Science, Risk and Statistics-based Cleaning Process Development and Validation

CONFERENCE

co-organized by Key2Compliance and ValidEire ApS
Sponsored by Novatek International

Conference description:
This two-day, intensive conference brings together the industry leaders on Science and Risk- and Statistics-based Cleaning Process Development and Validation. The conference will go beyond presentations on best practice and consists of workshops complemented with plenary Q&As. Attendees will therefore gain a deeper understanding of the new ASTM E3106 Standard, PDA TR 29 revision, Annex 1, HBELs, new draft and use of statistics in cleaning validation, as well as risk evaluation and data integrity in cleaning validation - among other things.

Conference objectives:

The objective of this conference is to provide participants with practical knowledge and understanding of regulatory requirements and techniques that can be put to use in their own cleaning process development and validation strategy. The presenters will focus on the newest information available and will cover a wide range of subjects relevant to cleaning process development and validation.

The conference is primarily relevant for R&D staff, Leaders, Supporters, Validation teams in production and Quality Assurance seeking the latest knowledge about risk- and statistics-based cleaning validation, as well as for engineering companies wanting to learn more about the viewpoint of the pharmaceutical industry and exchanging experience.

Further information

Plenary Q&A

The speakers will be available to answer questions either relayed beforehand by mail or live at the plenary Q&A.

Workshops

The workshops also will be dual communication between the facilitator and attendees. These will be held at the times displayed in the table and be.

DAY ONE 29th November 2021 Presentations (all times CET)	DAY TWO 30th November 2021 Presentations (all times CET)
08:50-09:00 INTRO BY MODERATOR 09:00-09:45	08:50-09:00 INTRO BY MODERATOR 09:00-09:45
Introduction to ASTM E3106 "Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation" and Upcoming Standards – *Andrew Walsh*	**Use of Statistics for Cleaning** – *Igor Gorsky*
09:45-10:30	09:45-10:30
Annex 1 Revision -*Pierre Devaux*	**Statistical Determination of Swab Recovery Factors in Coupon Studies -** *Ioanna-Maria Gerostathi*
BREAK 3O MINUTES	**BREAK 30 MINUTES**
11:00-11:45	11:00-11:45
ASTM "Standard Guide e3219 for the Derivation of Health Based Exposure Limits (HBELs)" for Drugs and Devices – *Andreas Flückiger*	**Implement a Risk-Based, Data Integrity Compliant Cleaning Validation Management System-** *Susan Cleary*
11:45-12:30	11:45-12:30
Sustainable Quality Assurance through the Application of QRM in Cleaning - *Ken Farrugia*	**Cleaning Process Risk Evaluation — A Quantitative Framework** - *Mohammad Ovais*
LUNCH 1 HOUR	**LUNCH 1 HOUR**
13:30-14:15	13:30-14:15
Analytical Development: A Useful Support for Cleaning Control and Validation – *S. Janvier*	**Lean Six Sigma Case Study Using Total Organic Carbon Analysis** - *Andrew Walsh*
14:15-15:00	
Application of Statistics to Cleaning Process Development - *Ruijin Song*	
BREAK 30 MINUTES	**BREAK 30 MINUTES**

Plenary
Question & Answers
With the presenters

DAY ONE 29th November Plenary Q&A (all times CET)	DAY TWO 30th November Plenary Q&A (all times CET)
15:30-16:30	14:45-15:45
Presenters: *Andrew Walsh, Pierre Devaux, Andreas Flückiger, Ken Farrugia, S. Janvier & Ruijin Song*	**Presenters:** *Igor Gorsky, Ioanna-Maria Gerostathi, Susan Cleary, Mohammad Ovais and Andrew Walsh*

Workshops facilitated by Cleaning Process SMEs

DAY ONE 29th November 2021 Workshops	DAY TWO 30th November 2021 Workshops
QRM on Cleaning Validation *Kenneth Farugia*	**Application of Statistics to Cleaning Processes** *Mohammad Ovais*
Visual Inspection Qualification *Andrew Walsh*	**Recovery method with Swabs** *Ioanna-Maria Gerostathis*
Review of HBELs *Andreas Flückiger*	

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DAY I

29th November 2021

Moderator: Laurence O'Leary, ValidEire Aps

08:50-09:00 Intro by Moderator

09:00-09:45 **Introduction to ASTM E3106 "Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation" and Upcoming Standards -** Andrew Walsh (CPCI) This presentation will provide the history behind the movement to the science and risk-based approaches to cleaning validation and introduce the American Society for Testing and Material (ASTM) E3106 "Standard Guide for Science Based and Risk Based Cleaning Process Development and Validation". The presentation will explore the structure of the new ASTM E3106 Standard and its foundation in ICH Q9 and the FDA's 2011 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. The presentation will also include a discussion of upcoming ASTM Standards and an analysis on the updated EMA Q&A on Setting Health Based Exposure Limits and its applicability to the E3106 Standard. A case study showing how the implementation of E3106 for a low risk pharmaceutical manufacturing facility provided improvements to the cleaning process (reduced temperature, cleaning time, cleaning agent and water usage) while simplifying and streamlining the cleaning validation.

