MYCENAX

WhitePaper

Effective Process Validation Accelerates Your Drug to Market

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Key Takeaways

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Conventional process validation typically entails a certain number of consecutive successful manufacturing batches at a commercial scale prior to submissions of major regulatory packages - such as BLA’ s. This approach has been and may still be practiced in many regulatory jurisdictions. Nevertheless, a more wholistic and integrated strategy has emerged over the past decades, calling for more lifecycle-oriented considerations. In essence, process performance qualification (PPQ) is now established on a more continuous basis over the entire product life cycle, hence continuous process verification (CPV).

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The conventional process validation approach is still appropriate but only as a subset of the overall process performance qualification effort. PPQ in conjunction with CPV encompasses the entirety of process performance metrics: building on the foundation of Quality by Design (QbD), emphasizing risk-based control strategies, effectively managing lifecycle knowledge, planning for continuous improvements, etc. They are now viewed as guiding principles for ensuring consistent manufacturing process performances.

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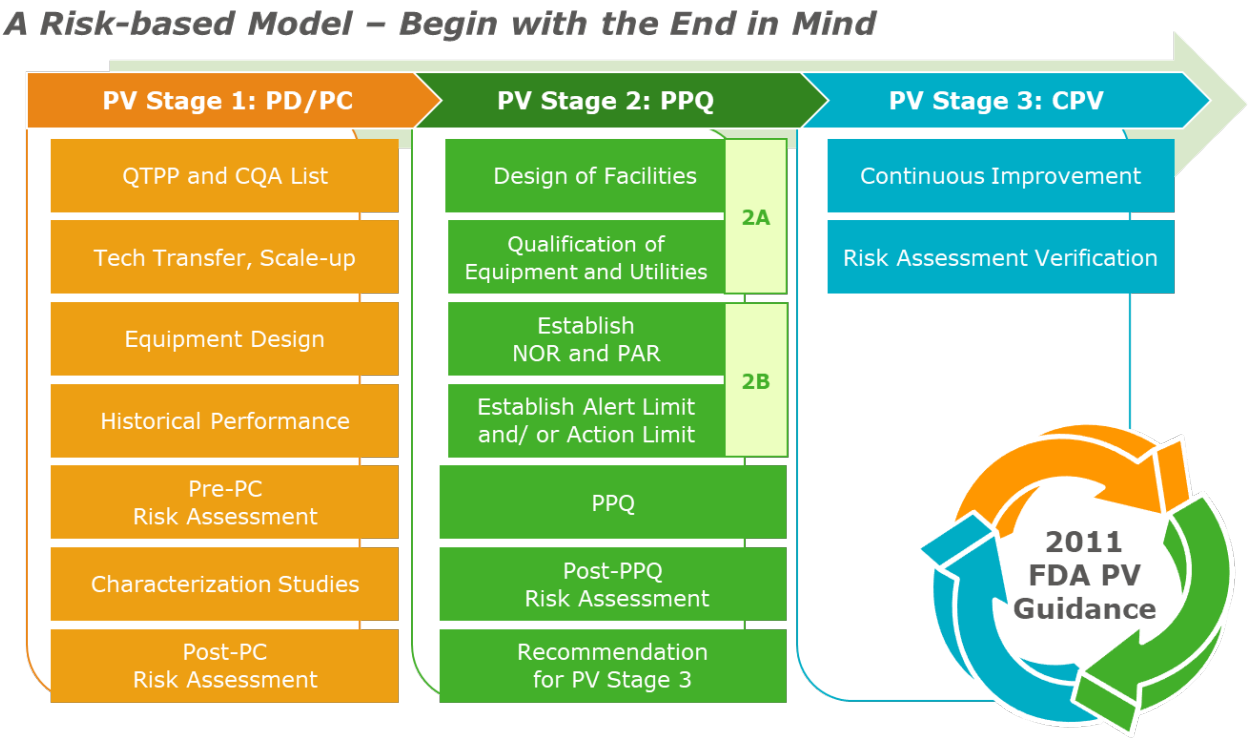
Chapter 01

