PharmaED RESOURCES, Inc.

# Cleaning Validation Summit 2018

**September 12–13, 2018, Philadelphia, PA**

**Pharma-Ed Exclusive: The new ASTM Cleaning Standard for Drugs and Devices**

**—Hear From All of the Authors—**

## Featured Speakers Include:

**Mohammed Ovais**
*Amgen*

**Andrew Walsh**
*CPCI*

**Jessica Graham**
*BMS*

**Robert Kowal**
*Johnson & Johnson*

**Stephen Spiegelberg**
*Cambridge Polymer Group*

**Fred Ohsiek**
*Bayer*

**Beth Kroeger**
*Steris Corporation*

**Thomas Altmann**
*Ecolab*

**Are you up to speed on the new Science, Risk and Statistics based approaches for Cleaning Validation? Today's regulators are now asking for, and expecting, ADE Monographs and Risk Assessments of Cleaning Validation Programs. This two-day intensive summit brings together industry leaders on science, risk and statistics-based cleaning validation to get you started in implementing these 21st Century approaches. These new approaches can reduce the level of effort, formality and documentation of cleaning validation based on risk, streamline the validation work and accelerate the introduction of new products.**

**The entire team that wrote the new ASTM Standard Guide for Science Based and Risk Based Cleaning Process Development and Validation will be there and presenting!**

## With Comprehensive Coverage On:

- ASTM Standard on Science and Risk-Based Cleaning Process Development and Validation
- Case Study for Low-Risk Manufacturing
- ASTM Standard on Derivation of Health Based Exposure Limits (ADEs/PDEs)
- How to use ADEs/PDEs for Setting Cleaning Acceptance Limits
- ASTM Standard for Validating Cleaning Processes Used During the Manufacture of Medical Devices
- Upcoming ASTM Cleaning Standards Covering Both Drugs and Devices
- Automation for Rapid Cleaning Process Development
- Application of Risk Assessments to Cleaning Processes
- Risk-based Selection of Analytical methods
- Risk-based Implementation of Total Organic Carbon Analysis (TOC)
- Application and Qualification of Visual Inspection
- Identification of Unknown Residues Found in Cleaning Validations
- Statistical Evaluation of Cleaning Validation Data
- Application of Bayesian Statistics to Cleaning

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## Wednesday, September 12, 2018

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

**7:50** *Welcome and opening remarks by Chairperson, Joe Cagnassola, Principal Validation Engineer,* Alcon, a Novartis Company

## *New ASTM Cleaning Standards for Drugs and Devices*

**8:00**

### FDA Involvement With and Support for ASTM Standards

***Colleen Thomas, FDA***

Approval Pending for our FDA Speaker

**8:45**

### New ASTM Standard for HBELs and Calculation of Cleaning Limits

***Jessica C. Graham, Ph.D., DABT, Senior Toxicologist, BMS, (ASTM, HBEL Team Member)***

This presentation will describe the work of a team of experts in toxicology and cleaning validation who comprise the ASTM's Health Based Exposure Limits Guideline Workgroup. Limit-setting to establish acceptable levels of unintended human exposure to active pharmaceutical ingredients (APIs) and other molecules related to the pharma manufacturing process (e.g. synthesis intermediates, cleaning agents) are necessary to comply with various global regulations as part of international cGMP quality requirements, needed as good product stewardship, and are considered the industry standard. ASTM is actively developing a standard for the derivation of Health Based Exposure Limits (HBELs) to assist industry in the derivation and documentation of HBELs. These limits can then be further utilized to calculate cleaning residuals limits used in quality risk assessment for the manufacture of pharmaceuticals. This standard will provide a scientifically justified, data driven, consistent approach to deriving safe limits for unintended exposures to individual substances. This presentation will focus on the key components of this standard (1) Hazard characterization, (2) Identification of the critical effect(s) including dose-response assessment, (3) Determination of one or several Points of Departure (PoD)s for the calculation of HBELs, (4) Application of PoD-specific Adjustment Factors (AFs), and (5) Calculation of HBELs including justification for the preference given to a particular derivation rationale if more than one was developed.

**9:30**

### Introduction to the New ASTM Cleaning Standard — Case Study For Low-Risk Products

CASE STUDY

***Andrew Walsh, President, Cleaning Validation SME, CPCI, (ASTM Cleaning Team Member)***

The presentation will be explore the structure of the new ASTM E3106 Standard and its foundation in ICH Q9 and the FDA's Guidance on Process Validation. The importance of using HBELs will be discussed in combination with Cleaning Process Development, Analytical Method Development and the statistical evaluation of cleaning data. A case study showing how the implementation of E3106 for a low risk pharmaceutical manufacturing facility provided improvements to the cleaning process (reduce temperature, cleaning time and water usage) while simplifying and streamlining the cleaning validation. The presentation will also include a discussion and analysis on the updated EMA Q&A on Setting Health Based Exposure Limits and its applicability to the E3106 Standard.

