PharmaED RESOURCES, Inc.

Process Validation 2019 Summit

June 12–13, 2019, La Jolla, CA

Featuring Lessons Learned and Case Studies From Industry Experts

Mariza Jafary
Compliance Officer, **FDA**

Doug Brown
Charles River Laboratories

Alan Golden
Design Quality Consultants

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Dushyant Varshney
Jubilant Pharmaceuticals

Katherine Giacoletti
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Mayank Bansal
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Robert Luo
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Robert Fasciano
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Mark Mitchell
Pharmatech Associates

Humberto Vega
Celgene

Rod Freeman
Beckman Coulter

Joe Cagnassola
Alcon

Ganeshkumar Subramanian
Bristol-Myers Squibb

Walid El-Azab
STERIS

And Comprehensive Coverage On:

- **Introduction to Recent Advances in Process Validation — Life Cycle Approach**
- **Regulations/ICH Guidance/FDA, EU perspective/PV, life cycle approaches**
- **Validation in the Biopharmaceutical Industry**
- **Continued Process Verification (stage 3) approaches, understanding & realization**
- **Quality-by-Design, PAT, Quality Risk Management — new product vs. legacy**
- **Statistical Process Control & Sampling Plans**
- **Global Tech Transfers and Process Validation Approaches**
- **Process Validation Biologics vs. Biosimilars, Biobetters**
- **Business Perspectives on PV**
- **Process Validation Biologics vs. Biosimilars, Biobetters, OTC Manufacturing**
- **Enhanced Sampling in Process Performance Qualification and Continued Process Verification**
- **Systematic Method for Process Development and Successful Implementation Based on Lessons Learned**
- **Process Validation as the Bridge from Clinical to Commercial**
- **Statistical Methods for Small Scale Model Qualification in Bioprocessing**
- **Benefits of Establishing a True End-to-End, Close to Real-time Robustness Monitoring Program**
- **And Much More!**

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Wednesday, June 12, 2019

7:30 *Complimentary Breakfast*

8:15 **Chairperson's Welcome and Opening Remarks**

8:30 **Meeting FDA Regulatory Requirements for Process Validation**

Mariza M. Jafary, Compliance Officer, Office of Pharmaceutical Quality Operations, FDA

Process validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110) and is considered enforceable under section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 351(a)(2)(B). An effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug product should be produced for its intended use. Process validation is 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. Process validation involves three stage of activities which takes place over the lifecycle of the product and process: process design, process qualification and continued process verification. The integration of process design, process qualification, and continued process verification provides assurance the product/process will consistently remain in control throughout the entire product lifetime.

9:15 **Life-Cycle Process Validation for Drug Substance & Drug Product Manufacturing**

Marzena Ingram, Senior Manager, QA and Compliance, Eurofins Alphora Inc.

Application of the life-cycle approach for process validation in both drug substance (DS) and drug product (DP) manufacturing requires unique and careful consideration. The small molecule drug substance manufacturing process involves development and manufacturing of RSMs, Intermediates and final API forms. Complex chemistry involved brings in challenges in process optimization and validation. Moving the DS through to DP requires further development and understanding of manufacturing process. Manufacturing of each necessitates fit for purpose tools. Process validation activities need to consider multiple regulatory requirements such as FDA PV guidance, ICH guidance, guidance from industry organizations etc. This session addresses the best practices in applying the following PV life-cycle stages for drug substance and drug product manufacturing:

1. Process design Stage 1A and Stage 1B
2. Qualification Stage 2A and Stage 2B
3. Continued Process Verification Stage 3A and Stage 3B

10:00 *Morning Break*

10:30 **Red is the New Black and Other CPV Paradigm Shifts**

Tara Scherder, Statistical Consultant for Pharmaceutical Development and Manufacturing, SynoloStats

The effort of data collection and analysis during Continued Process Verification can bear huge business and patient benefit. This is only possible if we: 1) understand the context and nuances of the tools that we use during this phrase, particularly control charts and process capability metrics, 2) change some relevant industry paradigms. Otherwise, manufacturers can waste resources and CPV becomes a cumbersome compliance exercise, instead of the source of substantial business opportunity. In this talk, several common non-value added (wasteful) approaches and philosophies are discussed. Alternatives that holistically consider the context and true goals of CPV, the control strategy, and proper statistical interpretation are presented.

