PharmaED RESOURCES, Inc.

Cleaning Validation Summit, 2019

Cleaning Standards and Best Practices for Drugs, Biologics, and Medical Devices

October 9–10, 2019, San Diego, CA

Can you implement the best science-, risk- and statistics-based approaches for cleaning validation? Today's regulators are now expecting ADE monographs and risk assessments of your organization's cleaning validation programs. This two-day intensive summit brings together industry leaders to illuminate best practices in cleaning validation.

Featuring Lessons Learned and Case Studies from Industry Experts

Robert Jernigan
GSK

Joe Cagnassola
Alcon

Beth Kroeger
STERIS

Elaine S. Mayhall
FDA

Danielle Gabrish
AstraZeneca

Mariann Neverovitch
Bristol-Myers Squibb

Fred Ohsiek
Novo Nordisk

Yuri Svirkin
Cambridge Polymer Group

Sheba Zaman
Novatek

Koshy George
Quantic Group

Chad Rhodes
Dober

Alan Golden
Design Quality Consultants

Osamu Shirokizawa
Life Scientia Ltd.

Stephen Spiegelberg
Cambridge Polymer Group

John Hyde
Hyde Engineering

Sharif Uddin
Rockline Industries

Ralph Basile
Healthmark & AAMI

And Comprehensive Coverage On:

- Understanding the 2018 FDA Guidance on Regulatory Submissions for Cleaning Validation
- Current Best Practices for Regulatory Audits of Cleaning and Cleaning Validation Practices
- ASTM Standards in Medical Device Cleaning Validation
- Science and Risk Based Cleaning FMEA and Cleaning Control Strategy
- Process & Cleaning Validation during Technology Transfer of Biologics & Vaccines
- Creating a Robust Cleaning Protocol and Report
- Statistics in Validation – For Non-Statisticians
- Writing Cleaning Validation Master Plans and Ongoing Cleaning Maintenance
- Analytical Approach for Implementation of Visual Inspection
- Establishing Cleaning Validation Limits for Residue
- Strategies for Lean Cleaning Validation Maintenance for Biologics
- Common Issues with Cleaning and Maintaining Stainless Steel Equipment
- Influence of Material Chemistry and Process History on Medical Device Cleaning Analysis and Chemical Risk Assessment
- Optimizing Manual Cleaning Validation Processes and Operator Qualification for Manual Cleaning
- And Much More!

Featuring Representation From:

Alcon A Novartis Division · gsk · novo nordisk · FDA · STERIS · JUBILANT PHARMA · Bristol-Myers Squibb · AstraZeneca · iatric

Cambridge Polymer Group · DOBER · eurofins Medical Device Testing · Hyde Engineering +Consulting · LifeScientia · NOVATEK INTERNATIONAL · healthmark

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Wednesday, October 9, 2019

7:30 *Complimentary Breakfast*

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

Regulatory Spotlight: Understanding FDA Requirements and ASTM Protocols

8:30 **How the FDA Uses Standards in General, and Specifically to Cleaning Activities in Medical Devices – The final 2018 FDA guidance on *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices***

Elaine S. Mayhall, Ph.D., Chemist/Scientific Reviewer, Office of Product Evaluation & Quality, FDA

FDA will present an overview of the US Standards Strategy and specific legislative activities related to the Center for Devices and Radiological Health recognition authority for medical device standards and how they are used in premarket submissions. Specifically, elements of the final 2018 FDA guidance on *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices* will be described, including use of the Declaration of Conformity and General Use of standards, the recognition process, and requests for recognition. The talk will then turn to information on reprocessing (including cleaning, disinfection, and sterilization) of reusable and single use medical devices with examples given with regards to FDA-recognized standards. The presentation will conclude with how to locate FDA guidance documents, recognized standards, and web resources.

9:15 **Creating a Robust Cleaning Protocol and Report**

Joe Cagnassola, Principal Validation Engineer, Alcon

The key to success in any cleaning program is having a cleaning protocol and report that captures the critical steps and provides audit ready documentation. Understanding the cleaning process/program helps the users write polished documentation that stands up to the scrutiny of auditors. This presentation will go step by step through the inception of the cleaning project through the completion of the report. Understanding the process flow will help expedite the Validation time and ensure compliance to internal and external requirements.

