FDA'S 2011 PROCESS VALIDATION GUIDANCE: 10 YEARS ON

By the ISPE Process Validation Team

In 2011, the US Food and Drug Administration (FDA) introduced the revised "Guidance for Industry: Process Validation: General Principles and Practices" [1]. The document incorporated principles from existing ICH guidance in place since 2005 (ICH Q8 and Q9) and 2008 (ICH Q10) [2–4]. ISPE formed their Product Quality Lifecycle Implementation (PQLI)® initiative to provide guidance [5] on the practical implementation of the concepts described in these ICH guidelines.

When the process validation (PV) guidance was published, the pharmaceutical industry was adopting quality by design (QbD) approaches to pharmaceutical development. This brought awareness of critical quality attributes and allowed critical process parameters to find their way into industry discussion and regulatory submissions. However, the FDA PV guidance created significant change to PV approaches with the introduction of the now-familiar three-stage life cycle approach and other science- and risk-based terminology and requirements. It was also known that the European Union (EU) regulatory authorities were planning to publish similar guidance for the EU.

THE ISPE PROCESS VALIDATION TEAM

Thus, the ISPE PQLI Team recognized the need for specific support around PV and a working group which became ISPE's Process Validation Team. This team has remained active since then, publishing a number of discussion papers [6]. In 2019, they also published a comprehensive Good Practice Guide, titled *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* [7].

In addition to publication of discussion papers and the Good Practice Guide, the group has facilitated industry and regulatory dialogue and discussion through many forums, including:

- Presenting best practices from ISPE member companies
- Hosting work groups and discussions on challenging subtopics
- Publishing articles in ISPE's *Pharmaceutical Engineering*® magazine and other industry journals
- Delivering relevant conference and workshop sessions

The team regularly facilitates full sessions at the ISPE Annual Meeting & Expo on PV-related topics and has organized five well-attended stand-alone PV workshops in 2012, 2013, 2015, 2016, 2017, and 2019. Additionally, the team developed the content for ISPE's popular three-day process validation training course and has provided the core group of instructors who present and maintain this offering.

LIFE CYCLE PV IMPLEMENTATION

Now that over a decade has passed since the publication of the 2011 US FDA Process Validation guidance, the team posed the question: What does the implementation of life cycle PV look like? This article is a collection of individual and collective responses from team members who are practitioners and industry participants in this field, representing a cross-section of pharmaceutical organizations, locations, and roles from all parts of the world.

Implementation and maturity of the life cycle approach to PV varies widely across the pharmaceutical sectors (including biotechnology) and markets around the world. For some early adopters, the principles and practices are now part of business as usual. However, even in these organizations, there can still be challenges to implementation or understanding. Some organizations recognize the business benefits of the life cycle approach, whereas others have implemented programs with a minimalist compliance perspective. The following summarizes our team's key observations regarding the evolution and current state of this approach.

THE KEY TO LIFE CYCLE PV: PLANNING WELL

It may first appear that the three stages of life cycle PV are wrapping Stages 1 and 3 around an existing proven validation program. To some extent that is true. However, it's not that simple, and the consequences of that simplification vary. The most benefit is realized when organizations break the traditional walls between development, technology transfer, validation, and operations and approach validation cross-functionally across the product life cycle.

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Stage 1

For new product introductions, the concept of a new "Stage 1" output demands increased effort and reliance on good science- and risk-based approaches to product development and technology transfer. While the 2011 FDA PV guidance was being finalized, the incorporation of ICH concepts, such as control strategy, was becoming an expectation for the registration of new products. To some extent this has been an evolution of development and regulatory practices moving in tandem so that regulatory submissions contain information compatible with Stage 1 concepts.

Although the concept of a "design space" submission was found to be challenging and did not always afford the anticipated regulatory flexibility, the efficient development and understanding of multivariate relationships of attributes and parameters using a design of experiments (DOE) approach has become more commonplace.

The situation becomes considerably more clouded in the case of existing products where development information is not necessarily aligned with ICH principles. In this case, organizations may need to evaluate development knowledge and/or retrospectively develop a control strategy using risk-based principles. Members of the PV team continue to see challenges with this approach where lack of science, process understanding, or data complicates implementation. Executing effective and complete Stage 1 programs can be a challenge for late-product acquisitions and breakthrough therapies.