11:15 **Benefits of Establishing a True End-to-End, Close-to-Real-Time Robustness Monitoring Program**

Ganeshkumar Subramanian, GPS – MS&T, Bristol-Myers Squibb

Product robustness monitoring program serves as a key leading indicator of product quality. A well-established process can identify negative trends and take actions to prevent product quality issues and mitigate the risk of batch failures. In addition to serving a compliance requirement, a true end to end close to real-time CPV process proactively reduces the risk of manufacturing failure due to shifts in raw material characteristics or process drift and provides an added layer of assurance, that every batch of the product will meet the highest standards of quality.

The talk will focus on how streamlining a fragmented process to a holistic end to end close to real-time monitoring was established and the benefits this has provided. Examples will include how the process has supported:

1. Quicker resolution of Deviations and Investigations
2. Yield and Efficiency Improvements
3. Stability OOT/OOS investigations
4. Parameters to focus during site transfers
5. Re-processed API tracking or new source qualification

12:00 *Complimentary Lunch*

1:00 **Validation Sampling Plans, Setting Acceptance Criteria and Statistical Process Control**

Alan Golden, Principal, Design Quality Consultants, LLC

I. What is Sampling?
   a. Sampling is the ability to make a quality determination on a large number of things without direct examination of each thing/

II. Validation Sampling
   a. Not the same as lot acceptance sampling
   b. Differences

III. Setting up a Validation Sampling Plan
   a. Pre-Sampling Determinations
   b. Steps to setting up sampling plans
   c. Variables vs Attributes Sampling Plans

IV. The concept of Acceptance Criteria
   a. Variance, how much is too much
   b. How to measure variance and why

V. Use of Process Capability
   a. The concept of process capability
   b. Cp vs CpK
   c. How to use process capability to set acceptance criteria

VI. Statistical Process Controls

2:00 **Statistical Methods for Small Scale Model Qualification in Bioprocessing**

Robert Luo, Manager, Downstream Process Development, GlaxoSmithKline

Qualification of small scale models for biopharmaceutical drug substance manufacturing processes is an important task. The challenge is the lack of clear guidance on design, execution, and data analysis. Different people have different assumptions, leads to confusions and questions. In this presentation, we will discuss these questions based on scientific, statistical, and practical considerations,

I Concepts and definitions for small scale model qualification

II Number of runs needed

III Statistical methods and examples

2:45 ***Afternoon Break***

3:00 **Continued Process Verification (Stage 3) Approaches, Understanding & Realization**

Robert Fasciano, Director of Quality at Hyperfine Research

The FDA guidance on process validation was released in 2011 for the pharmaceutical industry, but it has been adopted in other industries. This guidance breaks validation into multiple stages. One of the least understood and often neglected is the final stage which is called "Continued Process Verification." This talk will briefly review the basic terminology in this FDA guidance, but primarily focus on Continued Process Verification. The presenter will interpret the guidance on Continued Process Verification, share best practices, and highlight potential pitfalls.

I. Statistical Process Control (SPC)
   - Define statistical process control and its use
   - What are the benefits for using SPC?
   - Typical tools and process control techniques

II. Control Charting Basics Using Microsoft Excel
   - Control chart structure, fundamental concepts, key terms and features
   - Types of control charts
   - Set control charting limits
   - Establish warning zones and out-of-control limit flags
   - Using control charts to explain process stability

3:45 **Continuous Process Verification of a Continuous Tablet Manufacturing Process**

Elizabeth Grieco, Director, Technical Operations, Vertex Pharmaceuticals, Inc.

Continuous Process Verification (CPV) methodology has been implemented at Vertex for validating drug products manufactured using continuous processes. The use of advanced manufacturing utilizing in-line, on-line, and/or at-line measurements generates a substantial amount of data, which allows a comprehensive understanding of process performance and variability during the development stage of the product lifecycle.

Execution of process development on the same equipment as is used commercially allows significant product development data to be leveraged for Process Validation (PV). Furthermore, our Quality by Design (QbD) approach to product development along with collection of significant amounts of in-process data during development and clinical batches manufactured on our continuous manufacturing line allows a comprehensive CPV approach to process validation. Our validation strategy, which prospectively states the relevance of development and clinical manufacture to demonstrate commercial process understanding and which may justify fewer than 3 PV batches, will be presented.

