PharmaED RESOURCES, Inc.

Cleaning Validation Summit 2017

October 2–3, 2017, Racquet Club of Philadelphia, PA

Featured Speakers Include:

Robert Jernigan
Validation Group Leader QA Validation Oversight at GSK Zebulon

Stephen Spiegelberg
President Cambridge Polymer Group, Inc.

Fred Ohsiek
Sr. Manager Cleaning Validation at Bayer

Mariann Neverovitch
Research Scientist at Bristol-Myers Squibb

Joe Cagnassola
Principal Validation Engineer Alcon, a Novartis company

Andrew Walsh
President at Center for Pharmaceutical Cleaning Innovation

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:

Cambridge Polymer Group · MedImmune, A member of the AstraZeneca Group · Bristol-Myers Squibb · Alcon, a Novartis company · Bayer · Ecolab, Everywhere It Matters. · ValSource · CPCI · Hospira · Dartmouth College · G&W Laboratories · Akorn · Amgen · Dober · Sandoz, a Novartis company · Steris · GlaxoSmithKline · Columbia University

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Monday, October 2, 2017

7:30 *Complimentary Breakfast & Chairperson's Remarks*

7:50 *Welcome and opening remarks by Chairperson: Edward (Ned) Wymann, Principal Scientist Validation, MedImmune*

Spotlight on Cleaning Limits and Visual Inspection

8:00

Health-Based Exposure Limits – Who, When & How

Dave Dolan, Occupational, Environmental & Quality Toxicology Expert, Amgen Inc.

Abstract coming soon

8:45

Analytical Approach for Implementation of Visual Inspection

Mariann Neverovitch, Cleaning Validation SME, Analytical Strategic Operations, Analytical & Bioanalytical Operations, Bristol-Myers Squibb

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.

9:30

Standard Operating Procedure for Cleaning Validation Methods Including Method Transfer Activities in an Analytical Lab

Salvador Lopez, Sr. Analytical Scientist, R&D, Akorn Pharmaceuticals

The key elements of a robust cleaning method validation that should be included in a standard operating procedure (SOP) will be discussed. A cleaning verification program in an R&D analytical laboratory setting should also incorporate and include the Method Transfer activities to a receiving laboratory. There must be a high level of confidence in the analytical results in order to verify the absence of residues at the prescribed limits on the various equipment surfaces. Typically the most common surfaces to be discussed will be SS316, Teflon, Red Rubber and Silicone.

This talk will also discuss the validation parameters to be performed during a cleaning method validation. Details on some key factors to consider during the cleaning verification in the Analytical Laboratory will be provided, while highlighting many common mistakes to avoid.

10:15 *Networking Coffee Break*

10:45

Development of a Modified SDS-PAGE for Quantifying Protein Degradation to Support Cleaning Validation

CASE STUDY

Dylan Wang, Dartmouth College

This Case Study will present an analytical method to quantify the degradation of biopharmaceutical protein products during cleaning processes. The degradation of proteins, in this way, can be accurately measured and proven instead of assumed. Based on the existing SDS-Page method, we have developed a highly accurate, low cost and time saving technique to analyze protein degradation. The time of exposure, cleaning agent concentration and temperature are controlled to mimic cleaning procedures. Using Design of Experiments(DOE) results can be analyzed to statistically evaluate the importance of each cleaning factor as well as their interactions, providing additional information to help manufacturers optimize their cleaning processes.

11:30

At-Line PAT Using TOC— A Lean Six Sigma Case Study

CASE STUDY

Andrew Walsh, President Center for Pharmaceutical Cleaning Innovation, (CPCI)

The Case Study will discuss how Total Organic Carbon Analysis can be implemented as an "At-Line" Process Analytical Technology (PAT) application replacing HPLC and greatly reducing the time and resources needed to release manufacturing equipment back into production through an example at a Solid Oral Dosage Form manufacturer.