Process Validation Overview

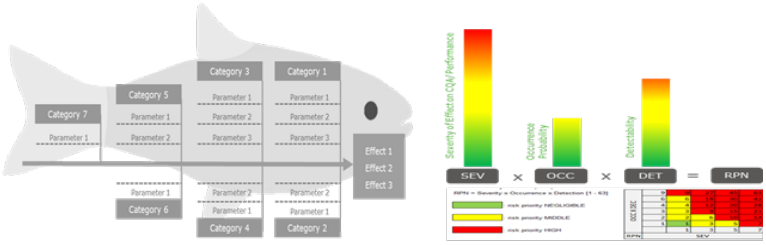
Process Validation Master Plan and Quality by Design



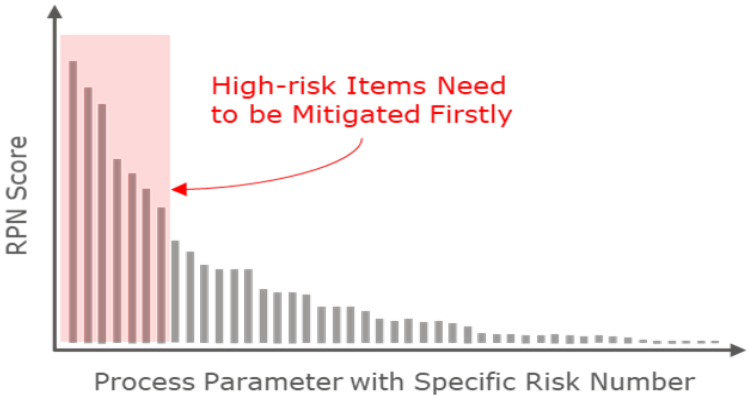
Mycenax Biotech Inc. follows the three (3) process validation (PV) stages published by the U. S. FDA to initiate PV activities with a product-specific master plan. This plan is built on the concept of QbD, which applies a parametric approach as opposed to an attribute-based approach to process design. The quality target product profile (QTPP), describing the design objectives for the product, is the basis for identifying critical quality attributes (CQAs).

Understanding process capabilities and their potential impact on product quality attributes identified during PV stage 1, process design, is the foundation for formulating process control strategies. The control strategies require risk management by linking CQAs to process capabilities and risk characteristics. Manufacturing campaigns with appropriate control strategies ensure that critical process parameters (CPPs) and CQAs consistently remain within acceptable limits, demonstration of which is the focus of PPQ: to evaluate and confirm if the process is capable of reproducing the process performance observed during PV stage 2. In PV stage 3, a CPV plan is applied during routine production to ensure that the process remains in a state of control. The objective is to generate documented evidence that the process, when operated within established parameters, can consistently reproduce a product meeting its predetermined specifications and quality attributes.

Risk Assessment and Risk Management



CQA, Specification, KPA, or Characterization	USL	Target	LSL	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Titer				High					
Purity						High			
Host Cell Protein (HCP)					Low	Medium		High	
Host Cell DNA (HCD)					Low	Medium			High
Leakage Resin-ligand						Low			
Endotoxin					Low				High
Aggregates					High			Medium	
Size Variants (H/LMW)							High		
Charge Variants							Medium	High	Low
Step Recovery, Yield						High		Low	