**10:15** *Mid-Morning Networking Break*

**10:40**

### ASTM Standards in Medical Device Cleaning Validation

***Stephen Spiegelberg, Ph.D President, Cambridge Polymer Group, Inc., (ASTM Device Cleaning Team Member)***

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 and disposable devices), as well as re-usable devices, (surgical tools and patient assist devices), to help companies design, test, and validate their cleaning processes. 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.

**11:30**

### Practical implementation of the ASTM E3107 in the Pharmaceutical Industry

***Thomas Altmann, Global CIP/COP Technical Manager, Ecolab Life Sciences, (ASTM Cleaning Team Member)***

In 2011, the FDA published general principles for process validation following a life cycle approach. The pharmaceutical industry has begun to apply these principles to cleaning process validation; however, to fully implement life cycle practices into cleaning process development and validation, the industry's challenge is to translate the 2011 guidance to a structured, practical, risk-based approach. The ASTM guide E3107 provides the framework and structure for science- and risk-based approaches. This presentation will provide practical guidance on the knowledge and information needed to perform risk assessments that ease cleaning process development and validation efforts. A risk assessment format and examples will be provided.

**12:15** *Complimentary Lunch*

## Risk Assessment

1:20 **Risk Assessment in Cleaning of Pharmaceutical Products**

***Robert Kowal, Cleaning Validation SME, Johnson & Johnson, (retired), (ASTM Cleaning Team Member)***

This presentation will discuss the concept and measurement of risk as it applies to the cleaning of pharmaceutical products. Attendees will learn how to apply risk tools to science based data to assist in measuring and assessing the risk associated with cleaning process failures as well as how these tools can be applied to develop a cleaning risk dashboard.

2:00 **Use of Statistics in Cleaning**

***Igor Gorsky, Cleaning Validation SME, Concordia Valsource, (ASTM Cleaning Team Member)***

Use of Statistics in Cleaning Validation Lifecycle proposes a number of statistical tools that help in evaluation of data attained in three stages of Cleaning Validation efforts – Stage 1: Process Design, Stage 2: Process Qualification and Stage 3, Continued Process Verification. In light of upcoming ASTM Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation, this information should be valuable to cleaning validation professionals, as it provides practical methods for data analysis and interpretation. The key learning objective of this presentation is to show that data obtained during cleaning validation lifecycle is not just measured on "pass" or "fail" merits, but can be understood on a more granular level. This should help to understand the cleaning processes which in turn should aid in optimization of the latter to improve consistency thus reducing risk due to cleaning for product's manufacturing and protection of patient's safety.

2:45 ***Afternoon Networking Break***

3:10 **Evaluation of Cleaning Data: More Than Just Pass/Fail**

***Mohammad Ovais, Cleaning/Process Validation SME, Amgen, (ASTM Cleaning Team Member)***

How clean is clean? Should the cleaning validation results be averaged? What should one do if any of the results are outside acceptance limits? These are some of the questions that one might have heard from scientists involved in validation of cleaning procedures. But there seem to be no definitive answers. This presentation will be an attempt to address these concerns.

This presentation will discuss some of the regulatory expectations related to cleaning validation, and current approaches to cleaning data evaluation and their limitations. It will then discuss how statistical thinking can be used for understanding of cleaning processes and associated variability. The highlight of the presentation will be a novel approach for estimating probability of exceeding cleaning limits. Using real-world examples, the presentation will demonstrate the application of the proposed approach.

3:50 **Automation of Cleaning Process Development**

***Sophie (Ruijin) Song, Cleaning Process Development Scientist, CPCI***

Newly developed automated, high throughput technologies will be presented that can be used to rapidly determine the Cleanability of Pharmaceutical, Biological, Cosmetic, etc. products as described in E3106. These devices can also rapidly determine the best cleaning agents, and rapidly determine optimal cleaning parameters for a cleaning process using Design of Experiments and other statistical techniques. Why bench-scale determination is the only legitimate means of selecting "hardest-to-clean" products will be presented. One of the automated, high throughput devices will be on hand for demonstration.

4:35 **The Science of Cleaning to Achieve Optimal Equipment Efficiency**

***Chad Rhodes, Business Development Manager, North America, Dober***

Abstract Pending

5:10 ***Complimentary Happy Hour Sponsored by Steris Corporation***

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## Thursday, September 13, 2018

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

7:50 ***Welcome and opening remarks by Chairperson, Joe Cagnassola, Principal Validation Engineer, Alcon, a Novartis company***

## Risk-Based Analytical Methods

8:00 **Risk-based Method Selection and Implementation of TOC**

***Andrew Walsh, President, Center for Pharmaceutical Cleaning Innovation, (CPCI), (ASTM Cleaning Team Member)***

A science and risk-based approach based on the ASTM E3106 Standard will be presented on how to select analytical methods using cleaning risk tools developed by the ASTM Cleaning Standard Team and how this approach can be used to justify selection of Total Organic Carbon (TOC) analysis, Visual Inspection or any other analytical method.