4:30 ***End of Day One***

Thursday, June 13, 2019

8:00 ***Complimentary Breakfast***

8:05 **Process Validation and Global Technology Transfer of Biologics & Vaccines**

Dushyant Varshney, Vice President, Technical Services, Operations at Jubilant Pharmaceuticals

In recent decades, there has been a rapid rise in the number of biologicals (e.g., therapeutic proteins, biosimilars) and novel vaccines developed by small and large biopharmaceutical companies. Development of such biologics is quite expensive and many companies lack in-house setup and capability to develop at commercial scale. In contrast, large companies, engaged in core or non-core business, have realized cost-saving by utilizing contract manufacturing organizations (CMOs) and improved productivity trends, as compared to investing in setting up and maintaining own facilities with required expert staff and regular updates. In such industry trends, technology transfer (TT) and validation of active pharmaceutical ingredients, analytical methods and drug products/process from development to market phase is

becoming increasingly common and important to deliver safe and quality products. A successful TT ensures quality of product during the entire life-cycle of manufacture and validation, in accordance with cGMP, providing predictable and consistent operation of the processes.

The talk will focus on the current challenges and solutions in global technology transfer, subsequent process validation and commercial manufacturing. Specifically, external vs. internal manufacturing consideration, typical global TT roadmap, types of TT, regulatory/geographical challenges & risk management, process validation approaches for liquid/lyophilized biologics & vaccines products delivered by parenteral route will be discussed.

8:50 ## A Practical Aspect of NPI and Technology Transfer Avoiding Common Pitfalls

Mayank Bansal, Assoc. Dir., Product Development R&D, Allergan

Every organization grows its business by introducing new products (or services) to the market. An effective approach for development and launch of new products ensures success by minimizing the chance of failure. The present talk is focused around three key facets of the new product introduction:

1. Structured Process
2. R&D, Scale Up, Tech Transfer
3. Execution

The presentation will discuss details on a process of taking the product from a concept to commercialization that provides rapid R&D time and cost efficiency, Stage Gate or similar concepts that lead to impactful product development, Strategic Project Management for flawless execution, managing R&D and Scale Up to prepare for larger markets, and addressing common failure points and unforeseen roadblocks.

9:35 ## Finding the Goldilocks Zone for Enhanced Sampling in PPQ & CPV

Katherine Giacoletti, Partner, SynoloStats

Eight years after the FDA Guidance which introduced the Lifecycle Approach to PV, the need for enhanced sampling during PPQ and Stage 3a is broadly recognized in the industry. But to find the optimal level of enhanced sampling – i.e. sampling beyond routine release requirements – requires understanding the underlying reasons for taking additional samples. Further, understanding how sample size relates to statistical uncertainty and how this knowledge can be used to choose sampling plans and interpret results is critical to making PPQ and CPV decisions that protect that patient and the business. This talk will discuss the role of statistical uncertainty in making inferences based on samples and the implications for designing sampling plans, in the context of the goals of lifecycle PV, particularly in the transition from PPQ to routine manufacturing. Through real examples, the talk will also point out some common pitfalls in the use of statistics and sampling plans in PPQ and Stage 3a.

10:30 *Mid-Morning Networking Break*

10:50 ## The Comparability Conundrum: Process Validation as the Bridge From Clinical to Commercial

Mark Mitchell, Principal Engineer, Pharmatech Associates, Inc.

