Process Validation: The Life Cycle Approach

Dr. Ajay Babu Pazhayattil

In 2011, the US FDA revised the Process Validation (PV) Guidance [1], marking a substantial conceptual shift. The framework applies equally to API/drug substance producers as well as to drug product manufacturers. Since its release, regulatory observations citing inadequate PV implementation have surged for both drug substance and drug product sectors, making it a persistent high-risk compliance area. In fact, applying the new PV concepts to drug substance manufacturing is more challenging, as the processes are inherently more complex and endpoint-based, making them far more difficult to control. Despite many subject matter experts entering and leaving the field, one truth has remained consistent: regulators expect companies to adopt the life cycle approach in practice or be prepared for recurring observations. The perspectives discussed are based on my direct contributions to all major industry guidelines related to PV (AAPS, ISPE, PDA, RAPS), a unique opportunity I have been fortunate to have [2, 3, 4, 5, 6]. If you are committed to transforming your approach to process validation, I invite you to read on.

Under the life cycle approach, process validation is no longer a finite activity conducted prior to commercialization. Instead, it is an ongoing exercise where a process is always in one of three stages [Table 1]

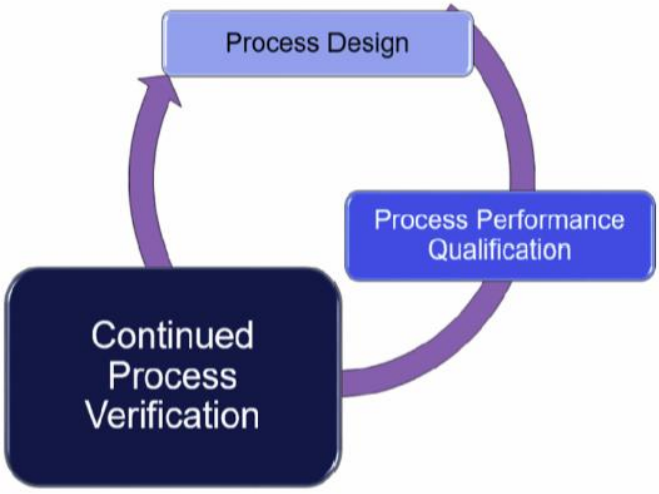
Table 1: Pre and Post 2011

Process Validation- In the Past	***Process Validation- Today***
Process Qualification Only (Similar to Today's Stage 2- PPQ)	Process Design (Stage 1- QbD) + Process Performance Qualification (Stage 2- PPQ) + Continued Process Verification (Stage 3- CPV)

In the past, PV largely ended with a singleton stage of running 3 batches with additional sampling and testing. Today, it is a continual cycle [Figure 1]. The newer Stage 3 introduces perpetual oversight, meaning your process will re-enter Stage 1 whenever statistical alerts or drift are detected. The shift requires far more rigorous process design. Scale-up factors and their impact on critical quality attributes (CQAs) must be understood up front. Without identifying the sources of variability and their magnitudes, achieving the required statistical confidence during Stage 3 becomes difficult. When a process is in Stage 3 CPV, a statistical alert and resultant analysis may result in returning to Stage 1. Conversely, processes with low inherent variability are more likely to meet Stage 3 criteria without any remediation. This connection has driven companies to invest heavily in Design of Experiments (DoE) and in mapping the influence of process parameters on CQAs early in development. Armed with Stage 1 insights, the development teams can best

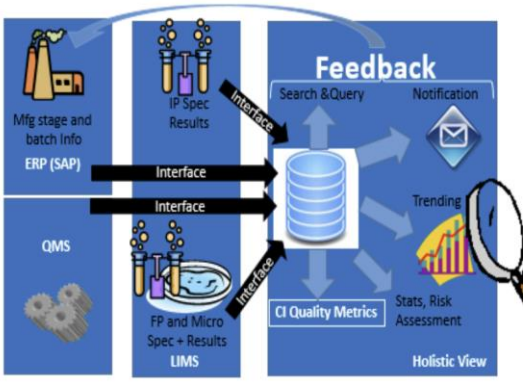
estimate the number of Stage 2- PPQ batches required [7], justify the sampling plans, and testing needed to statistically prove process robustness. This informed Stage 2 execution increases the likelihood of seamless progression into Stage 3- CPV.

Figure 1: The Cycle of Process Validation



When Stage 2 PPQ concludes, many organizations jump straight to routine Stage 3 monitoring. In 2014, we proposed an intermediate Stage 3a [8], which is a targeted, protocol-driven, heightened monitoring phase. Stage 3a is aimed at confirming that the process behaves as predicted during QbD based development [9]. It involves close monitoring of a substantial number of commercial batches under intensified sampling and the use of advanced statistical tools for analysis [10]. Stable parameters with minimal impact on CQAs can thus be eliminated from routine monitoring. The outcome is a detailed, scientifically sound, and statistically substantiated report that captures the most comprehensive understanding of the process and determines ongoing monitoring requirements.

Figure 2: Data Enablers for Stage 3 CPV



Stage 3b is the ongoing, SOP-driven phase of process monitoring and trending. It detects early signals of process drift and triggers escalation where necessary prior to a failure. Effective Stage 3b execution primarily requires an integrated electronic data system that consolidates process

parameters from equipment and instruments, quality attribute data from LIMS or similar solutions, quality events information from QMS, and material/batch information from ERP systems [Figure 2]. Change management under the life cycle approach demands a different mindset as well. Any change affecting a process in Stage 3 requires a return to Stage 1 for evaluation/process redesign. A process in Stage 3 never moves directly back to Stage 2 PPQ without first revisiting Stage 1. Since a transition always requires the active involvement of the process development team, and the Stage 3a assessment, as well as Stage 3b signals, need regular input from the same group, it is advisable to shift process validation responsibility from the traditional quality or operations teams to the site's technical operations or process development groups.

Many may question whether the additional effort and cost are justified. The greatest advantage of fully embracing PV expectations is a dramatic reduction in failures. With a deep understanding and control of variability, the risk of process failures becomes minimal. Combined with early detection of process drift, the lifecycle approach to PV ensures consistently smooth and reliable operations. The resulting decrease in failures and enhanced operational stability translates into significant financial benefits often exceeding those achieved through conventional lean methods. The implementation enables greater flexibility in managing changes because their effects are predictable and quantifiable, leading to substantially lower change management costs. Lastly, organizations that fully implement the process validation lifecycle approach are viewed by regulators as mature and reliable, which greatly reduces the likelihood of enforcement actions.

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