09:45-10:30 **Annex 1 Revision** -Pierre Devaux, Theraxel

Abstract (to follow)

11:00-11:45 **ASTM "Standard Guide for the Derivation of Health Based Exposure Limits (HBELs)" for Drugs and Devices** – Andreas Flückiger

Limit-setting to establish acceptable levels of unintended human exposure to active pharmaceutical ingredients (APIs) and other molecules in the pharma manufacturing process (e.g. synthesis intermediates, cleaning agents) is necessary to comply with the cGMP quality regulations of numerous countries. By the adoption of the pertinent texts of the EMA by PIC/S, it has become globally recommended industry practice. ASTM has developed a standard for the derivation of Health Based Exposure Limits (HBELs) to assist industry in the setting and documentation of HBELs. These limits are utilized to calculate cleaning limits used in quality risk assessment and risk management during the manufacture of pharmaceuticals, particularly where multi- product facilities are used. This standard provides a science and data driven consistent approach to deriving safe limits for unintended exposures to individual substances. As a more detailed document, it

complements pre-existing guidance with the ultimate objective to contribute to a more harmonised approach in setting HBELs. 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 (PoDs) 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.

11:45-12:30 **Sustainable Quality Assurance through the Application of Quality Risk Management in Cleaning –** Ken Farrugia

The presentation will provide a practical approach for managing the risks associated with cleaning validation with the aim of generating a practical and applicable classification leading to a guided sustainable mitigation and control strategy. In the light of current financial pressures impacting the pharmaceutical industry, a case study based on a real event will be presented, showing how a holistic risk assessment strategy can result in financial security, whilst maintaining confidence in the quality of the product received by the patient.

13:30-14:15 **Analytical Development: A Useful Support for Cleaning Control and Validation**

-S. Janvier (SERVIER)

The scope of this presentation is to provide the strategy used in Servier Industry in France to develop analytical methods in order to perform cleaning validation assays and to follow the exercises of verification. It is always difficult to know exactly how you proceed to develop these methods and if it's necessary to reproduce exactly in details all the aspects performed for an analytical method in order to release a batch. The conference will explain the difficulty to attain the limit of quantification to correspond to the acceptance criteria very lows.

14:15-15:00 **Application of Statistics to Cleaning Process Development** - Ruijin Song (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 "Hardest-to-Clean" product, the best cleaning agents, determine the "Time-to-Clean" 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.

15:30-16:30 **Plenary Q&A**

16:30- **Workshops**

Workshops			
Facilitator	Andrew Walsh	Kenneth Farugia	Andreas Flückiger
Workshop	**Statistical Qualification of Visual Inspection to comply with EMA Q&A #7 & #8** Visual Inspection Qualification This workshop will provide training in statistics-based qualification of Visual Inspection for release of equipment after cleaning as described in the recent EMA Q&As #7 & #8 on Health Based Exposure Limits. Attendees will be demonstrated an actual qualification study using a set of Visual Coupons, able inspect the coupons, collect the inspection data on a Tablet and analyze the data in statistical software (Minitab). The upcoming ASTM "Standard Practice Guide for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues" will be reviewed and how it was specifically developed to meet the EMA's criteria in Q&A #7 & #8.	**QRM on Cleaning Validation**	**Review of HBELs** In practical application of the guidance given by the EMA, PIC/S and ASTM e3219, in this workshop, several HBELs will be elaborated in co-operation with the audience. The objective of these exercises is to enable participants to critically review HBELs and HBEL monographs and to subject them to a plausibility check.

17:30-17:40 **Wrap-up by Moderator**

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DAY TWO
30th November
2021

Moderator: Laurence O'Leary, ValidEire ApS

08:50-09:00 Intro by Moderator

09:00-09:45 **Use of Statistics for Cleaning -** Igor Gorsky (Valsource)

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 the 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.

09:45-10:30 **Statistical Determination of Swab Recovery Factors in Coupon Studies**
- Ioanna-Maria Gerostathi

Recovery studies are probably the only kind of studies that can link the quantity of residues recovered by analysts while sampling to the actual quantity of residues on equipment surfaces, at the end of cleaning operations. For that reason, recovery studies are under frequent regulatory scrutiny. In this presentation we will discuss representative case studies of recovery analysis and how we can make the most out of our results via statistical analysis. Typical challenges and misconceptions will be addressed using practical applications of specific statistical analysis methods, that include linear regression (multiple and simple), Gage Analysis and Hypothesis testing. In this manner we will show how to set a risk-based concept for decision making.

