Short Course: Surfactants and Biopharmaceuticals - A Love - Hate Relationship

Surfactants play an important role in providing protection to therapeutic proteins against interfacial stresses. It is for this reason that nearly all therapeutic proteins in development and on the market today contain surfactants. Although the exact mechanism of stabilization of a protein by surfactants is not always known, surfactants are universally regarded as critical functional excipients by the industry and by regulators. However, surfactants, especially if of poor quality, can also result in degradation of the therapeutic protein itself. It is therefore important to understand their composition, function, and the mechanisms of degradation, in order to formulate and to manufacture stable products.

The primary surfactants used in therapeutic protein formulations are the nonionic polysorbates, and to a lesser extent poloxamers. These are complex mixtures that require sophisticated and sensitive methods for raw material characterization and product analysis. Novel degradant characterization methods have also been developed over the last decade, which in turn have enabled a better understanding of the mechanisms of surfactant degradation. A better appreciation of the complex but critical role of surfactants has also resulted in enhanced requirements for a proper control strategy for these excipients in the therapeutic product.

This is a course designed to cover the topic of "Surfactants in Biopharmaceuticals" in a comprehensive manner for the practicing pharmaceutical scientist. It will provide a cross-disciplinary view of this topic starting from synthesis to use, analytics, control, safety, and regulatory aspects.

- Understand explore a complete cross-disciplinary picture of the current state of knowledge and issues related to this topic.
- Apply knowledge gained for formulation development, but also to have a holistic approach to surfactants, starting from raw material storage to final control strategies.
- Discuss the latest concepts and analytical tools to help with product development and problem solving.

Presentations

All presentations will be available for day one and day two of the workshop no later than 24 hours following the workshop. Presentations will remain online for registered attendees until August 7, 2019.

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Workshop Planning Committee

Satish K. Singh, Ph.D., Lonza
Atanas Koulov, Ph.D., Lonza

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Workshop Agenda

Sessions will take place in the Washington Convention Center, room 207 A

Saturday, November 3, 2018	
9:00 am – 9:15 am	**Introductions and Welcome** Satish Singh, Ph.D., Lonza Atanas Koulov, Ph.D., Lonza
9:15 am – 9:45 am	**Surfactants Used in Biopharmaceutics Today: An Overview and a Safety Perspective** Satish Singh, Ph.D., Lonza
9:45 am – 10:15 am	**Synthesis and Control of Polysorbates for Biopharmaceutical Applications** Sreejit Menon, Ph.D., Croda
10:15 am – 10:45 am	**A Brief Introduction to the ins and outs of Poloxamer Synthesis** Benjamin Süeess, Kolb
10:45 am – 11:00 am	Coffee Break
11:00 am – 11:45 am	**Mechanisms of Stabilization of Proteins by Surfactants** Tarik Khan, Ph.D., Roche
11:45 am – 12:30 pm	**Mechanisms of Oxidative Degradation of Proteins by Surfactants** Christian Schöneich, University of Kansas
12:30 pm – 1:30 pm	Lunch Break
1:30 pm – 2:30 pm	**Mechanisms of Hydrolytic Degradation of Surfactants - focus on enzymatic hydrolysis** Vincent Corvari, Ph.D., Lilly
2:30 pm – 2:45 pm	Coffee Break
2:45 pm – 3:30 pm	**Degradation of Surfactants and Impact on Product Quality - focus on impact on product quality** Barthélemy Demeule, Ph.D., Genentech
3:30 pm – 4:00 pm	**Behavior of Surfactant During Processing - UF/DF, filter adsorption** Hanns-Christian Mahler, Lonza
4:00 pm – 4:45 pm	**Control of PS80 Degradation During Bioprocessing** Jie Chen, Ph.D., Bristol-Myers Squibb

