aizon

WHITE PAPER

The Road to Continued Process Verification (CPV)

Introduction

This paper explores how the pharmaceutical industry can effectively adopt and integrate Continued Process Verification (CPV) into existing production processes to optimize the increasingly pervasive continuous manufacturing ecosystem of today, as biopharma pivots from the lengthy and multi-step batch manufacturing norm of yesterday.

CPV offers pharmaceutical companies a compelling dual advantage: manufacturing processes are monitored in real time and redirected ahead of possible deviations. The ability to course correct in the midst of the production stream eliminates lengthy and costly back-end quality control testing upon batch completion, empowering biopharma to achieve Real Time Release (RTR) of therapeutics.

Though not yet widely implemented, CPV will soon become a necessity in pharmaceutical manufacturing, if companies wish to retain a competitive advantage. Actually, the FDA strongly recommends including CPV in chemistry, manufacturing and controls submissions and in annual product review deliverables. However, the legacy classical statistical analyses largely being utilized throughout the industry today do not lend themselves to CPV. The complexities related to material variability and the interconnected manufacturing processes and procedures that are the hallmark of biopharmaceutical drug production outstrip the abilities and insights offered by classical statistics. To enable CPV in the complex, multivariate operations of today's drug manufacturing environment, artificial intelligence (AI) must be deployed as an analytical tool. Aizon is complementing traditional statistical calculations with AI to implement CPV in real time and correct potential production deviations by means of a full process understanding.

CPV: The Anchor of Process Validation

In 2011, the U.S. Food and Drug Administration (FDA) published "Process Validation: General Principles and Practices." The FDA defined process validation as " the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."[1] Essentially, process validation

encompasses the chain of events that occurs during the product production lifecycle. The FDA's protocol outlined three stages to ensure the manufacture of safe and high-quality pharmaceutical products that consistently meet established quality standards and expectations: Process Design, Process Qualification, and Continued Process Verification (Figure 1).

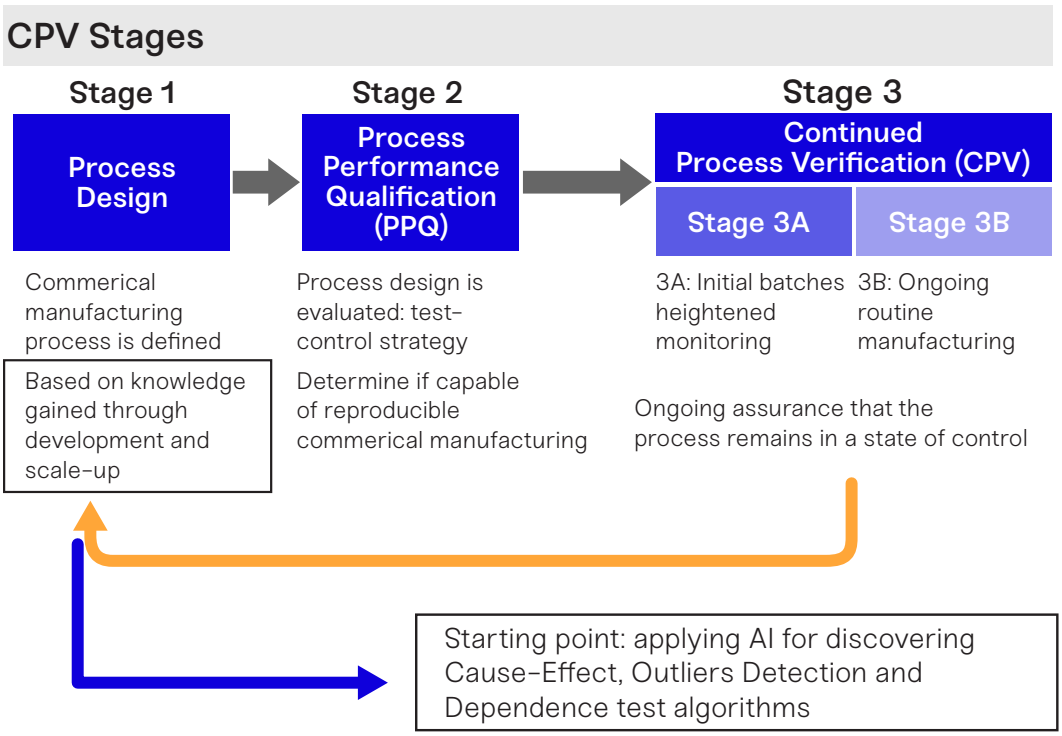

Fig 1: Representation of the three stages of process validation as defined by FDA (source BioProcess) including the continuous loop proposed by Aizon in order to permanently improve the AI continuous life cycle.