11:00-11:45
Implement a Risk-Based, Data Integrity Compliant Cleaning Validation Management System
- Susan Cleary (Novatek International)

Session Description:
This session will discuss Data integrity and Compliancy for computerized systems used to manage the Cleaning Validation Process. The session looks at cleaning validation management from a risk-based approach, including remediation through automation.

Key Learning Points:

- Understand Data integrity and Compliancy for Cleaning Validation Management
- Learn about Worst Case analysis methods with multiple weighted criteria
- Learn about MAC equations and calculations
- Identify Risk points and understand Automation of Cleaning Validation Risk Assessment

111:45-12:30 **Cleaning Process Risk Evaluation — A Quantitative Framework**
- Mohammad Ovais

Qualitative methods, typically based on risk matrices, are commonly and widely used for comparing the estimated risk to given risk criteria. Though simple to apply, these methods are subjective and often result in biased risk evaluation. This presentation will present a framework for performing quantitative risk evaluation that incorporates likelihood and potential severity of harm to evaluate the significance of the estimated risk. The proposed technique can be used for making robust and objective risk decisions.

13:30-14:15 **Lean Six Sigma Case Study Using Total Organic Carbon Analysis**
- Andrew Walsh (CPCI)
This presentation will be a Case Study on how Total Organic Carbon Analysis (TOC) was implemented as part of a "Lean Six Sigma" project that replaced HPLC and greatly reduced the time and resources needed to release manufacturing equipment back into production through an example at a Solid Oral Dosage facility.

14:45-15:45 **Plenary Q&A**

15:45- **Workshops**

Workshops		
Facilitator	Mohammad Ovais	Ioanna-Maria Gerostathi
Workshop	Application of Statistics to Cleaning Processes	Recovery method with Swabs

16:30-16:40 **Wrap-up by Moderator**

BIOGRAPHIES

Laurence O'Leary

CEO, ValidEire ApS

Co-Arranger of Conference.

Laurence is Founder of ValidEire ApS and has over 20 years working in Pharmaceuticals and Medical Devices. Laurence has a long- track experience in QA, Compliance, Cleaning Validation and Process Validation roles. He presently works as a Validation Consultant. He is a seasoned trainer inhouse for all of his previous clients in Compliance subjects including Process Validation, Cleaning Validation and GAMP.

Laurence also creates Life Science events including conferences and is the creator behind the agenda at this event. Laurence also initiated Copenhagen's Life Science Risk-based and data driven Process Validation industry network group.

Pierre Devaux

Pharmacist-CEO Theraxel-Point Forty Five

Theraxel-Point Forty Five is a Company specialized in consulting, technical assistance, regulatory audits and training around the control of the chemical risk, Microbiological, particulate and pyrogenic for non- sterile, sterile and biotechnological pharmaceutical industries as well as related industries such as cosmetic industries. - Specialist in Part I, Annex 1 and Annex 15 of the European GMP, ICHQ9 and FDA guidelines on aseptic and validation processes and ISO22716- For 6 years, responsible for the quality control laboratories and the management of the environmental monitoring of the ZAC of the Excelvision Fareva French site;- For 5 years, Qualified Person/Quality Director of the ACM Pharma French laboratory, while carrying out consulting missions via the company UPS Consultants.- Head within the French Association A3P of the Common Interest Group on GMP Annex 15 and Cleaning Validation. Speaker for ISPE Nordic and Trainer for A3P Services as well as for Scandinavian Company Key2Compliance AB.

Andrew Walsh

B.S. and M.S. in Biology (Microbiology), certified Lean Six Sigma Black Belt.

Andrew is President of the "Center for Pharmaceutical Cleaning Innovation" (CPCI), a not-for-profit organization that provides research,

education (on site and online) and consulting services (contract and laboratory) for Cleaning Process Development and Cleaning Validation to pharmaceutical, biologics, nutraceutical, cosmetic and medical device companies. CPCI has been guiding companies in the implementation of science and risk and statistics-based approaches to

Cleaning Process Development and Validation using their trademarked "Cleaning Validation for the 21st Century®" and "Clean6Sigma®" programs. Andrew has over 30 years of Manufacturing experience and over 20 years of "hands-on" Validation experience working for Pharmaceutical and Biologics companies such as Johnson & Johnson (three companies), Schering-Plough and Hoffmann-La Roche. Prior to joining the Pharmaceutical industry Andrew worked for 10 years at the Colgate-Palmolive and Clorox companies as an Analytical Chemist and Microbiologist.