Stage 2

The concept and related activities of intra- and inter-batch variability (within and between batches) introduced in the FDA guidance was initially challenging for most manufacturers. Although the sampling and analysis necessary to provide adequate evidence of control of both variability components has become well-established for some manufacturers, it remains unclear for other organizations.

The introduction of the life cycle approach to PV eliminated the automatic magic number of three batches for PV Stage 2. It even opened the door for potentially fewer than three PV batches for highly automated processes, or process changes with very limited risk. However, most manufacturing organizations deliver products globally and many markets still expect a three-batch PV. Organizations that execute a risk analysis prior to PV, to determine the number of batches, will often perform additional PV Stage 1 development work, in lieu of doing more than three PV batches.

The level of input variability already studied or level of experience in the commercial manufacturing setting are not always key factors in the evaluation. Due to supply availability or lack of planning, it is not always possible to include worst case variability as part of PV. Although between-batch variability evaluation is required per the life cycle approach to PV, most organizations delay statistical analysis of this component until Stage 3 (continued process verification [CPV]).

Stage 3

Creating a CPV/ongoing process verification (OPV) program (like those required for Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme [PIC/S] and the EU) can seem reasonably straightforward. The concepts and tools are readily understood. However, the program can become problematic without careful planning and well-designed procedures. It is not as simple as trending all results of heightened and routine testing. Such an approach could result in an unmanageable and wasteful increase in data and effort for its management. Thus, most adopters have come to recognize that you cannot effectively implement Stage 3 without Stage 1.

Stage 1 understanding gives an organization the foundation required to manage resources and focus efforts where it matters most, and the framework to manage responses to the variation we see in processes when monitoring these more frequently. Understanding interactions between material characteristics, process parameters, and extended control strategy variables—such as different operators, equipment trains, and shifts—is vital to establishing a meaningful testing and monitoring plan.

With no real Stage 1 inputs, the resources required to adopt and manage Stage 3 can quickly become overwhelming. This impacts the validation or technical operations departments and the quality department, which manages the additional process information and its significance (or insignificance) to product quality. They must assure batches are not released until all heightened testing results are confirmed within limits.

Our first observation: If an organization has a life cycle PV program in place (and hopefully most do), it is understood that this is a journey that requires considerable effort and will evolve as you gain experience. For those just starting the journey, a comprehensive plan is required. This will take considerable time to implement and there are many potential pitfalls, beyond what may appear to be resource needs.

EXPECTATIONS FOR LIFE CYCLE PV COMPLIANCE VARY GLOBALLY

Life cycle PV is founded on the principles of process understanding and control, which has obvious business and patient benefit. However, there is also a compliance component, which in our experience, varies substantially across the global pharmaceutical sector.

Based on recent (and not so recent) 483 observations in the US and other markets, it is clear that the FDA has adopted principles and concepts of life cycle PV. However, it would appear from our experience that other regulatory authorities may be slower to observe deficiencies to validation programs in this area. It is our impression that there is a gap in the level of implementation of these principles based on geography and market. This gap is unlikely to persist, and ISPE has recently seen significant international demand for content related to original concepts developed by the PV team when it was presented in webinar format.

There appears to be a delay with adoption of these principles in audits in some markets and jurisdictions. We expect part of this delay is to permit some inspectorates to develop the process and statistical skill sets necessary to inspect in this area. Nonetheless, industry should not be waiting for inspection observations to change to implement life cycle PV.

We feel this lag is not due to hesitancy; it is recognition of the challenge inherent in application of science- and risk-based principles to a pharmaceutical process. Essentially, it takes some time to develop the skill set. For instance, proper use of statistical methods requires knowledge of both the process and the appropriate statistical tool. However, few process experts are statisticians and even fewer statisticians are process experts. Building the necessary capability within an organization to effectively leverage statistical methods requires an investment of time and resources.

Our second observation: The best adopters have planned to make sensible tools and decisions available widely. They have structured a learning environment where knowledge and understanding of the process grows within the business. These organizations generally build capability at the processing level and leverage subject matter experts as needed for specific issues and situations.

