PharmaED RESOURCES, Inc.

Cleaning Validation Summit 2016

May 23-24, 2016, Racquet Club of Philadelphia, PA

Featured Speakers Include:

Dushyant Varshney
Dir. Manufacturing Assessment, Hospira

Mariann Neverovitch
Research Scientist at Bristol-Myers Squibb

Michele Levenson, PMP
Manager at Pharmatech Associates

Andrew Walsh
President at Center for Pharmaceutical Cleaning Innovation

Beth Kroeger
Technical Services Manager at STERIS Corporation

Fred Ohsiek
CV Engineer, Astellas Pharma

With Comprehensive Coverage On:

- **Ensuring your Cleaning Program is FDA Audit Ready**
- **Cleaning Validation and Continued Process Verification**
- **Risk-Based Approach**
- **Cleaning Limits and Visual Inspection from the Analytical Perspectives**
- **Determine Cleanability and its Applications in Cleaning Validation**
- **Process Validation & Cleaning Strategies during Technology Transfer of Sterile Injectables**
- **EU GMP Changes and Its Impact on Cleaning Validation**
- **Quality by Design for Effective Cleaning Procedure**
- **Writing Cleaning Validation SOPs**
- **And Much More**

Are you compliant with FDA requirements for cleaning validation? Today's regulators are applying more fine-grained specifications and demanding more sophisticated procedures for planning, executing, and documenting your processes throughout a drug product's lifecycle. This two-day intensive summit brings together industry leaders to help you exceed regulatory thresholds and avoid costly FDA inspection findings.

With Representation From:

MedImmune
A member of the AstraZeneca Group

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Monday, May 23, 2016

8:15 *Complimentary Breakfast & Chairperson's Welcome and Opening Remarks*

Regulatory Considerations

8:45 **Don't Play Dirty with the FDA: Ensuring your Cleaning Program is Audit Ready**

Beth Kroeger, Technical Service Manager, Life Sciences Division, STERIS Corporation

Throughout the cleaning validation life cycle, it is important to review the process for any changes that may have occurred. It is also important to monitor the process in an attempt to identify any differences or process drift between the validated process and the current state. This review should be performed yearly with the product review and/or with the cleaning validation life cycle review, which ensures the operation is always in a state of control and audit preparedness.

To ensure audit readiness, as it relates to a validated cleaning process, a facility should:

- Understand current focus of FDA inspections by reviewing current findings from regulatory inspections and identify trends relevant to Cleaning Validation.
- Review any Change Controls that were issued which could impact the validated state or process
- Verify that training programs and documentation adequately address the needs of a robust cleaning program
- Review manufacturing in-process data to ensure that the process has not "changed" which could affect the ability of the cleaning process to be successful.
- Review data from cleaning validation reassessment and compare to validation process data for consistency
- Review risk assessment of cleaning validation life cycle approach to identify areas for continuous improvement.

The presentation will cover recent trends in FDA inspections pertaining to cleaning validation and where to focus attention for upcoming inspections. Attendees will better understand the inspection process and the role of the internal stakeholders during an FDA inspection.

9:45 **Cleaning Validation and Continued Process Verification**

Michele Levenson, Manager, Pharmatech Associates

In January 2011 the FDA issued the New Process Validation Guidance and the current definition eliminated the concept that success is measured by three successful commercial batches of product. Instead, the new guidance emphasizes scientific and statistical data on a continuous lifecycle as the foundation for understanding processes and predicting process performance. The modern Process Validation process is divided into three stages and it is Stage 3 that introduces the most significant departure from the 1987 concept: that is, Continuous Process Verification throughout a product's lifecycle. This presentation will evaluate the integration of the Cleaning Validation program into the Continuous Process Verification program and demonstrate the benefits that your organization can gain from establishing this program successfully.

10:45 *Networking Coffee Break*

11:15 **Improving Regulatory Compliance and Manufacturing Efficiency Through Risk-Based Approach to Cleaning Systems Design, Qualification and Ongoing Monitoring**

John M. Hyde, Chairman and Founder, Hyde Engineering + Consulting, Inc.

