop techniques that adhere to their specific process and organization. However, it can also result in confusion regarding definitions and the specific tools, techniques, and resources necessary. Additionally, there are a number of complexities that companies face when implementing CPV programs.

It is challenging to be proactive. The reality of the manufacturing environment is that investigations are launched retrospectively to determine why batches fail. Companies must make time to change their approach from looking back at what went wrong to a pre-emptive, proactive environment. It is difficult to find resources to do this. In reality, both must occur. If a batch fails, companies are required to investigate. However, they must put processes in place that understand the root-cause and prevent future failures. When launching corrective and preventative
actions (CAPA), time must be devoted to the preventative as well as the corrective. The global monitoring maturity model addresses that challenge.

Companies must aggregate their data to monitor it. They need to do this in an automated and scalable fashion. After accumulating data, specialists analyze it by creating statistically sound outputs and reporting on them. To do this effectively, they should strip the overhead out of the process by automating the creation of outputs and reports, and then scale the process. Often professionals in life science companies spend as much as 80% of their time aggregating, organizing, and cleaning data, and only about 20% of their efforts analyzing it. That ratio should be reversed—80% of the time should be spent analyzing the data.

Life science organizations may need to monitor tens of thousands of parameters in the manufacturing process of a single biological drug. To scale to that level, these parameters must be organized and accessible. To add to this already difficult task, the life science manufacturing environment is increasing in complexity with the growing use of contract manufacturing organizations (CMOs). Regulatory agencies have recently highlighted the responsibilities of both sponsor companies and manufacturing facilities to adhere to monitoring requirements.[3] Due to the high stakes of a successful implementation, management at life science manufacturing organizations have a desire to implement cost-effective, global monitoring programs. FDA guidelines[3] clearly state that to achieve success, global monitoring requires a collaboration of team members with expertise in quality, manufacturing, and statistical analysis. But resourcing a collaborative team is a challenge, especially in a global environment. If team members are assigned from internal resources, typically they are already very busy with their ongoing responsibilities. If they are hired directly out of school, they haven’t yet acquired a full range of technical expertise yet. When a cooperative monitoring team involves CMOs in their process, there may be diverging goals across the organizations. A group of responsible individuals must be assembled who can devote the necessary time to executing the program. They must be able to collaborate with each other, and they must already have the necessary technical proficiency and knowledge.

Maintaining a state of control isn’t enough. Life science companies need to display evidence of relevant activities for regulatory authorities. However, many of them lack proof that they are implementing and maintaining CPV. They can create good programs, but if they don’t plan for providing appropriate confirmation that they have achieved key milestones, regulatory authorities may lack necessary visibility into the particular process.

All of these challenges point to the need for a scalable solution that addresses continued process verification.

**CPV Maturity Model: Deploying for Success**

The maturity model shown in Figure 1 can help companies face the challenges discussed above. It is designed to help companies understand their key milestones, objectives, and necessary tasks to successfully implement CPV and provide evidence that they have done so.

There are seven phases to the maturity model detailed in Figure 1. Companies may move up and down through the various phases of the working model as they implement and expand their monitoring initiatives. They will work on

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**FIGURE 1. Seven phases for CPV maturity.**
Companies move within the framework, returning to earlier phases as needed to scale, align, and globalize their programs. In the description of each phase, I will highlight decisions that may accelerate long-term scalability and management oversight.

**Phase 1: Develop a CPV Initiative**

Many companies begin the CPV journey with small-scale monitoring efforts that are isolated and manual. However, most life science companies desire a full-scale global program with standardized deployment and tools that provide management with visibility. A global CPV program typically requires a change in company culture to develop and maintain.

Companies either develop a new CPV initiative or incorporate CPV monitoring techniques into current initiatives such as quality by design (QbD), product robustness, and quality monitoring. The determination of the initiative is company-specific and mostly dependent upon the internal dynamics. The CPV initiative should outline the general rationale, procedures, and expectations. It is critical to establish a company culture that can embrace the new initiative. Typical pitfalls include a lack of understanding and acceptance of the need to monitor, lack of time for sites to implement CPV, and the absence of accountability and clearly defined responsibilities.