ADOPTION OF CPV/OPV IS BECOMING EMBEDDED AND WELL UNDERSTOOD

Once the initial challenges of managing resources and processes for implementation of a CPV/OPV program are overcome, the process is generally easy to understand for staff and management. There are clear business benefits to having increased visibility over process performance. However, some refinement and learnings are required.

Early in the program, organizations must reconcile the balance between the cost of data collection (sample size and effort) and process understanding. Early estimates of process variation can paint a conservative picture of process control. Gathering insufficient information to truly understand underlying sources of variability in processing can make control look less effective. True process control understanding requires a good data set, which takes time to collect and process. Once initial data collection efforts commence, focus is required to ensure that efforts are prioritized into areas that improve product quality and reduce risk.

CPV/OPV programs must maintain the flexibility to allow process owners the ability to manage and react to learning while operating within the pharmaceutical quality system (PQS) and GMP rules. Frequent data collection and evaluation (both formal and informal) are key to an effective program. Operations that are out of trend are not necessarily out of specification, and terms such as "not under control" can have different meanings across the business and to management. Successful CPV/OPV implementation requires a common understanding of the intent and language of process control across multiple functions.

Our third observation: The CPV/OPV program is the stage where adoption of life cycle PV is most advanced in many organizations. Once the initial framework is established, the program provides business, operational, and patient benefits that are clear to those involved and serves a mutual purpose to improve process understanding and management. CPV/OPV is not simply an extension of the annual product quality review (APQR) program; it is more nuanced than this.

LIFE CYCLE PV FORMS THE BASIS FOR PRODUCT ROBUSTNESS PROGRAMS

Although there are compliance requirements for implementing CPV, organizations can realize significant benefits. But these can only be achieved if an organization truly understands how to use CPV to leverage process knowledge and understanding.

The deliverables of CPV should be seen as:

- Confirming the ongoing robustness of the manufacturing process
- Creating a proactive approach that provides early identification of a performance change and potential intervention, thereby avoiding process quality issues (e.g., out-of-trend [OOT] and out-of-specification [OOS] results)
- Using routine CPV trending and process understanding to support process changes
- Supporting the identification of improvement projects

The CPV plan should define what parameters/attributes should be trended; the frequency of trending; and whether additional samples are required to support assessment of process robustness/capability. These details will depend on the robustness of the manufacturing process, the process capability of the parameters/attributes, the level of process knowledge that exists (e.g., development batches, data from other manufacturing sites), and the level of input variability already experienced by the process, and relationship to allowable limits.

Some organizations may judge these activities as requiring too many resources and choose to implement the plan to only meet the compliance requirements. It is only by fully implementing CPV that the wider benefits can be realized. Many organizations have recognized the benefits of enhanced process understanding and are using the data and information to build additional robustness into manufacturing and business processes. Information from life

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cycle PV can be used to enhance "platform knowledge," enabling faster and smoother tech transfers and more rapid new product introductions.

Understanding external sources of variability in processes—such as factors within supplier networks—can enable significant improvements to products and processes. It can also reduce the risk and effort required for onboarding new suppliers and developing efficiencies in materials management, in turn helping assure the reliability of supply.

Understanding the capability and variability of a process can prioritize efforts elsewhere in the manufacturing organization to maximize benefit and minimize risk; for example, reduction of measurement error, optimal quality control testing, in-process monitoring, and automation.

As process understanding grows, the effort required to maintain and improve a process decreases. For well-understood processes, smaller and more focused efforts often bring measurable or significant improvements, and the process becomes self-perpetuating as the risk associated with improving diminishes.

Our fourth observation: Organizations with relatively mature CPV/OPV programs soon recognize benefits and begin leveraging PV efforts to improve manufacturing robustness.

DEVELOPING OF SCIENCE- AND RISK-BASED UNDERSTANDING IS NOT EASY

Although realizing gains through measurement and improvement is somewhat intuitive to manufacturing organizations, the development of science- and risk-based understanding and application to develop more robust processes or improve them is less tangible and more difficult to implement.

Most manufacturing organizations hold inherent process knowledge and when presented with new data or information can reconcile that in the context of that knowledge. However, more fundamental or new process understanding can be more difficult to master when organizations do not expect or understand this.