The cleaning of processing equipment and interconnecting piping systems is an essential process in pharmaceutical and biopharmaceutical manufacturing facilities. Cleaning is used to remove post-production and cleaning agent residues to acceptable levels prior to the production of the next batch or product. Cleaning processes are often not developed based upon risk analyses or sound science, resulting in cleaning that is often either inefficient, ineffective or both. The materials presented in this session will address contemporary approaches to cleaning cycle and equipment design, cleaning process development, cleaning cycle qualification and ongoing cleaning process monitoring.

The session will specifically address:

- Role of Quality by Design (QBD) in effective and efficient cleaning system and cycle design
- Applicability of concepts outlined in the new FDA Process Validation Guidance to the validation and ongoing monitoring of cleaning operations
- Value of the generation of lab and pilot scale cleaning design space data to support cleaning cycle development and cleaning process scale-up
- Utilization of risk analysis management to determine the scope of full scale cleaning testing and the focus of ongoing monitoring
- Development of an ongoing monitoring strategy and the application of statistical process control (SPC) tools in the real time assessment of cleaning process efficacy and stability
- Effectual strategies for the development of sampling and analytical methods for verification of cleaning efficacy and efficiency
- Science based methodologies for the establishment of visual residue limits
- Practical and risk based approaches to the establishment of post-production cleaning limits including the effects of residue degradation from the cleaning process
- Organization and definition of scientific rationale and execution methodologies through effective master planning

12:00 *Complimentary Lunch*

CASE STUDY

Spotlight on Cleaning Limits and Visual Inspections

1:00

Cleaning Limits and Visual Inspection From the Analytical Perspectives

Mariann Neverovitch, Research Scientist, Bristol-Myers Squibb
Contributing Authors: M. Neverovitch, E. Moroney and A. Fernandez

Visual inspection following equipment cleaning is a mandatory step in the cleaning verification workflow for pharmaceutical equipment. Equipment must pass visual inspection before swab sampling for analysis can be performed. However, since a significant number of low risk compounds are visible well below established safety levels, it is possible to justify equipment as "visually clean" without performing swabbing analysis. Internal studies performed at BMS showed that over 90% of participants could identify residual product at a level of ~2 ppm without preliminary training. The implementation of a robust visual inspection qualification program and clear "Visually Clean" inspection parameters can enable visual inspection to be used to qualify equipment in lieu of swab analysis for low risk products.

1:45

Use of Statistics in Cleaning Validation

Igor Gorsky, Senior Consultant, ValSource, LLC

CASE STUDY

This presentation will examine a number of tools that may be utilized for the measurement of Equipment Cleaning Process during all three stages of its continuum: Development of Cleaning Procedures by Research and Development groups, Validation of Cleaning Procedures by Technical or Quality groups and Application of Cleaning Processes by Operations/Manufacturing organizations. The key factor to control for any process resides in the understanding of its variability. How much do we know about the variation of our processes or systems and are we in the state of control? These questions require answers to achieve success in the execution of ECP. Understanding, detection, response, and control, from input through output of variation, consumed a focus of the revised FDA Process Validation Guidance to Industry which principles could be successfully applied for Cleaning Processes, as well. Several case studies will be discussed to show how data collected from Cleaning Validation runs could be evaluated, and analyzed to help understanding Cleaning Processes and built Knowledge base that will allow for more efficient and effective manufacturing activities.

2:30

The Three Stages of Cleaning Validation

Fred Ohsiek, Cleaning Validation Engineer Astellas Pharma US, Inc.

The presentation will discuss the three stages of cleaning validation: design and development; performance qualification; and continued verification. The elements and benefits of each stage will be discussed. The presentation will also include strategies for leveraging worst-case scenarios during cycle development or using risk assessments to reduce level of cleaning validation required. For each stage, possible problems and solutions will be given.

3:15 *Afternoon Networking Break & Raffle*

3:45

A Method to Determine Cleanability and its Applications in Cleaning Validation

Andrew Walsh, President, Center for Pharmaceutical Cleaning Innovation

A newly developed procedure for assessing the "cleanability" of pharmaceutical/biological products will be presented. This new procedure also provides many additional capabilities for Cleaning Process Development, such as Cleaning Agent Selection, Design of Experiment, etc.