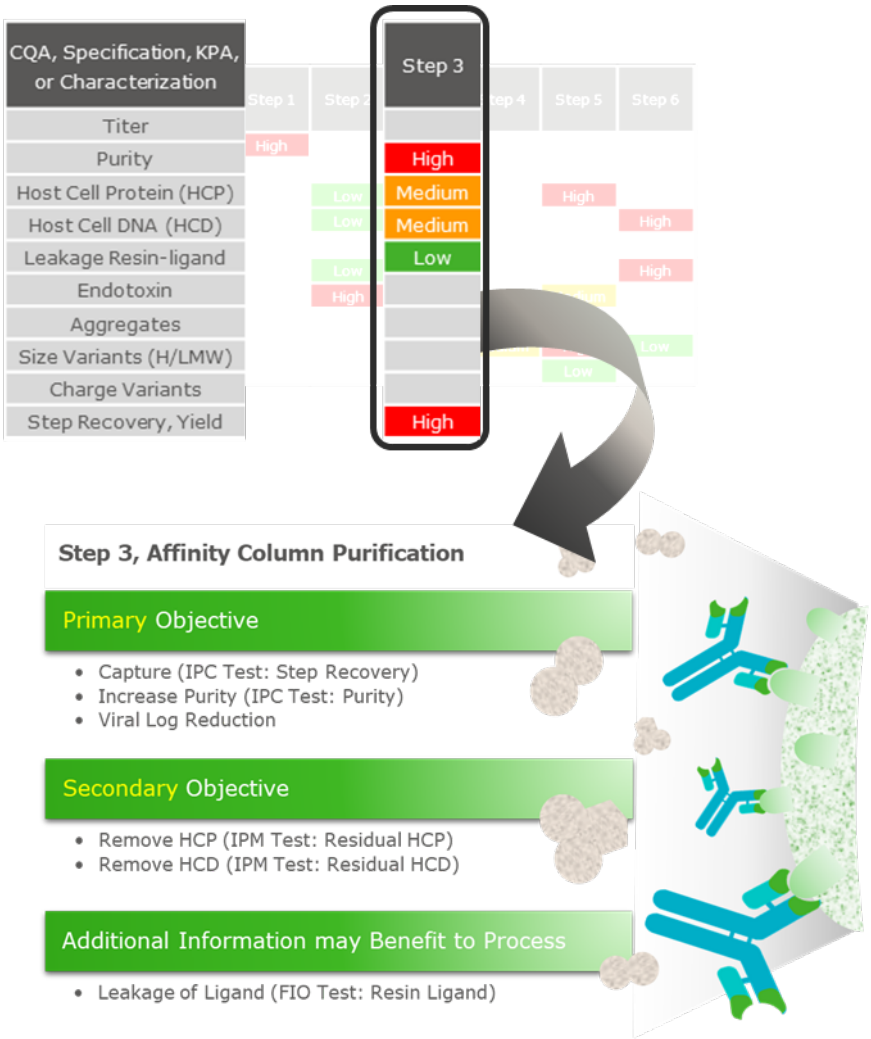
The outcome of risk assessments should be verified, traceable, and documented throughout the product lifecycle. Besides "process" risks, assessments of raw materials, microbial control, extractables, and leachables, etc. are all essential to ranking the studies needed to ensure that a process remains in control. Thus, an integrated team would use the knowledge gained from process development (PD), process characterization (PC) studies, and manufacturing experiences to evaluate the risks.

A high-level risk assessment can clarify which CQAs are influenced by each process step and identify unit operations that require further characterization to mitigate risks. Following the causes and effects of a potential impact on product quality, failure mode and effects analysis (FMEA) analysis can help to quantify the risks based on severity (SEV), occurrence (OCC), and detectability (DET). Items with High-risk priority numbers (RPNs, the multiplication product of SEV, OCC, and DET) are prioritized for risk mitigation to achieve proper manufacturing controls and reduce the overall risks to the product.

Chapter 02

Building Process Knowledge and Understanding Process Capabilities

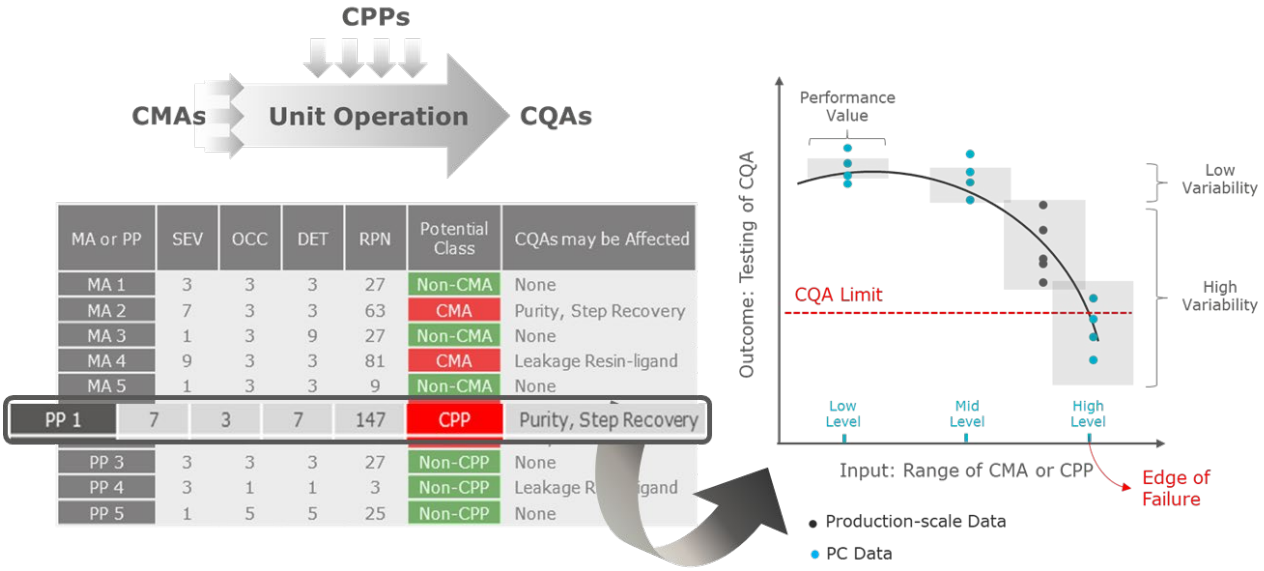
Define Unit Operations with Step-specific Objectives