To overcome these pitfalls, most organizations move toward a top-down approach, with management setting an expectation of accountability for CPV-related activities. Management should identify leaders in information technology (IT), quality, manufacturing, and statistics, and define their roles in the initiative. These leaders can help everyone understand the need for continued process verification and the value of developing a CPV initiative.

A successful initiative typically involves significant organizational adjustments. As previously discussed, it is critical to provide evidence of key milestones in each phase of the maturity model. For the initiative and culture phase, key evidence may include developing and revising an initiative document to include CPV monitoring with roles and responsibilities defined, as well as buy-in and support from executive management and key stakeholders. Efforts should be devoted to advancing an internal culture that fosters change and the adoption of a global CPV program.

**Phase 2: Technology Solutions**

Life science companies must make the critical decision about what technology solutions they need to support CPV implementation. Technology solutions should be utilized to increase the scalability and maintenance associated with the aggregation of data, computation of data visualization and analysis, as well as reporting and dashboards for the results. The technology solutions adopted to deploy a CPV initiative must be GMP-compliant and will require validation. There are many software choices available, as well as many homegrown systems.

Potential technology solutions should be evaluated based on the following components:

- **Usability.** (How many people can utilize it? How long does it take to learn? Does it require special skillsets?)
- **The maintenance and hardware associated with supporting the technology solution.**
- **The ability to automate data aggregation and data cleaning to reduce the amount of time compiling it.**
- **The ability to convert paper to electronic data in a compliant manner, if necessary.**
- **Automated analysis and reporting to reduce the amount of manual calculations needed.**
- **Using “monitoring by exception” to receive automated alerts vs. the need to physically review every chart.**
- **Appropriate statistical tools to account for various processes.**
- **Dashboards (or control panels) and reporting capabilities to increase management insight and decrease the overhead for CPV-related reports.**

Many groups struggle with implementing a single global technology solution due to varied technological preferences and budget allotments. They should adopt solutions that align with their long-term needs. In an attempt to keep costs low, software programs such as Microsoft Excel® are often used initially until the lack of harmonization and scalability limits their feasibility. Therefore, it is critical to select the appropriate solution for the size of the company and long-term CPV goals. Companies should also provide proper training for individuals who will use the technology. The implementation, validation, and training associated with CPV technology solutions are common forms of evidence used to demonstrate accomplishment of this phase.

**Phase 3: Guidelines/Standard Operating Procedures**

While guidelines can be developed prior to adopting a technology solution, they are usually revised based upon the technology solution. Typically, life science companies vary regarding the amount of procedural documentation developed and who owns each document. Four general documents are often used. The most general of them is a high-level initiative guideline that provides company-wide expectation and procedures. A monitoring procedures guidance document is typically created to highlight the expected procedures for each site and product. It is not
prescriptive, allowing sites to develop specific techniques. Sometimes a technical statistical document is developed independently of the monitoring procedures to display detailed statistical techniques and discuss statistical process control concepts. Finally, at the most detailed level, site-level and product-level monitoring plans are developed to define specific monitoring procedures, tools, and responsible individuals for each site and product.

The site-level and product-level monitoring plans should state exactly how the sites and products will implement these procedures. Below are key areas that should be listed in the monitoring procedures and the site/product-level monitoring plans:

- What parameters will you monitor (critical quality attributes [CQAs], critical process parameters, business parameters, etc.)?
  - What risk assessment procedures should be used?\(^4\)
  - How will risk levels be defined?
  - What statistical tools should be used?
  - When should you use a control chart, run chart, cumulative sum (CUSUM) chart, etc.?
  - How will you address a special cause variation?
  - What run rules should be applied? When should you receive alerts?
  - What adjustments should be made for dirty data (non-normal, autocorrelation, outliers, limited sample sizes, etc.)?
- How frequently will you add new data to the system? And how frequently will you conduct analysis and review data visualizations?
- Who is responsible for configuring and automating the monitoring?
- What actions should be taken for out of trend (OOT) alerts?
  - Differentiating between out of specification (OOS) and OOT investigational procedures.
  - How will actions be documented? Consider the audience that will consume the information.