12:15 *Complimentary Lunch*

1:15

Establishing a Cleaning Program for a New Facility Including Surface (Swab) Sampling Locations

Danielle Gabrish, Associate Scientist II at AstraZeneca BioIolgics (MedImmune)

Abstract coming soon

2:00

Three-Legged Stool Approach to Stage 1 for Cleaning

Edward (Ned) Wymann, Principal Scientist Validation, MedImmune

In this presentation, we will review the three main aspects of Stage 1 (Process Design) Cleaning Validation:

- Product Characteristics (Active Ingredient and other raw materials):
  - Bio/chemical Properties
  - Tox info
  - Denaturation studies

- Small-Scale Studies:
  - Recovery studies
  - Cleanability studies vs. worst-case materials
- The Commercial-Scale Validation/Verifications requirements are based upon above
  - Hardest-to-clean: Full Blown Validation
  - Not harder-to-clean: Commercial-Scale Verification
  - Easier-to-clean: Minimal Sampling

2:45 **Quality by Design for Effective Cleaning Procedure**

Walid El Azab, Technical Service Manager STERIS N.V. / S.A., A Subsidiary of STERIS Corporation

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.

3:30 **Cleaning Validation Protocols and Contents**

Fred Ohsiek, Sr Manager of Cleaning Validation and Site Cleaning Validation SME for Bayer U.S. LLC

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).

4:15 **Designing an Effective Cleaning Process**

Beth Kroeger, Technical Services Manager, STERIS Life Sciences

An effective and robust cleaning program can reduce equipment downtime and minimize the risk of cross contamination in multi-product facilities. Building an effective cleaning program from the onset is important and should consider equipment design aspects, residue selection and conditions and establish adequate cycle parameters. Part of this process is establishing correct limits within process capability to avoid excessive cleaning equipment changeover. This discussion will cover cleaning design issues, development of cleaning cycles, how to establish limits and culminate it tying it all together with lessons learned from a process capability cleaning issue demonstrating the need for process understanding to improve your current cleaning validation program.

5:00 ***Round Table Discussion***

5:30 ***End of Day One***

Tuesday, October 3, 2017

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

Edward (Ned) Wymann, Principal Scientist Validation, MedImmune

Regulatory Considerations and Risk Identification

8:45 **Using the ADE/PDE Concept for Implementing a Science and Risk-based Cleaning Program**

Andrew Walsh, President, Center for Pharmaceutical Cleaning Innovation, (CPCI)

This presentation will discuss how cleaning limits based 0.001 dose / 10ppm should be replaced by the ADE/PDE which are truly "science-based" and provide for appropriate assessments of Risk which can allow for greatly simplified cleaning validation programs, reducing the effort, formality and documentation necessary for cleaning validation, allowing the use of much easier and faster methods and simplifying new product introductions.

9:30 **ASTM Activities in Cleaning Validation**

Stephen Spiegelberg, President, Cambridge Polymer Group, Inc.

The improvements in medical device design and surgical procedures in the past several years have resulted in a higher standard of clinical success for medical devices. As fewer complications arise from previous issues of material failure, product design, or surgical technique, emphasis is now being placed on the cleanliness of medical devices. Ideally, manufacturers would like to produce parts with no contaminants. Practically, this goal is not achievable, and manufacturing costs increase dramatically as manufacturers attempt to reduce the levels of contamination. Two key questions that most quality assurance engineers are asking these days are "how clean is clean enough?" and "how does one assess cleanliness?".

The FDA has provided guidance for cleaning validation of processing equipment for pharmaceutical compounds since 1993, but there has been little guidance for medical devices. Past product recalls relating to device cleanliness have helped to spur activities within ASTM, as well as inclusion in ISO and USP standards. Working

with medical device manufacturers, analytical laboratories, NIST, the FDA, and medical device consultants, an ASTM task force has been working for the past 16 years to address issues of cleanliness in biomedical components. Standards have been developed to determine the level of manufacturing residues on medical devices, formulations for test soils to develop and verify cleaning procedures for re-usable devices, and guides for validating cleaning lines. This presentation summarizes the current and pending standards that are available to assist in matters involving cleaning processes for the medical industry.

10:15 *Networking and Coffee Break*

10:45 **Manual Cleaning . . . Why Validate?**

Maria Ramirez-Marrero, Sr. Scientist II, Technical Services, G&W Laboratories, Inc.

The presentation will discuss the importance of validating the manual cleaning process of the GMP equipment used in the pharmaceutical industry. It will include definitions, FDA guidelines, the cleaning parameters to consider when performing a manual cleaning validation, effective cleaning instructions, situations to avoid that could compromise the repeatability of the process, how to implement the successful results into an effective manual cleaning procedure, and how to verify the effectiveness of the validated procedure.