Early-phase PD aims to develop a process with detailed step elements and generate sufficient quantities of molecules for preclinical and clinical uses, while building a list of CQAs. Late-phase PC studies may optimize the unit operations with systematic thinking and more refined step-specific objectives based on the high-level risk

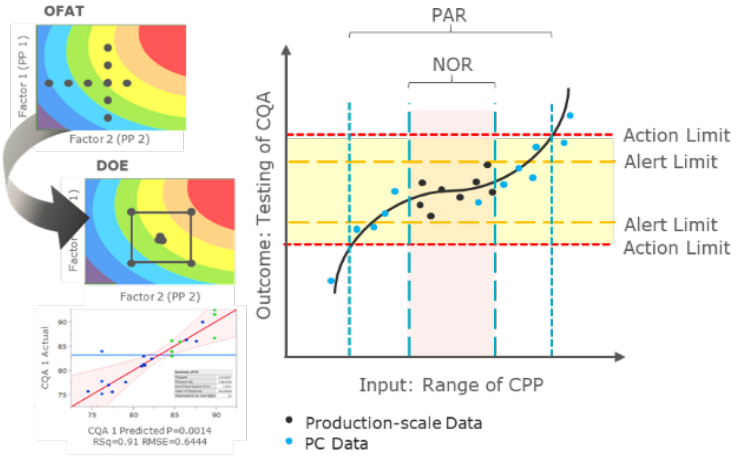
assessment. An affinity column purification is shown as an example in a monoclonal antibody manufacturing process. The affinity column, a commonly employed purification step, fulfills multiple purposes, including capturing the target biomolecules and allowing impurities, such as HCP and DNA, to flow through. Further, it is also known that the resin ligands may leak after several reuse cycles, potentially impacting column performance. This historical knowledge and public scientific information provide useful guides for setting appropriate study purposes during PC and in subsequent PPQ. In this example, the step yield and the purity of the target biomolecule are set as in-process controls (IPCs), which can reveal performance with respect to its primary objective of capturing the target molecules. Other information, such as residual HCP, DNA, and leaked ligand, which may not directly reflect the primary functions of the affinity column, can be monitored as in-process monitoring (IPM) or for-information-only (FIO) test items.

Identify CPP based on Product Quality Risk Assessment



The QbD approach emphasizes controlling controllable inputs (such as critical material attributes, CMAs, and critical process parameters, CPPs) while monitoring the outcomes (CQAs, lot-release results, or performance indicators). Initially, input materials or process parameters that impact CQAs are classified as potential CMAs or CPPs. For instance, the five production-scale data shown above indicated that the ranges of IPC results are highly variable within the operating range of process parameter 1 (PP1). This observation suggests the operating ranges of PP1 may impact IPC results. Thus, the PC team may need to generate more data in the design space study with multiple levels of PP1 to verify whether PP1 is a CPP. This study also helps to identify the proper operating ranges for PP1 (sufficiently away from the edges of the CQA limits) as a mitigation strategy to reduce process variability.