Sunday, November 4, 2018	
9:00 am – 9:30 am	**Analytical Toolbox for Characterization and Control of Surfactants in Biopharmaceuticals** Michael Jahn, Ph.D., Lonza
9:30 am – 10:00 am	**Surfactant Analytics in Biopharmaceutical Development – Case studies** Zhihua Liu, Ph.D., Bristol-Myers, Squibb
10:00 am – 10:45 am	**Regulatory Perspective on Surfactant Monitoring and Control** Ashutosh Rao, Ph.D., U.S. Food and Drug Administration *(invited)*
10:45 am – 11:00 am	Coffee Break
11:00 am – 11:30 am	**Surfactant Control Strategy (1)** Atanas Koulov, Ph.D., Lonza
11:30 am – 12:00 pm	**Surfactant Control Strategy (2)** Robert Kopf, Roche
12:00 pm – 1:00 pm	**Control Strategy Panel Discussion**
1:00 pm – 2:00 pm	Lunch Break

Speaker Abstracts and Biographies

Surfactants Used in Biopharmaceutics Today: An Overview and a Safety Perspective

Introduction to the use of surfactants in biopharmaceuticals. A review of the safety aspects of the use of these surfactants, especially from parenteral perspective and with a particular emphasis on the hypersensitivity reactions.

Satish K. Singh, Ph.D., Lonza

Satish Singh is the Head of Drug Product Process Development, in the Drug Product Services group at Lonza AG., where he is responsible for drug process development and characterization capabilities for the newly established group. Prior to joining Lonza in September 2016, Satish was Research Fellow and Group Leader at Pfizer's BioTherapeutics Pharmaceutical R&D unit. Satish has more than 25 years of experience in the industry and has deep expertise in all aspects of (bio)pharmaceutical Drug Product development. His experience includes ophthalmics and parenterals, encompassing primarily biologics but also small molecules, and he has been involved in the submission of several BLAs and INDs. Satish has a strong technical background, complemented by an appreciation for regulatory challenges and the evolving regulatory landscape. He has more than 80 scientific publications and is involved in various professional groups within AAPS and USP where he is a member of the USP<788> Expert Panel. He obtained his B.Tech from the Indian Institute of Technology, New Delhi, and an M.S. and Ph.D. in Chemical Engineering from Kansas State University. He holds the position of Adjunct Professor at the Dept. of Physical Pharmaceutical Chemistry at Uppsala University, Sweden and was selected Fellow of AAPS in 2017.

Synthesis and Control of Polysorbates for Biopharmaceutical Applications

Polysorbates (PS) which belong to the family of non-ionic surfactants, consisting of both hydrophilic and hydrophobic ends are extensively used in biopharmaceuticals to prevent against interfacial stresses, protein aggregation and surface adsorption mainly encountered during different stages of drug product manufacturing process.1, 2, 3 Majority of biopharmaceutical products today are formulated with PS20 or PS80 owing to their high surface activity observed even at low concentrations due to their high HLB values and low critical micellar concentration. Other significant advantages polysorbates enjoy over its competitors is its excellent stabilizing properties and very low toxicity.

In recent years, heavy emphasis has been around addressing stability of these products and how quality and stability helps define the stability and efficiency of the final drug product. Quality and stability of polysorbates are governed by multiple factors, all the way from synthesis to storage to handling samples during formulations. This talk will focus on the key steps to be looked at during the manufacturing and packaging stage of polysorbates.

At the end of today's talk, we will be able to better understand how these materials are made, what are the different synthetic approaches adopted, what are some of the key steps taken during production and storage of these materials that help deliver high quality polysorbates. We will also address upcoming challenges and possible ways to address them.