Process Design is the activity defining the commercial manufacturing process that will be reflected in planned master production and control records. Process Design is informed by knowledge gained through development and scale-up activities.

Process Qualification involves monitoring the process and evaluating if the Design of Experiment (DOE) defines a process capable of reproducible commercial manufacturing. In this stage, it is the quality, not the quantity, of data that is crucial; gathered information must be capable of being converted into actionable insights.

Continued Process Verification focuses on ensuring, in real-time, that the process remains in a state of control (the validated state) during commercial manufacturing. Systems for detecting deviations and anomalies from the process as designed are essential to accomplishing this goal. Evaluating the performance of the process enables identification of problems and determines whether action must be taken to correct, anticipate, or prevent such problems, to ensure that the process remains in control. This phase requires a real time multivariate approach in order to get the right recommendations at the right time, and these are great conditions to introduce AI as a critical tool.

AI to Optimize CPV

As a multivariate system, pharmaceutical manufacturing is a labyrinth of intricate parameters, processes, and data points. Proper identification must be made of the relevant factors (RF) that impact product quality and safety and ensure that the initial conditions for the process are suitable for the correct manufacturing of the pharmaceutical products. Univariate graphs and classical statistics tools are usually used. An analysis of patterns and trends for critical parameters is also carried out. However, to optimally realize CPV, direct, real-time, and simultaneous line-of-sight to all manufacturing variables must be facilitated. Critical process parameters are usually the main variables considered in the CPV control. In the best cases, they are used as independent variables to create models where critical quality attributes work as dependent variables. This goal is not attainable with traditional statistics. AI-informed multivariate analytical tools can enable model creation to accomplish this, as well as detect other potential RFs that might have not been identified initially, but which could have a major impact on the final yield of the process. AI provides multivariate interpretation of the complex reality, and it also includes power computing, fast model understanding and rapid predictions and recommendations.

Journeying Towards AI-Powered CPV

Currently, there is no AI model life cycle manufacturing strategy in the market where an AI model is built, qualified and validated into a specific process. However, applying AI in a CPV context is achievable through a strategically developed DoE that includes the critical factors and the AI elements are considered in its strategy (Figure 2).

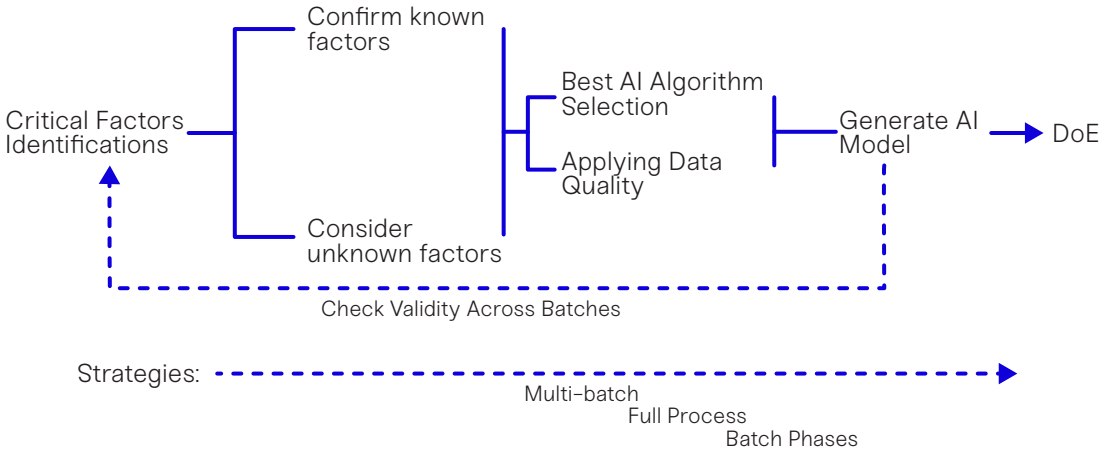

Fig 2: Proposed strategy for the development of a DoE where CPP, CQA, other variables and the AI elements needed to comprehend the system are included as factors (Manzano, 2020)