Learning Goals for this presentation include:

- User Requirements
- Pre-Requisites to get started writing
- Understanding the Writing Process
- Execution and Report Writing

9:55 *Networking and Exhibit Viewing Break*

10:20 **ASTM Standards in Medical Device Cleaning Validation**

Stephen Spiegelberg, President, Co-Founder, Cambridge Polymer Group, Inc., and Ralph Basile, VP of Healthmark & Member of AAMI's Sterilization Standards Committee

ASTM has been active in developing standards for medical device cleaning activities for the past two decades. These standards are being used for single use devices (permanent implants, disposable devices) as well as re-usable devices (surgical tools, patient assist devices), to help companies design, test, and validate their cleaning processes. These ASTM Standards are also referenced in the standards of allied organizations, including AAMI and ISO documents and guidance documents authored by the U.S. FDA. This presentation summarizes the current and pending standards that are available to assist in matters involving cleaning processes for the medical industry, along with how the standards are being used in the industry.

11:00 **Science and Risk Based Cleaning FMEA and Cleaning Control Strategy**

Osamu Shirokizawa, President, Life Scientia Ltd.

This presentation will discuss how Cleaning FMEA will be conducted under the concept of the ASTM E3106 Standard and why cleaning SOPs should have FMEAs performed on them. It takes a science and risk-based approach, making the most of the set of cleaning risk tools developed by the ASTM Cleaning Standard Team. The presentation will also include how to set up a Risk-based Cleaning Control Strategy based on the result of the Cleaning FMEA.

11:40 **Current Best Preparatory Practices for Regulatory Audits of Cleaning and Cleaning Validation Practices**

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 process efficacy and its validation are often the subject of regulatory audits because of concerns for drug product adulteration. The materials presented in this session will address best practices for regulatory audit preparations for both pre-approval inspections (PAIs) and periodic GMP inspections for critical aspects of process equipment cleaning and cleaning validation activities.

The session will specifically address:

- Country specific and global cleaning validation requirements and expectations including 21 CFR 211, Eurdralex Vol. 4 Annex 15, ICH Q7, US FDA Cleaning Validation Guidance, Health Canada Cleaning Validation Guidelines, PIC/S PI 006-3 and others
- GAP analysis methodologies for audit preparation
- Best practices for cleaning validation program design and documentation
- Effective organization and presentation of cleaning validation testing methodologies and data to regulatory auditors

12:20 *Complimentary lunch sponsored by*

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Critical Issues—Cleaning Validation for Biologics

1:20 **Lean Cleaning Validation Maintenance**

Danielle Gabrish, Manager, Validation, AstraZeneca Biologics

In this presentation, we will review the transition from initial cleaning validation to cleaning validation maintenance of large-scale biologics:

- High Level Initial PQ (conservative approach)
  - 3X Worst case, typically 1X remaining
  - Sampling Requirements
- Lean Cleaning Validation Maintenance:
  - Time-based revalidation / maintenance
  - Periodic Review using risk-based approach
- Cost Savings:
  - Reducing TOC Swab
  - Reduce product-specific sampling
  - NPI matrix approach for cleaning verification
- Controls and Detections
  - Solution Solubility / Concentration Assessments
  - Quality Systems
  - PM Program
  - Calibration Program
  - Recipe / Formula Revisions

2:00 **Writing Cleaning Validation Master Plans and Ongoing Cleaning Maintenance**

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

This presentation will provide details for writing Annual Cleaning Validation Master plans, what should be included: equipment description / surface areas, swab sites, Maco limits. These documents, if clearly detailed will be the basis for writing Cleaning Validation Protocols across the manufacturing areas. Presentation will also include discussion for authoring and documenting Ongoing Annual Maintenance.

2:40 *Networking and Exhibit Viewing Break*

Critical Issues—Sound Approaches to Visual Inspections

3:05 **Analytical Approach for Implementation of Visual Inspection**

Mariann Neverovitch, Research Scientist, 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.