Andrew was also an Industry Professor in the Pharmaceutical Manufacturing and Engineering Graduate Program at Stevens Institute of Technology from 2008 to 2015 where he created and taught courses in Pharmaceutical Validation and Lean Six Sigma.
Andrew was an author of ISPE's Risk-based Manufacture of Pharmaceutical Products Guide (Risk-MaPP) and also chairing a team working on the ASTM Standard and Manual for Science and Risk-based Cleaning and Cleaning Validation.
Andrew has a B.S. and M.S. in Biology (Microbiology) and is a certified Lean Six Sigma Black Belt and accredited Trainer.

Andreas Flückiger

Andreas Flückiger, MD, holds Swiss Governmental certifications in General Internal and Occupational Medicine. Before his retirement from the company in 2018, he was ChiefOccupational Health Officer for the Roche Group for over 32 years. In this corporate function, he managed Roche's occupational health and it its hazard assessment programs. This activity included standard-setting, auditing and teaching activities in the broader field of SHE, but in particular in occupational health. Between 1986 and 2018, he and his team have set health-based exposure limits for over 2000 molecules. He is has participated in numerous training courses on the GMP context in which these limits are used, in particular quality risk management in multi-product facilities. Andreas Flückiger is a member or honorary member in several professional organizations.
He now continues to work as a consultant mainly in the areas of occupational toxicology and exposure control.

Kenneth Farrugia

BSc(Hons) MLS, CertOHS, DipM, CertToxicol

Kenneth Farrugia is a Subject Matter Expert in Cleaning Validation and the Prevention of Cross-Contamination. Working with big names within the Generics Pharmaceutical sector such as Teva, Allergan, Actavis and Watson Pharmaceuticals, Kenneth has gained invaluable experience in this field. He is currently the QA Manager for Natrix Sciences Ltd. and ZenPharm Ltd., two emerging companies with great potential, based in Malta. In the past six years Kenneth was the leading brain behind the harmonisation and implementation of the cleaning validation lifecycle approach within the global structure of the aforementioned companies. Having a drive for continuous improvement, he was the founder and chairman of the Community of Practice for the Prevention of Cross-Contamination within Teva Pharmaceuticals. Incorporating the best quality assurance principles possible within a cost effective, efficient and sustainable system is always the main goal behind each project. On a more personal level, Kenneth is the President of the Shotokan Karate-DO Association in Malta and a committed Karate practitioner for the past twenty years. Preserving very strong family values, Kenneth is also a very dedicated family person and a proud father of one. Well… life becomes boring without adding that spice here and there!

Ioanna-Maria Gerostathi

Ioanna-Maria works as a Qualification and Validation Consultant for the Pharmaceutical Industry. She has five years experience in cleaning validation, equipment, facilities and utilities qualification and as well as aseptic manufacturing and process validation. She has worked in Quality Assurance, Validation and Engineering in the Pharmaceutical Industry. She has set sampling plans and trained people in sampling activities for cleaning validation. She holds a Master's degree in Chemical engineering with a specialization in biotechnology and a Master's degree in Materials Science and Technology, both from the National Technical University of Athens.

Susan B. Cleary, Novatek International

B.CS, M.B.A

Susan B. Cleary, B.CS, M.B.A. is the Director of Product Development at Novatek International. Previously holding the position of Program Manager and Lead SOFTWARE Engineer for the core LIMS and Environmental Monitoring software programs. Susan has 20 years of experience in designing, developing, implementing and managing large scale LIMS, Quality Management, and Validation Management software implementations. Susan works with pharmaceutical, biotech, and medical device companies and specializes in data integrity, and working with clients to streamline their procedures and manage their data more effectively for LIMS, Environmental Monitoring, Cleaning Validation, and Quality Management Systems

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Solenn Janvier is Pharmacist and PhD in organic synthesis.
She has worked for the Pharmaceutical Industry for 15 years in Chemical development and Analytical development.
She has worked on cleaning validation analysis for more than 5 years. She has taken part to the A3P group "Cleaning validation" for 4 years.
She has worked for Pierre Fabre Group in Gien (France) since January 2020 as a team leader. Her team is in charge of analytical transposition, troubleshooting and cleaning validation.

Ruijin (Sophie) Song

M.S. Chemical Engineering.

Sophie is a Senior Cleaning Process Development Scientist at the Center for Pharmaceutical Cleaning Innovation where she has been doing research on Cleanability studies for Pharmaceuticals, Biologics and Medical Devices and developing mathematical models of cleaning processes. Ruijin is also engaged in the development and design of an Automated High Throughput Cleanability Testing Device, the automation of a Model CIP System and on using Design of Experiments to optimize cleaning processes of Pharmaceutical products. Ruijin has presented at two Industry Conferences on Cleaning Validation and published a research article last year on cleanability. Sophie has a M.S. degree in Chemical Engineering from Columbia University.

Igor Gorsky (Valsource)

To be added.