4:30

Large Molecule Multi-Product Equipment Cleaning

Edward (Ned) Wymann, Principal Scientist Validation, Medimmune

For multiproduct equipment cleaning validation, the conventional approach for setting cleaning acceptance limits for residual process materials is based on the maximum allowable carryover (MAC) of the active pharmaceutical ingredient (API) using product dosage or health based exposure limits such as Acceptable/Permitted Daily Exposure (ADE/ PDE). The MAC approach was originally derived for small molecule products and as such, the use of the MAC approach for large molecule, biological products may not be applicable or appropriate. Biological products such as monoclonal antibodies and therapeutic proteins rapidly degrade and denature when exposed to pH extremes and/or heat, and thereby become pharmacologically inactive. If the cleaning of biopharmaceutical manufacturing equipment is performed under conditions that ensure degradation and inactivation of protein-based products, then only breakdown products such as smaller peptide fragments or amino acid derivatives, may be present after cleaning. Since these breakdown products do not exhibit the pharmacological activity of the intact product, the use of health based exposure limits using ADE/PDE limits of the active and intact product is no longer required. Subject matter experts from twelve biopharmaceutical companies met to determine alternative, scientifically justified and safe levels of potential residue present on the inner surface of the manufacturing equipment after cleaning. The experimental approach and analytical methods for assessing inactivation of the API during cleaning, and four alternative approaches (Cleaning Process Capability, Safety Factor, Toxicology Threshold, or Performance Control) for setting safety-based acceptance limits for inactivated product and process residuals will be discussed.

5:15 **Process Validation vs. Cleaning Validation Approach Examining the Similarities and Differences—Round Table Discussion**

Dushyant Varshney, Hospira
Edward Wyman, Medimmune
Mariann Neverovitch, Bristol-Myers Squibb
Walid El Azab, STERIS Corp.
Andrew Walsh, Center for Pharmaceutical Cleaning Innovation, Validation Edge, LLC

5:45 *End of Day One*

Tuesday, May 24, 2016

8:30 *Complimentary Breakfast & Chairperson's Remarks*

8:45 **EU GMP Changes and Its Impact on Cleaning Validation**

Walid El Azab, Technical Services Manager, STERIS Corp.

The presentation will shed the light on the current European changes and how these changes are now linked to each other. The presentation will also detail and explain the changes of recently effective and draft documents as the annex 15, annex 16, chapter 2, chapter 3, chapter 5 and finally the EMA guidance on setting limit. Following that, the presentation will explain the impact of these changes on cleaning and how manufacturer senior management and the qualified person need to ensure compliance. In addition, the presentation deep dive on how to assess setting limit in cleaning validation and explain the difference with the ISPE and EMA guidance. Finally, the presentation will share the common questions ask by manufacturer on cleaning and process validation over the world and what regulatory agency are expecting to be in place.

- Understand the EU GMP change and the link between them .
- Understand the impact of these change on cleaning validation including calculating residue limits.
- Understanding on how to implement these changes in short and long term

9:45 *Networking Coffee Break*

SPECIAL In-Depth Coverage

10:00 **Process Validation & Cleaning Strategies During Technology Transfer of Sterile Injectables**

Dushyant B. Varshney, Ph. D., Director, Manufacturing Assessment, MS&T, Hospira, Inc.

Biologicals (e.g., therapeutic proteins, biosimilars), oncolytic and novel vaccines are developed as sterile injectable dosage form 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. On the contrary, 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 manufacturing process is becoming increasingly important to deliver safe and quality products. Moreover, challenges unique to each modality warrant special attention to cleaning methods and manufacturing process transfer during the entire product lifecycle in accordance with cGMP. The talk will focus on the current challenges and solutions during global technology transfer including process and cleaning validation. Specifically, process validation roadmap and cleaning strategies for liquid/lyophilized biologics & vaccines products manufactured as sterile injectables will be discussed.

11:30 **Application of the ADE/PDE to Cleaning Validation**

Andrew Walsh, President, Center for Pharmaceutical Cleaning Innovation

How the ADE/PDE should be applied in Cleaning Validation will be discussed, in particular the benefits of using ADEs/PDEs over current approaches. A newly developed model for using ADEs/PDEs in combination with Process Capability in a Risk Assessment/FMEA will be presented.