3:45 **Common Issues with Cleaning and Maintaining Stainless Steel Equipment**

Beth Kroeger, Technical Services Manager, Life Sciences, STERIS

Stainless steel equipment is ubiquitous in the Pharmaceutical manufacturing environment. How well it is maintained or not can impact the manufacturing schedule, the product, or the piece of equipment itself. Stainless steel has the unique ability to maintain a chemically resistant, chromium enriched, passive layer when exposed to oxygen. Acids such as nitric, phosphoric, citric as well as proprietary acid blends are commonly used to enhance the rate of formation of this passive layer. When the passive layer is exposed to adverse conditions there can be damage to the passive layer is exposed to adverse conditions there can be damage to the passive layer resulting in surface non-uniformities. This presentation will review standard recipes to enhance the passive layer formation as well as common test methods to evaluate the passive layer for predictive maintenance rather than reactive. The presentation will also include laboratory studies that investigate cleaning, passive layer monitoring, and preventative maintenance approaches to prevent surface non-uniformities and costly un-scheduled equipment downtime of process equipment, vessels, and piping.

4:30 *End of Day 1*

Thursday, October 10, 2019

7:45 *Complimentary Breakfast*

8:30 **Chairperson's Remarks**

8:45 **Statistics in Validation – For Non-Statisticians**

Alan Golden, MS, Principal, Design Quality Consultants, LLC

In this presentation, we will discuss the common statistics tools and techniques used in validation. Through real world examples and interactive exercises, we will demonstrate the basic concepts of statistics and how to apply them to your validation projects.

I. Introduction
- What is Statistics
- Why do you need Statistics for Validation?
- Regulatory expectations

II. The Concept of Variance (and why it is important)
- Sources of variance
- Measuring variance
- Normal and non-normal distributions
- Measuring Variance

III. Expressing Variance
- Variance
- Standard deviation
- Interactive exercise: Measuring Variance
- Coefficient of variation

IV. Process Capability
- Can your system do what you want (need) it to do?
- Measuring capability
- Using capability to set acceptance criteria for validation

V. Acceptance Sampling for Validation
- How much?
- How many?
- How often?

VI. Conclusion and Discussion

9:45 **User Requirements & Implementation of a Risk Based, Compliant Cleaning Validation Management System Based on the Draft Guidance on DATA Integrity**

Sheba Zaman, Head, Product Specialists & Training Services, Novatek International

This presentation will address the following topics:

- Manual systems vs. Computerized systems
- Benefits of compliant computerized cleaning validation system
- Components of a compliant cleaning validation system:
  - Cleaning validation user requirements based on inherent risks
  - New FDA draft guideline "data integrity"
  - Supplier qualification
  - Implementation, validation and training

10:30 *Mid-Morning Networking & Exhibit Viewing Break*

10:50 **The Medium is the Message: Influence of Material Chemistry and Process History on Medical Device Cleaning Analysis and Chemical Risk Assessment**

Yuri Svirkin, Senior Research Scientist, Cambridge Polymer Group

This presentation will discuss modern strategies for medical device cleaning assessments; covering experimental design and analytical testing as inputs for performing a toxicological risk assessment. The presentation, leveraging the chemical risk assessment framework of ISO 10993 and FDA guidance communications, will discuss the holistic process of evaluating medical device materials of construction, end use environment, and manufacturing processes to justify selection of extraction conditions and analytical techniques. Specific discussion will include consideration of manufacturing residues and material-specific impurities, and how such context can fill in the blind spots of typical "survey scan" analytical workflows, as well as how such context of the underlying chemistry/process may facilitate identification of compounds not found in conventional mass spectral databases, reducing the cost and effort associated in resolving "unidentified" extractable compounds. Challenges associated with quantitation of surfactants and chelation agents shall be highlighted in case studies.

11:35 **Establishing Cleaning Validation Limits for Residue**

Fred Ohsiek, Senior Specialist Cleaning Validation, Novo Nordisk

One of the most confusing and stressful activities in cleaning validation is how to calculate the limits for residue. Residue limits need to be determined for active and cleaning agent residue. Even though the actual calculations can be complicated, using the correct or "best" method for calculating the limit can be overwhelming, especially today.