Risk Analysis (Cleaning Process Development)

11:30 **Cleaning Process Development from Lab Bench to Full Scale—A Lean Six Sigma Case Study**

CASE STUDY

Sophia Song, Process Development Scientist, Center for Pharmaceutical Cleaning Innovation, (CPCI)

This Case Study will show how improvements in laboratory techniques for Cleaning Process Development incorporating Design of Experiments were used to optimize and simplify cleaning processes at a Semi-Solid Dosage Manufacturer resulting in significant time, energy and resource savings while executing a compliance remediation project. This presentation will also showcase new technologies that have been developed for use in bench scale analysis.

12:15 *Complimentary Lunch*

1:15 **Do What You Say, Say What You Do, Ensuring Cleaning Procedures Match Actual Practice**

Joe Cagnassola, Principal Validation Engineer at Alcon, A Novartis Company

In today's heightened regulatory scrutiny, customers demand for faster turnaround times and ever changing production priorities the difficulty is establishing a robust repeatable cleaning program is easier said than done. The foundation of the cleaning program is based on concise and repeatable procedures that include design, regulatory and personnel considerations. The cleaning scope includes but is not limited to legacy and new installations automated and manual cleaning processes, personnel training and continued verification.

The cleaning procedures should be based on the actual process steps, but as many individuals have encountered not all cleaning procedures are specific or detailed enough to dictate that the cleaning process is followed as expected. This gap is what auditors are looking at when reviewing a firms cleaning approach. To ensure that the hard work that is applied to cleaning process is value added, cleaning procedures need to meet and or exceed the required regulatory, customer expectations but provide reasonable turnaround times that rapid pace manufacturing facilities require. To accomplish this we will review the development of a Cleaning SOP, form, protocol and report that will provide guidance for how to document the cleaning program that anyone from the new employee to the site SME will be able to understand and defend.

Examples of Cleaning Problems

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used.

The deviation indicates that the most probable cause was human error in that the SOP cleaning instructions were not properly executed.

Risk Evaluation (Risk-Based Method Selection)

2:00 **Risk Based Approach for Cleaning Validation**

Walid El Azab, Technical Service Manager STERIS N.V. / S.A., A Subsidiary of STERIS Corporation

The presentation will explain the impact of the changes in EU and EMA guidelines regarding cleaning validation. Following that, the presentation will deep dive on risk-based approach to be used to ensure compliance with the international cleaning regulatory. Finally, through a case study (used as an example) the presentation will present rational to develop risk based cleaning validation limit and program: (1) assess and prioritize the toxicological value, (2) assess the safe threshold value versus the cleaning process capability, (3) understand the influence of the recovery rate, LOQ/LOD of the analytical methods on setting cleaning limit, (4) when visual residue limit could be used only. The risk assessment objective is to rationalize the numbers of validations run, prioritize the workload and demonstrate effective the cleaning process in place. Finally, we will share different approaches implemented by manufacturers around the globe.

2:45 **Cleaning Protocol Development and Program Maintenance**

Robert Jernigan,Validation Group Leader, QA Validation Oversight, GSK Zebulon

Cleaning validation protocols should describe the equipment to be cleaned and state the cleaning methods to be used. Protocols should describe the extent of the cleaning and list any critical parameters to be monitored and/or controlled. Protocols should provide analytical methods used for sample analysis. Cleaning Protocols should also state method of sample collection i.e. swabbing vs rinses and how samples will be collected and labeled. Protocols should also clearly indicate areas where samples will be taken. Finally, residue limits should be stated and limits should be practical and verifiable. Limits should be based on minimum known pharmacological or physiological activity of the API. Also, cleaning procedures should be periodically examined to ensure procedures are robust and remain effective.

3:30 ***Afternoon Networking Break***

3:45 **Use of Statistics For Cleaning Validation**

Igor Gorsky, Senior Consultant at ConcordiaValSource, LLC

Abstract coming soon

4:30 **Lifecycle Management of Analytical Methods for Cleaning verification Support**

CASE STUDY

Mariann Neverovitch, Cleaning Validation SME, Analytical Strategic Operations, Analytical & Bioanalytical Operations Bristol-Myers Squibb

Equipment Cleaning is a critical GMP element of the Manufacturing Process. It ensures quality and safety of future batch. Cleaning Validation/verification is a measurement of the effectiveness of the cleaning process

In this presentation we will go over advantages and challenges of specific and non-specific analytical methods based on risk assessment of the residual product.

Case studies, training and qualification programs will also be discussed.

5:15 ***Close of Program***

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