Sreejit Menon, Ph.D., Croda

Sreejit Menon grew up in Mumbai, India and completed his MS in Chemistry from Institute of Chemical Technology (formerly UDCT), Mumbai. After spending close to 2 years with BASF as a Research Chemist working in their Crop Protection team, he moved to the US in Fall 2011 to start his Ph.D. program with Prof. Joseph Schmidt at University of Toledo, Ohio. During his Ph.D., he developed a new route to covalently attach calixarenes on solid supports and used this to develop new calixarene based stationary phases to study separation of lanthanides. During the summer of 2015 he worked as an intern at PeroxyChem in Houston, Texas. In May 2016 after successfully defending his Ph.D. thesis, he moved to Michigan and worked with Mitsui Chemicals as their Lead Process Development Scientist and was involved in improving reaction efficiency and lowering production costs in the manufacture of thermal coloformers. In July 2017, he joined Croda's Health Care business to lead their new product development team with current focus on developing new products for health care, investigating and improving purification technologies and overseeing successful transfer of products from lab to production.

A Brief Introduction to the ins and outs of Poloxamer Synthesis

Never in the field of human pharmacology was so much owed to so many poloxamers. (adapted quote by Sir Winston Churchill)

This session will give an overview of what exactly poloxamers are and what makes them so special in terms of their properties. Crucially, it will give a research/technical chemist's perspective on how they are developed, produced, and characterized. The delicate nature of poloxamers and which in- and post-process controls ensure high product quality will be discussed. Moreover, as poloxamers are indispensable for pharmaceuticals or biotherapeutics, quality attributes central to the highly regulated pharma industry will be highlighted.

It will be tied together nicely with the story 'from the lab into production' and will aim at providing a deeper understanding of these particular EO-PO-block copolymers and how to master their manufacture.

Benjamin Süeess, Kolb

Benjamin Süess is part of the synthesis and technology team at KLK Kolb, a manufacturer of non-ionic surfactants and esters, where he is responsible for the product development of alkoxylates. This includes ethoxylates and propoxylates of fatty alcohols, fatty acids, esters, oils and other specialties such as poloxamers. This also includes wet-chemical characterization of the products as well as development and implementation of new analytical methods for both in- and post-process control. He has a deep understanding of how different reaction conditions relate to changes in product quality.With a strong technical background, Ben supports and supervises industrial-scale test productions of new products at sites across Europe. His experience includes polysorbates and poloxamers with focus on synthesis, analytics and manufacture of pharmaceutical products for medicinal applications. He appreciates the high expectations pharmaceutical customers have regarding process deviations, batch-to-batch variations and their tentative approach to any production process changes. With his technical expertise and communication skills, Ben supports product management at customer meetings and trade fairs. Ben has a very high concern for standards and obtained his B.Sc. in Chemistry from the Zurich University of Applied Sciences in Switzerland. He has worked with non-ionic surfactants for more than three years.

Mechanisms of Stabilization of Proteins by Surfactants

This presentation will educate attendees on why surfactants are added to protein formulations. The content will focus on explaining the molecular mechanisms by which surfactants protect proteins and the analytical methods that can be employed to study the protective mechanisms.

Tarik Khan, Ph.D., Roche

Tarik Khan is a Senior Scientist in Late-Stage Pharmaceutical and Processing Development at F. Hoffmann-La Roche Ltd. In this role he is also a Pharmaceutical Project Leader working on formulation development and drug product process development, process design of biological and chemical entities for parenteral administration, quality-by-design, and technology transfer to commercial production. He received a doctorate in chemical engineering from The University of Texas at Austin, working in the fields of protein engineering and vaccines/biologics formulation. After his graduate studies, he received a Whitaker International Postdoctoral Scholarship to work at ETH Zurich developing more accurate experimental/bioinformatics methods for next-generation sequencing of antibody repertoires. He then became a postdoctoral fellow at Roche/Uni-Basel studying surfactant behavior in protein formulations and the mechanisms driving “low endotoxin recovery.” Dr. Khan is also very active within AAPS.