In the past, limits have been calculated using the therapeutic dose, default limits, toxicological data, and research data/scientific rationale. Mainly because it is mandated by the EMA, the current trend is to establish limits using a health-based approach.

In this presentation, we will:

- Review brief history for setting residue limits
- Dissect the residue limit calculation conceptually
- Discuss the different methods for calculating the active and cleaning agent residue limits
- Consider drug substance and drug product manufacturing
- Discuss limits for biological and synthetic manufacturing
- Debate legacy limit approaches

12:15 *Complimentary Lunch*

1:30 **Understanding API Solubility and the Impact on Cleaning**

Chad Rhodes, Business Development Manager, North America, Dober

Recent trends show an increase and diversity of molecules being used in drug delivery. R&D scientists are now developing formulations that contain poorly soluble or insoluble active pharmaceutical ingredients APIs. As pharmaceutical companies and CDMOs begin scaling up from the R&D phase to commercial operations, there is a growing need for cleaning solutions to address these solubility concerns. Dober will discuss current cleaning practices for some recent industry challenges of poorly soluble APIs, specifically evaluating and comparing both commodity chemicals and formulated detergents. Additionally, we will calculate the rinsability and conduct TOC analysis for these cleaning methodologies to address residue removal of commodity chemicals versus formulated detergents to support cleaning validation processes.

2:15 **Why Validate Manual Cleaning Process?**

Koshy George, President, Koshy & Associates Consulting Services

At least some manual steps are involved in almost all cleaning processes. At some pharmaceutical facilities all cleaning processes are manual. Manual cleaning processes involves human intervention. This involvement can be intentionally systematic or at random. Manual cleaning processes are almost always fully operator controlled, while semi-automatic processes involve operator intervention at different stages of the process. The outcome of the manual cleaning processes, the success or failure of the process, depends upon the operator input. For a successful outcome, a deliberate and systematic approach by the operator to the cleaning process is required.

Operators must be trained and their training documented, which is a compliance requirement. Operators must follow a written standard operating procedure. SOPs for manual processes must be written in detail with no ambiguity so that any operator can follow the instructions without getting confused. The cleaning process must be repeatable with a consistent outcome. For manual cleaning process the main variable is the human input. Critical Cleaning Parameters (CCPs) such as TACT (Time, Action, Concentration, Temperature) must be monitored during manual cleaning processes also. It is a regulatory expectation that all processes in the pharmaceutical industry are validated and the processes are repeatable, consistent and meets certain predetermined limits. Manual cleaning processes are validatable despite claims from some people that manual cleaning processes are not validatable. This presentation will cover points to consider for successful manual cleaning processes and explain why manual cleaning processes must be validated.

3:00 ***Afternoon Networking Break***

3:15 **Hygienic Design of Equipment – A Critical Step for Successful Cleaning Validation**

Sharif Uddin, Ph.D., Senior Engineer, Process Cleaning, Global Quality Assurance, Rockline Industries

Cleaning and cleaning validation are an integral part of pharmaceutical industry. Cleaning is a life cycle event which starts with equipment design and selection of cleaning parameters. To perform a successful cleaning validation, equipment and piping systems need to be designed in such a way, so it could be cleanable to an acceptable level. The level of hygienic design required for equipment and manufacturing facilities is always a topic of discussion. Different applications require different levels of hygienic design. The right combination of materials, surface finishes, and accessibility will drive the design and evaluation of equipment and associated systems.

It is always better to address hygienic equipment design at the beginning of the project and to involve your equipment manufacturers and engineering team up front. Establish your expectations and track them throughout the process. The bottom line is the more due diligence you put in, the easier your cleaning validation will be. The presentation will cover basic principles of hygienic design and an overview of critical design parameters which would provide guidance to cleaning and validation professionals to run a successful validation campaign to prevent any micro-contamination from one product to another. The presentation will also provide a tool developed on risk-based approach to evaluate hygienic design of an equipment and process piping.

4:40 ***Close of Conference***

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