Selection of the right data analytics platform and provider to facilitate this process is critical. Data silos present one of the greatest obstacles to securing a 360-degree view of the data needed to implement CPV. In pharma, stringent regulatory requirements have led to the creation of very isolated data silos that make the use and analysis of data a troublesome task. The removal of such data silos is still a very challenging process, because pharma is typically slow to trust and embrace new technology.

Partnering with Aizon for Optimal AI-Powered CPV

Biopharma can ease the transition to AI-powered CPV by selecting an analytics partner with the right solutions. The Aizon platform is a cloud-based Software as a Service (SaaS) offering a data lake built on serverless architecture where the data from different sources can be easily ingested, visualized and analyzed. Aizon breaks data silos in a compliant way, from both structured and unstructured data, enabling data integration and helping to guarantee quality. Aizon's analytical and exploration tools allow users to obtain deep knowledge of the process and data needed to facilitate CPV:

- → Real-Time Principal Component Analysis (PCA): A powerful multivariate exploratory tool that transforms a number of possibly correlated variables into a smaller number of uncorrelated variables in real time. PCA is a fundamental tool to analyze manufacturing processes with a high number of parameters, simplifying complexity while retaining trends and patterns. PCA provides a range of ways to explore data, including viewing projections in real time, and enabling users to understand which variables present higher variance and may have more impact.

- → AI Causality Detection: A widget to aid identification of relevant factors by identifying dependent and/or independent variables, as well as hidden dependencies and the directional cause-effect inferred by the produced values. Furthermore, the values are binded in sets that indicate when each factor is expressing the cause-effect reaction.

- → Data Comparison: Allows the user to compare simultaneous and parallel data from multiple entities/components optimized for time-series and event data, merging representations into a single graph.

- → Dimensional Analysis: Extracts knowledge about processes and associations; unknown correlations can be identified and the number of variables that need to be controlled can be reduced, decreasing complexity.

- → Process Normalization: Analyzes and compares processes (similar or not) with values of distinct types and scales to enable comparison.

- → Discovery Notebook: Monitors data from an entity or multiple entities simultaneously in real time, allowing for the discovery of patterns, trends and correlations.

- → Context Query: Enables data retrieval and organization in the unstructured data inside the GxP data lake.

- → Best in Class Cloud Infrastructure: Aizon is built on top of AWS leveraging the most secure and scalable foundation available.

Conclusion

Biopharmaceutical manufacturing in the third decade of the 21st century is a new – and as a result of COVID-19 also a rapidly-evolving – reality. CPV as a concept is being embraced by industry following FDA recommendations, but biopharma must determine how best to implement it in everyday manufacturing operations. AI as a tool to analyze the multivariable and complex operations of drug production offers an exciting and viable path forward, but the industry must first be willing to relinquish their current, validated, but soon-to-be outdated legacy processes. Aizon offers the opportunity to ease that transition by creating a parallel path, layering AI into existing systems and processes until both old and new paths converge and previously unimaginable manufacturing insights become discoverable and usable through CPV.

About Aizon

Aizon is a software provider that transforms manufacturing operations with the use of IoT, Cloud, advanced analytics, artificial intelligence, and pharma 4.0 technologies focused on optimizing pharmaceutical and biotech companies. The Aizon analytics platform seamlessly integrates unlimited sources of structured and unstructured data to deliver actionable insights across all manufacturing sites. Aizon offers an intuitive way to gain meaningful operational intelligence with data by enabling real-time visibility and predictive insights in a GxP compliant manner with end-to-end data integrity. The company is based in San Francisco, California and also has a European office in Barcelona, Spain.

To learn more about advanced AI analytics as a tool to implement CPV, visit https://connect.Aizon.ai/CPV.html

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Footnotes

[1] https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf

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