Characterize Process Capabilities and Establish an Operating Design Space

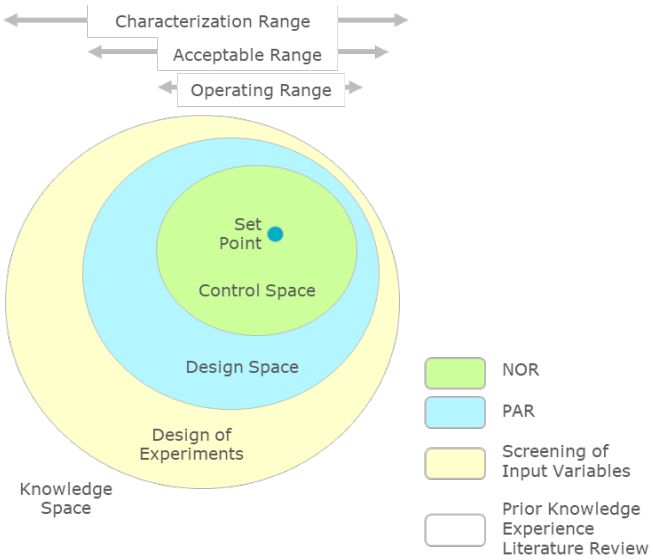


Design of experiments (DoE) approach provides a high-throughput platform for identifying CPPs and CMAs with a minimum number of experiments by leveraging statistical analysis.

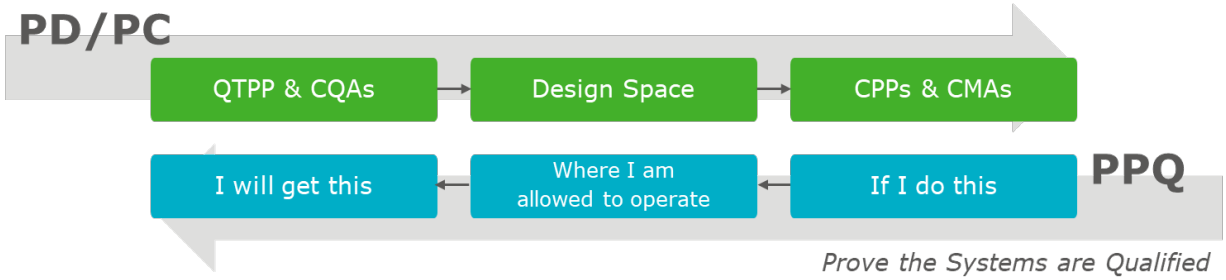
Furthermore, these DoE-selected CPPs can be identified as univariate or multivariate for further investigations into their respective normal operating ranges (NORs) and proven acceptable ranges (PARs). A relatively large buffer between an NOR and a PAR is considered robust for that particular parameter; a relatively small one signals that adequate process control should be applied to ensure that the parameter consistently perform within its NOR.

Establish Material and Process Control Strategies

A control strategy should summarize the parametric mitigation approach with QbD considerations. This may include the setpoint, NOR, and PAR of a CPP, and the alert limit and action limit of an IPC as a proposal for PPQ activities.



During PV stage 1, CPPs and CMAs are examined and characterized from large pools of process parameters (PPs) and material attributes (MAs), highlighting their potential impacts on CQAs. In stage 2, a PPQ campaign is performed to demonstrate that the process can produce quality products when CPPs and CMAs are adequately controlled within their design space boundaries.



Chapter 03

PV Stage 2 to Meet BLA Submission Requirements

03 PV Stage 2 to Meet BLA Submission Requirements

During this stage, the process design is verified as capable of consistent performance during manufacturing. Both facility and equipment (stage 2A) and process performance parameters (stage 2B) are qualified to gain sufficient confidence in the expected manufacturing outcome. The number of predetermined batches conducted for validation, while commonly practiced, is not the only acceptance criterion. However, it is a legitimate way to obtain at-scale data to supplement the data package.

Current Thinking on Process Validation: PPQ

Stage 2A aims to confirm that the facilities, equipment, utilities, and instruments (collectively called manufacturing systems) are capable of meeting all process requirements identified during stage 1. Manufacturing systems should be suitable and capable of their intended purposes. Engineering and commissioning studies provide essential information to ensure system reliability and consistency. Thus, qualification studies should be completed, reviewed, and approved to confirm system designs are aligned with process requirements before the start of stage 2B, the PPQ campaign.