8:45 **Identification of Unknown Residues in Cleanliness Assessments: How Confident Are We Really?**

***Adam Kozak, Research Scientist, Cambridge Polymer Group, Inc.***

Cleanliness assessments often include determination of both known compounds (e.g. processing aids) as well as unknown residues, which may be introduced to a component via unintentional contamination or chemical change products during cleaning/manufacturing. Commonly, chemical analysis techniques like GC-MS and LC-MS are employed to identify and quantify such unknown residues, with the results of these analyses feeding into toxicological evaluation per ICH M7(R1) or ISO 10993-17. The applicability of an overall risk assessment therefore hinges crucially on the quality of the identification and quantitation processes performed on the unknown residues. This presentation discusses the uncertainties associated reliance on "best library matches" or molecular formula generation for compound identification, as well as the uncertainty associated with semi-quantitation against model compounds. Also discussed are cases in which "close seconds" on library hit lists may present a significantly different toxicological risk than its associated "best" library hit (and relative confidence in each). Finally, we discuss the (in)feasibility of performing "gold standard" identification workflows against reference standards or chemically synthesized intermediates/degradation products as part of typical cleanliness assessment project scopes.

9:30 *Mid-Morning Networking Break*

9:55 **Analytical Approach for Implementation of Visual Inspection**

***Mariann Neverovitch, Cleaning Validation SME, BMS, (ASTM Cleaning Team Member)***

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.

## *Cleaning Program Development*

10:40 **Knowledge and Risk-Based Optimization of Cleaning Validation Programs**

***Sunil Patel, Senior Global Technical Manager, Ecolab Life Sciences***

It is a large undertaking for pharmaceutical manufacturers to change decades-old legacy cleaning validation programs. Without known cleaning issues or historical regulatory inspection findings, there is little impetus to change current practice. In most cases, legacy cleaning procedures were developed based on excessive cleaning strategies rather than characterization by scientific data and correlation between critical cleaning performance parameters (CCPP) and their impact on cleaning performance. This presentation will examine a scientific and risk-based cleaning validation program optimization based on ICH Q9 principles and the newly published ASTM E3106 standards. It will outline how scientific data and performance of risk assessments throughout the cleaning validation life cycle can be leveraged to optimize and deliver a compliant and efficient cleaning validation program. Case studies will be shared to demonstrate the time, water, chemistry or energy savings achieved utilizing this approach.

11:20 **Cleaning Validation Protocols and Contents**

***Fred Ohsiek, Sr. Manager Cleaning Validation, 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.

12:00 *Complimentary Lunch*

1:05 **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 also describe the extent of the cleaning and list any critical parameters to be monitored and/or controlled. Furthermore, 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.

1:50 **Cleaning Development; Using a Quality by Design Approach to Stop Cleaning for Long Hours**

***Walid El Azab, Technical Service Manager, Steris Corporation***

The presentation will share a systematic cleaning development method to a science and a risk-based approach for product residue cleaning. The following concept will be discussed during the presentation; determination of the cleaning critical parameter, critical quality attribute, the design of space, and cycle development. The understanding of this concept is crucial to implementing effective cleaning processes and avoid complex cleaning process and long cleaning time. During the presentation, different tools, case studies and lessons learned will be shared to demonstrate the benefit of a robust cleaning development.

2:30 ***Afternoon Networking Break***

2:55 **Developing and Writing Cleaning Procedures**

***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 firm's cleaning approach. To ensure that the hard work that is applied to the 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.

3:40 **User Requirements & Implementation of a Risk Based, Compliant Cleaning Validation Management System Based on the Draft Guidance on DATA Integrity**

***Parsa Famili President & CEO, Novatek International***

In the pharmaceutical manufacturing, risk of contamination is from a broad range of factors such as crosscontamination (other pharmaceutical active ingredients), cleaning agents and micro-organisms.

Additionally, the risk of contamination may in some cases be from a calculation error which results in choosing the wrong Maximum Carry-Over Limit (MAC). For example, can you consider the number of calculations required for an equipment train, with twenty (20) sample points, having different surface areas (swab sample area), different sampling types (swab/rinse), five (5) products manufactured on the equipment train, and each product has ten (10) production stages, and two (2) different cleaning agents are used. There is a huge risk associate with calculating the Maximum Carry-Over Limit (MAC) manually.

Automation has played a key role in decreasing risks associated with various processes. Data integrity, is an important component of industry's responsibility to ensure the safety, efficacy, and quality of pharmaceutical products.

4:20 ***Close of Program***

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| | |
|---|---|
| **Dates:** | September 12–13, 2018 |
| **Venue:** | The Racquet Club of Philadelphia |
| **Venue Address:** | 215 South 16th Street<br>Philadelphia, PA 19102 |
| **Venue Phone:** | (215) 735-1525 |
| **Hotel Room Block:** | Radisson Blu Warwick |
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