For example, multivariate interactions can occur in quite simple unit operations and may be difficult to measure or explain, even to experienced operators. When a process is tolerant to these interactions, this may not be material to process control. However, if these interactions are significant to the process and resulting product, they need to be understood.

Understanding and communicating or transferring process knowledge still presents challenges in some organizations, even those with a high level of competency in other areas of PV. It can be a struggle to capture, maintain, and communicate this knowledge effectively, which can impede realizing all the benefits of a life cycle PV program or recognizing sources of variability in processing. We have observed—from ISPE training and workshops, as well as experience in our own companies—that the utility of risk management and control strategy for knowledge management is underutilized.

The risk assessment tools traditionally used in the pharmaceutical industry may not be optimal to communicate science- and risk-based knowledge. Successful development and validation programs are more effective at managing this knowledge and can effectively transfer process understanding to operations in a format that is readily understood and can be maintained and improved. Effective quality risk management links knowledge and understanding from all phases of the product life cycle. When this does not occur, suboptimal risk assessments or failure to recognize and control risks can result.

Facilitating the linkage between development and manufacturing as well as feedback from the process in operation requires careful planning and can be difficult to achieve. Common errors include:

- Poorly founded or developed hazard analysis that does not reflect the true situation
- Difficulty in recovering platform-relevant data when it has been collated in product-specific databases
- Subjective scoring or ranking, which distorts residual risk levels or the relative importance of risks
- Difficulty in capturing actual capability in risk estimates, due to lack of visibility and feedback

Our fifth observation: Organizations with highly effective PV programs have structured tools for capture and communication of science- and risk-based information. These tools are interactive, allowing for learning and improvements.

NOT YET SEEING FULL BENEFITS THROUGH REGULATORY ACTIVITY AND CHANGES

Industry and regulatory authorities have long desired a state where regulatory flexibility could occur with product submissions based on understanding of science and risk. The adoption of ICH Q12 internationally has created a framework where this is possible. A few organizations are using this approach for new product registrations, and there is general interest in the potential benefits from these approaches within industry. Although the number of new products registered in this manner is increasing, the proportion of approvals worldwide remains relatively small.

The use of science- and risk-based approaches for development and validation facilitates product and process understanding, which would support plans for regulatory flexibility but does not directly enable it. This knowledge certainly assists in managing operations and potentially reduces issues, including those that are reportable or of concern. There is some potential leverage from an effective PV program for compliance programs such as annual product quality review (APQR), but while these programs overlap in terms of their focus on process variability, both PV and APQR are required to be operated within the organization's PQS.

It can be difficult to realize the benefits of effective product and process understanding when the rationale for reduction of compliance efforts is not clearly justified—an issue related to challenges in communication and maintenance of knowledge.

Some regulatory authorities and inspectors appear, like industry, to be still building the technical competence to confidently operate a science- and risk-based environment. They may distrust the motivation of a manufacturer using these techniques unless they fully comprehend the data. While organizations are looking to register products in a number of markets, the divergence of understanding and the rate of adoption for this life cycle approach presents an unintended impediment to the realization of full benefits, such as regulatory flexibility. Some organizations are championing this by presenting packages that reflect high levels of process control and understanding.

Recent trends to accelerate medicine approvals for products such as vaccines or new-generation medicines appears to have encouraged both manufacturers and regulatory agencies to focus more on the use of science- and risk-based approaches and understanding to facilitate availability of medicines.

Our sixth observation: Organizations with well-established product and process understanding are often those that seek and gain some degree of regulatory flexibility.

CONCLUSION

Technology for pharmaceutical development, manufacturing, and data management is advancing and the products are becoming more specialized. At the same time, industry and regulators are being exposed to techniques and applications that demand better utilization of science- and risk-based techniques. These products and technologies challenge the paradigm of historical risk, knowledge-management practices, and our application of PV. They also create an environment that encourages our industry to explore new techniques.

The pace of learning is increasing, but there is a significant gap between understanding and application of science- and risk-based techniques for older products and in some markets. This gap might be accentuated as pharmaceutical organizations look to divest or rationalize. As an industry, we need to focus on building robustness into manufacturing pharmaceutical products at both ends of the spectrum to ensure better outcomes for our operations and patients worldwide.

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