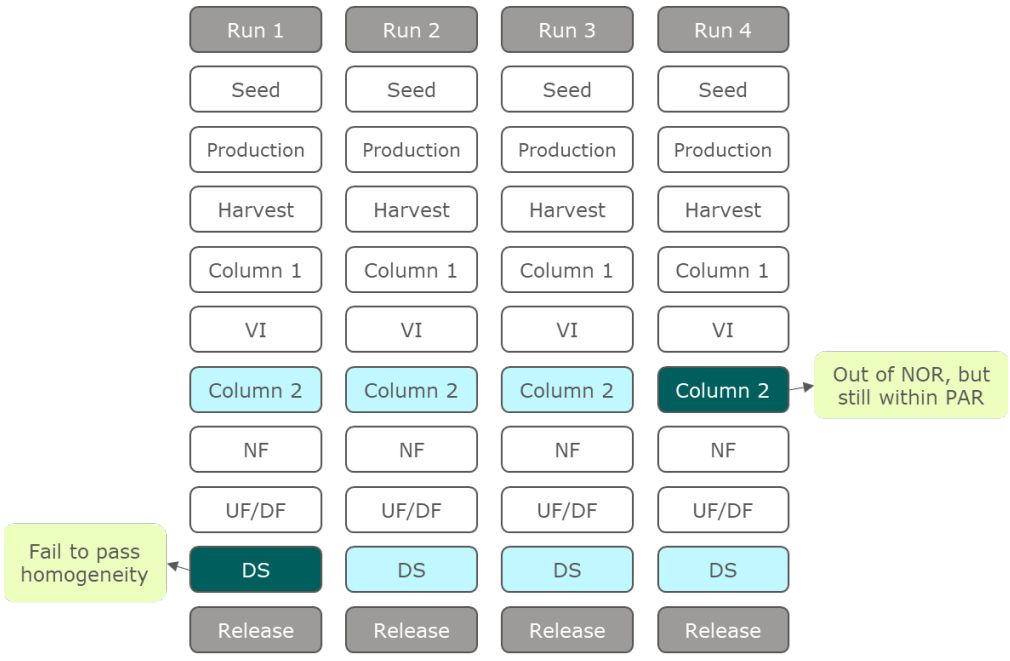
PPQ vs. Conventional Validation Approaches

Three (3) batches are conventionally employed but may no longer be adequate under the current PPQ/CPV concept. A risk-appropriate approach based on three (3) aspects, i.e., product knowledge, process knowledge, and control strategy, is adopted to determine the appropriate number of PPQ runs. The overall risk level determined from the risk assessment serves as the basis for three different approaches:

- ✓ Use a pre-set number of batches based on rationales and experience
- ✓ Translate risk levels and target confidence for process capability index (CpK) to the number of batches
- ✓ Translate risk levels and expected coverage into the number of batches

In addition, other approaches, such as consultation with internal subject matter experts, external consultants, or regulatory agencies, may also be appropriate to further evaluate the number of PPQ runs necessary with respect to the current regulatory expectations.