It is common in the pharmaceutical industry to supply clinical trials with product produced with a small-scale process, which is not suitable to supply commercial needs. The FDA Process Validation Guidance (2011) recognizes the challenges of scaling to a commercial process through the implementation of the concepts of Quality by Design in PV Stage 1: Process Design. The product quality attributes from the clinical lots along with characterization studies based on Design of Experiments form the basis of a Process Control Strategy. The Process Performance Qualification ensures not only that the commercial process can produce product meeting quality attributes, but also that the commercial product is comparable to the clinical product. Key topics include:

- The difference between "equivalent" and "comparable"
- Statistical significance versus "practical" significance
- Using Risk Analysis to justify characterization studies and build a control strategy
- Construct PPQ acceptance criteria / action levels to ensure clinical comparability
- Interpreting "Failed" PPQ acceptance criteria
- Statistical tools used in comparability analysis

11:45 ## Statistical Process Control (SPC) and Sampling Plan Guidance for Process Validation

Joe Cagnassola, Principal Validation Engineer, Alcon

Statistical Process Control (SPC) is one of the most effective and efficient operational techniques available to simultaneously improve both quality and cost. SPC is useful in reduction of variation, centering a process, early warning of quality problems and predictive maintenance. In addition, understanding the different types of sampling plans that may be utilized during process validation ensures the process complies with regulatory requirements and is cost effective and value added for the company. In addition, the risk assessment process for the process validation should be considered when determine sampling criteria. Participants learn approaches to gain process understanding and optimize:

1. Understanding Variation in the Process
2. Types of Variation
3. SPC in a Pharma Environment
4. Acceptance Sampling Guidance
5. Sampling Plans
6. Process Validation Testing Requirements and Acceptance Criteria
7. Risk Assessments in relation to Process validation

12:30 *Complimentary Lunch*

1:30

Quality by Design: A Systematic Method for Process Development and Successful Implementation Based on Lessons Learned

Walid El-Azab, Technical Service Manager, STERIS Corporation

The presentation will discuss the different GMP requirements regarding "Stage 1" process validation. Following that, the presentation will share a systematic method to a science- and risk-based approach for product and process development linked with the production and patient need. The following concept will be discussed during the presentation quality target product profile, determination of the critical quality attribute, the design of space. These concepts are crucial to implementing effective control strategy and robust process and product lifecycle. During the presentation, different tools, case studies and lessons learned will be shared to demonstrate the benefit of a robust Stage 1 to control process variability and failure during Stage 2 and Stage 3. Finally, the pre-requisite before starting the Stage 2 will be discussed.

2:15

Identifying the Right Metrics to Drive Improvement in your Process Validation Program, and Using those Metrics

Rod Freeman, Senior Manager, Global Quality organization, Beckman Coulter

Metrics drive today's decision making beyond manufacturing and marketing. This session will review the move towards metrics around Quality Systems, discuss some of those proposed for industry, and describe how to identify metrics within your organization that are leading and actionable.

Topics covered:

- The difference between Leading and Lagging metrics and why it matters
- How to identify actionable metrics
- Gleaning insights and improvement ideas from the data you collect
- Tools an approaches

3:00 ***Afternoon Break***

3:15

Statistical Process Control – Using Control Charts to Monitor the Stability of a Process

Douglas Brown, Scientist II, Methods Development and Validations, Charles River

This session introduces a method for monitoring the stability and control of processes. Using statistical process control, the development of a system to monitor and control processes and procedures assists with enhancing product conformity, reduction in waste and identifying product drift and potential loss of system control. A primary focus for process control is to ensure that the behavior of validated processes and procedures has not changed and is continuing to perform as previously established. This session focuses on understanding how to create and monitor the stability of a validated process and how to interpret the results.

4:00

Technology Transfer and Process Validation for CAR T Products

Humberto Vega, Senior Director MS&T, Celgene

Chimeric antigen receptor (CAR) T cell therapies are being investigated to provide patients with hematologic cancers an alternative treatment using the immune system. These biological products are unique in that they are produced by adding chimeric antigen receptors (CARs) to a patient's T cells; the CAR can recognize and attack cells that display particular protein (antigen), including cancer cells.

As any pharmaceutical drug product or medical device, technology transfer activities and process performance qualification are part of the product lifecycle. This presentation will focus on key elements of Technology Transfer (TT) and Process Performance Qualification (PPQ) Activities involving CAR T products considering the key differences between a traditional drug product and this innovative technology: (1) Patient Leukapheresis; (2) Culture Media; (3) Transduction of T Cells; (4) Cell Expansion and (5) Preservation.

The author will present a high-level comparison of TT and PPQ between typical pharma products (sterile and solid dosages), biopharma and CAR T cell therapy and highlight key differences and rationale for those, focusing on CAR T.

4:45 ***Closing Remarks and Close of Conference***

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