12:15 *Complimentary Lunch*

1:15 **Cleaning Validation Protocols and Contents**

Fred Ohsiek, Cleaning Validation Engineer Astellas Pharma US, Inc.

The presentation will discuss the different types of cleaning validation protocols (i.e. verification, cycle development, validation, clean hold time, and campaigning). It will cover the progression and timing of the protocol types. Protocol sections will be discussed in detail: Purpose; Scope, Rationale; Acceptance Criteria; and Equipment and Product Release. Finally, the presentation will discuss issues during protocol execution (i.e. visual, swab, and cleaning procedure failures).

2:00 **Surface Sampling Training and Qualification**

Tabitha Ross, Supervisor of Cleaning Validation, Apotex Inc

Do you have human or robot surface samplers within your cleaning validation department? We'll discuss how to come as close as possible to the latter, by reviewing the process of developing a well-defined surface sampling procedure and qualification/training program for

your staff to follow and document the surface sampling process including:

- Preparation steps for the sampling event, including documentation and gathering of clean sampling tools,
- Presampling considerations in the production environment, and the checks to perform prior to sampling the equipment,
- Sampling execution and what to do if something dirty goes down,
- Sample review and submission, as well as documenting the event,
- Chemistry vs. microbial sampling; extra considerations, and
- Qualifying your staff to ensure consistency amongst your samplers, including visual techniques for them to follow, testing their surface recovery, and checking their performance and skill against the approved procedures to follow.

2:30 **Stage 3 of Cleaning Validation – Using Statistics to Establish Process Control Limits**

Edward (Ned) Wymann, Principal Scientist Validation, Medimmune

During the initial Cleaning Validation, the acceptance criteria are to be established based upon scientific rationale. After successful completion of the Cleaning Validation, sampling may continue over time due to various reasons (e.g., revalidation, new product introduction, process discrepancies). There needs to be a way to track/trend this subsequent cleaning data to determine if there is any drift from the initial results in order to identify a potential issue before exceeding the acceptance criteria.

This session will provide an in-depth look at establishing process control limits for cleaning data.

- Overview of cleaning validation
- Setting the initial cleaning validation acceptance criteria
- Statistical concerns related to cleaning validation data.
- Potential statistical tools that can be used to determine process control limits
- Implementation of the process control limits

3:15 ***Afternoon Networking Break***

3:30 **Key Elements of Lifecycle Approach for Cleaning Validation**

Parveen Bhandola, Ph.D., President, Validation Edge, LLC

Cleaning validation is a legally enforceable cGMP regulatory requirement. The FDA expects firms to develop their cleaning validation programs aligned with the science and risk-based lifecycle approach. The lifecycle approach described in the FDA Process Validation Guidance (2011) is directly applicable to cleaning validation. From the lifecycle perspective, cleaning validation is not a one-time event starting and finishing with the execution of cleaning validation protocol. It is rather an ongoing process that continues throughout the product lifecycle. Application of lifecycle principles to cleaning validation provides a structured approach for developing compliant, effective, and efficient cleaning validation programs. A clear understanding about the key elements of lifecycle approach application for cleaning validation can help ensuring the overall success of cleaning validation programs.

4:15 **Quality by Design for Effective Cleaning Procedure**

Walid El Azab, Technical Services Manager, STERIS Corp.

Today's pharmaceutical and biopharmaceutical industries use various methods to clean process equipment. Cleaning devices range from manual wipes and brushes to sprayers, baths, and washers. The presentation will share the advantage/disadvantage of the available cleaning methods. For effective cleaning procedure, the critical process parameters and the cleaning cycle should be developed based on the soils proprieties and the equipment design. As such, the presentation will explain in detail the importance of efficient equipment design including technical and organization aspect to ensure effective cleaning procedure. Finally, based on a benchmark, the monitoring and preventive maintenance to be in place would be explained to help user to avoid biofilm, rouging or ring generation in their process systems.

5:00 ***Close of Program***

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Dates:	May 23–24, 2016
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Venue Phone:	(215) 735-1525
Hotel Room Block:	Radisson Blu Warwick
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