Execution Strategy

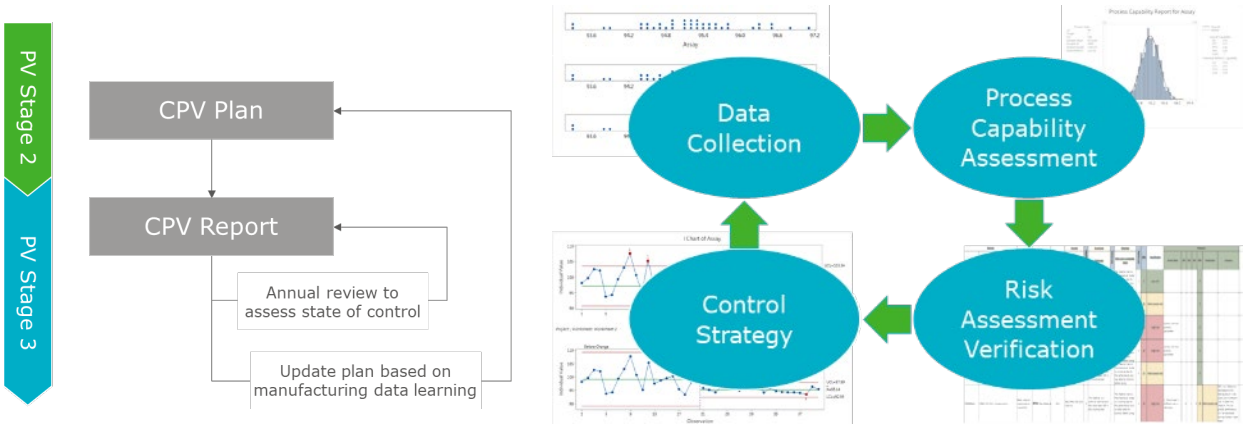


The PPQ objectives can be achieved by performing the PPQ with a focus on each individual unit operation in order to build more flexibility in the PPQ execution plan. Each unit operation is validated in that it is performed at least a certain number of runs- pre-defined and meets the acceptable ranges of CPPs and IPCs. Here, a successful PPQ with two well-justified deviations serves as a case study. Three consecutive successful runs for the unit operation are identified as its PPQ run strategy in this case. However, its drug substance concentration fails to pass the homogeneity test in the first lot. After a careful investigation, the root cause was identified as follows. The operator did not empty the buffer solution remaining in the pipeline, resulting in unexpected dilution at the beginning of the dispensing operation. As a consequence, the beginning samples with lower concentrations are disposed of, while the rest meeting the acceptable concentration and homogeneity criteria are released. A second example has to do with the NOR range being too restrictive due to insufficient at-scale experiences. In this example, one of the column' s load capacity is out of the NOR during the fourth PPQ lot. However, it is still within the PAR, as supported by the design space study and the viral clearance study; therefore, the deviation is adequately closed. As manufacturing experience accumulates, this parameter will be continually evaluated and adjusted as appropriate during CPV.

Chapter 04

PV Stage 3 with Product Lifecycle Approach

04 PV Stage 3 with Product Lifecycle Approach



Process-specific Improvement Opportunity

The commercial manufacturing data is expected to be translated into knowledge and documented in the CPV report and the annual product review (APR), governed under an overarching quality management system (QMS). Due to the complex nature of biologics manufacturing processes, not all sources of potential variabilities can be identified during stages 1 and 2. Thus, the CPV plan should focus on cataloging potential improvement opportunities first observed during PPQ runs.

Manufacturing Process Monitoring Plan and Data Analysis

Statistical analysis and risk-based tools always help to ensure that manufacturing data are captured and understood and employed to enable CPV. Upon identification of a relevant signal, a cross-functional review should be initiated to evaluate the significance of the issue and formulate appropriate actions to address the issue. CpK, which indicates the degree of process robustness, can also be used to inform suitable responses. For instance, the control chart of an IPC showing an outliner signal with a Cpk less than 1.33 may need to be evaluated to improve the control strategy.

Chapter 05

Concluding Remarks

05 Concluding Remarks

- Biologics manufacturing process validation aims to demonstrate the capability of a manufacturing process to deliver quality products consistently over time. The basic components of a process validation package include identification of key process variables and establishment of control strategies to ensure that all process variables stay within acceptable boundaries.
- As more knowledge and experience accumulate in the biologics manufacturing space, the rules and regulations as well as industry practices concerning process validation have evolved over the past several decades. It is important to recognize that today, a successful biologic manufacturing process validation program requires not just periodic PPQs but also an active CPV over the lifecycle of a given product - not just a moment in time. As such, it is imperative to build a product development program with a long-term vision and, at an early stage, adopt a more wholistic and integrated PPQ and CPV strategy.

Glossary

APR	Annual Product Review
CPV	Continuous Process Verification
CMA	Critical Material Attribute
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DoE	Design of Experiments
FMEA	Failure Mode and Effects Analysis
FIO	For-information-only
IPC	In-process Control
IPM	In-process Monitoring
MA	Material Attribute
NOR	Normal Operating Range
CpK	Process Capability Index
PC	Process Characterization
PD	Process Development
PP	Process Parameter
PPQ	Process Performance Qualification
PV	Process Validation
PAR	Proven Acceptable Range
QbD	Quality by Design
QMS	Quality Management System
QTPP	Quality Target Product Profile
RPN	Risk Priority Number

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