It is critical to find a balance between including enough technical information and not making the documents too complex. The following techniques help make documents more useful: (1) using flow diagrams; (2) limiting the length of the document; (3) placing equations in appendices and not in the body of the text; and (4) providing training regarding statistical process control and monitoring techniques (more than standard statistical training).

Key milestones for providing evidence of appropriate and usable company-level guidelines include: (1) annual reviews and updates to guidelines; (2) ensuring that guidelines/SOPs have enough detail and are understandable; and (3) updating responsible parties on the site/product monitoring procedures.

**Phase 4: Standard Monitoring**

After establishing the CPV initiative, adopting a technology solution, and developing guidelines, statistical techniques for standard monitoring should be created. Standard monitoring procedures are typically simple techniques for crucial parameters such as CQAs. These techniques deliver quick “wins” that can help companies learn about their process.

Standard monitoring procedures include setting up trending (run and control charts) and process capability or performance estimates for all CQAs. This phase typically includes setting up basic small-scale dashboards as well as presentations to stakeholders.

The proper use of control charts involves many decisions and may require statistical guidance. For example, users need to determine the correct control chart to use based on the desired distribution, assumption testing (distribution testing, autocorrelation), and baseline control limits by setting them based on historical data.\(^5\) The proper use of monitoring procedures is related to how prescriptive and usable the guidelines are and the availability of supportive personnel such as subject-matter experts and statistical support personnel. The improper setup of standard monitoring tools typically results in an inappropriate signal/alert, which leads to a lack of system utilization.

Once the basic outputs are set up—typically up to 20 parameters per product/process—they are displayed in a simple organizational dashboard. These dashboards are usually created for a specifically focused group to provide key insights and are rarely large-scale at this phase. However, they do provide valuable information and allow site-level individuals to see the value of the monitoring program, which also helps to increase their process knowledge. It is also an excellent point in time to present information to key stakeholders and management. Therefore, it is critical to define stages for a monitoring setup to gain buy-in and allow an extended group of individuals to see the value of the CPV initiative.

If they utilized a manual process (as mentioned earlier), people will often arrive at phase 4 of this model and realize that they can’t scale with the technology solution and guidelines they developed in the earlier phases. The manual process becomes even more time-consuming and guidelines they developed in the earlier phases are limited to one or two parameters, and they can only monitor a minimal number of parameters. Companies in this situation usually realize that they can’t scale with the technology solution, and developing guidelines, statistical techniques for standard monitoring should be created. Standard monitoring procedures are typically simple techniques for crucial parameters such as CQAs. These techniques deliver quick “wins” that can help companies learn about their process.

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This is an example of when it is necessary to move
downward through the model to revisit earlier phases, as shown in Figure 2.

Vital evidence of milestones related to standard monitoring techniques include reports defining the number/percent increase in parameters monitored, the number of OOT/OOS alerts, reduction of OOT/increase in process capabilities as well as a dashboard of CQA, and a training roadmap.

**Phase 5: Advanced Monitoring**

After a company has successfully undertaken the foundational steps, it can progress to advanced monitoring techniques for more technically focused individuals. More parameters can be monitored, including techniques for time series data, multivariate monitoring, and advanced dashboards and reporting. Again, the goal is to automate this process to provide the right information to the right customer. Various levels of reports should be delivered for different needs. The following procedures typically target technically savvy individuals to increase process knowledge. They can configure and automate advanced monitoring and investigational procedures, including:

- Critical process parameters (CPPs) and other business variable monitoring.
- Relationships between CPPs and CQAs.
- Efficient behaviors to deal with assumption testing. Many companies return to their guidelines and revise them to achieve better signal and process information.
- “Golden batch” analysis.
- Continuous monitoring capabilities.
- Multivariate analyses program.
- Automated CPV report generation.
- Link monitoring outputs to OOT standardized investigational analysis.
- Advanced dashboards with drill-down capabilities.
- Advanced trending techniques for specialized use cases (control charts based on other distributions).

The most common evidence of advanced monitoring milestones include: (1) an increase in the number of parameters and analyses conducted; (2) a decrease in the time spent reporting and communicating CPV monitoring information; (3) a reduction in time spent on OOT investigations; (4) an increase in analysis complexity; and (5) a rise in the number of individuals that consume CPV information.

As shown in Figure 2, the need to revisit earlier phases often emerges at this phase as well. Companies realize they can’t do advanced process monitoring with their existing technology, so they return to phase 2 to seek a more appropriate solution.

**Phase 6: Expanded Data Access**

After monitoring tools have been configured and automated, it must be determined how data will be added into the system to adjust for process changes and to increase process knowledge. A CPV initiative is a dynamic process that will be continuously updated over time. As a company analyzes the data it has been processing, personnel will derive valuable manufacturing process knowledge. As understanding increases, more questions will be asked. Additional parameters can and should be monitored to answer those questions. Continuous improvement involves movement through the CPV maturity model to

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**FIGURE 2.** It may be necessary to revisit earlier phases in the maturity model.
increase and modify monitoring procedures. Companies should plan for increasing data amounts and measure their average need for additional data, after initial implementation, to assist in resource and budgetary planning.

Common milestones of expanded data access include multiyear plans and budgets for growing data needs, reports of data access changes, and resources devoted to maintaining data access and aggregation.

**Phase 7: Meta-Monitoring**

A conclusive decision cannot be made based on monitoring for a single parameter. To gain a holistic understanding of a product, site, and overall company status, hundreds of thousands of statistical outputs and data visualizations must be combined to make educated, data-driven business decisions. For example, if a product is manufactured globally at multiple sites, many parameters and tools are monitored across those sites that must be combined to determine the status of the product.

Meta-monitoring is the process of combining information to gain an overall understanding of the status of a process or product. Simply stated, meta-monitoring means monitoring the monitoring process. Drawing from research terminology, meta-analysis combines several types of analyses so users can make sense of them. Meta-monitoring is the same concept, but applied to CPV monitoring.

**Figure 3** describes how monitoring for each individual parameter needs to be combined to access the status of a process step, and then combined again to access the status of a site or product and finally, combined again to access the overall status of all company products and sites.

During this step, companies usually discover a lack of alignment among sites that produce the same drug or use similar processes. Companies typically undergo harmonization procedures to better align parameters across sites and products. In the first attempt at meta-monitoring, it is common that only 10–20% of parameters can actually be compared across sites. Therefore, companies typically move back to the previous step to revise or add parameters for comparison purposes.

Different statistical techniques need to be applied when conducting meta-monitoring procedures (e.g., effect sizes) to ensure that a true comparison is made. It is easy to use the simplest comparison methods (e.g., \(t\)-tests) and make false conclusions based on incorrect statistical comparisons, such as failing to account for the influence of sample size. These pitfalls are common and can discourage buy-in from stakeholders because the site/CMO displays poor performance due to a statistical artifact, not a true difference.

A company doing commercial-scale production can use meta-monitoring to determine if all of its products, sites, and process steps are satisfactory and suggest where to invest in improvements. Common evidence of meta-monitoring includes annual company-level monitoring reports that address process, site, and meta-monitoring analyses indicating data-driven decisions based on monitoring dashboards and reports.

**FIGURE 3.** Meta-monitoring includes parameter-level, process step-level, and site-level monitoring.
Summary

To maintain a state of control, life science companies should implement a CPV initiative. In the process of developing and maintaining a scalable and sustainable monitoring program, companies are likely to face various challenges. A maturity model can help companies meet these challenges and navigate the major steps to implement a global monitoring plan for continued process verification. A successfully implemented monitoring program helps life science companies adhere to regulatory guidelines, increase process understanding, reduce process variability, and improve process consistency and predictability. Hopefully, the framework presented here will help companies efficiently implement continued process verification.

References


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