Mechanisms of Oxidative Degradation of Proteins by Surfactants

The chemical degradation of surfactants proceeds via various hydrolytic and oxidative pathways resulting in the generation of a large number of products. Many of these products are reactive towards proteins, degrading proteins via oxidation and/or addition, potentially leading to cross-links. Significant heterogeneity of protein degradation products originates from (i) the class of surfactant degradation products, (ii) the chain length and origin of these degradation products (depending on the type and heterogeneity of the surfactant), and (iii) the generation of stereoisomers. Calculations predict that the oxidative degradation of polysorbate 80 would generate reaction products, which could lead to > 100 different reaction products when reacted with a single lysine residue of a protein. Therefore, a combination of high-resolution separation and mass spectrometry techniques is required for the full characterization of protein modification as a result of surfactant degradation.

Christian Schöneich, University of Kansas

Christian Schöneich is the Takeru Higuchi Distinguished Professor for Bioanalytical Chemistry and Chair of the Department of Pharmaceutical Chemistry at The University of Kansas. Between 1987 and 1991 he worked in the Department of Radiation Chemistry at the Hahn-Meitner Institute in Berlin, Germany, and he received his Ph.D. in Chemistry in 1990 from the Technical University Berlin, Germany. He joined the Department of Pharmaceutical Chemistry at The University of Kansas as a post-doctoral fellow in 1991, and as a faculty member in 1992; in 2004, he was a Visiting Professor at the ETH Zürich, Switzerland. His research focuses on oxidation reactions of peptides and proteins in vivo and in vitro, and their potential consequences for the development of stable protein pharmaceuticals, biological aging and age-related pathologies. He has published >250 papers in the field of peptide and protein oxidation reactions.

Mechanisms of Hydrolytic Degradation of Surfactants - focus on enzymatic hydrolysis

Polysorbates can undergo chemical and enzymatic hydrolysis. Chemical hydrolysis is slow under normal formulation pH conditions. Over the last few years, reports have been published about the occurrence of enzymatic hydrolysis in protein drug product over time leading to the loss of polysorbate and increase in subvisible and visible particulate formation. The enzymes are host cell proteins (HCP) that are co-purified with the active protein. Loss of polysorbate should be investigated to determine the mechanism (oxidative and/or hydrolysis). If the presence of an enzymatic hydrolytic degradation is confirmed, significant resource and effort would then be required to address the root cause, or the result may be a significantly shorter shelf-life.

Vincent Corvari, Ph.D., Lilly

Vincent Corvari received a B.S. degree in Pharmacy from Philadelphia College of Pharmacy & Science and a Ph.D. degree in Industrial Pharmacy from the University of Maryland. He held various positions at Cephalon and Biogen before taking his present position at Eli Lilly & Company. Over the past 26 years, Dr. Corvari's area of technical expertise focused on drug product development of protein therapeutics spanning early phase candidate selection through late phase clinical development and commercialization.

Degradation of Surfactants and Impact on Product Quality - focus on impact on product quality

Surfactants are an important tool in the formulation of biopharmaceuticals. This session of the short course will cover what happens when surfactants degrade; in particular, we will review which attributes may impact the protein's stability. The session will be focused on polysorbates, which are currently the most used surfactants in biopharmaceutical Drug Products. At the end of the session, you will be able to articulate what impact oxidative degradation may have on your Drug Product, identify quality attributes that may be impacted by polysorbate degradation, and devise strategies to account for potential loss of surfactant on stability.

Barthélemy Demeule, Ph.D., Genentech

Barthélemy Demeule is a Sr. Scientist and Sr. Group Leader at Genentech, Inc. Dr. Demeule obtained his Ph.D. in Pharmaceutical Sciences at the University of Geneva, Switzerland, where he started his investigations on the physico-chemical stability of biopharmaceuticals. After a postdoctoral work at Genentech, Inc. focused on the effect of the in vivo environment on antibody-antigen interactions, he stayed in the company where he held positions of increasing responsibilities. After 10+ years of experience in the company he is currently a Sr. Group Leader overseeing a group of scientists responsible for the pharmaceutical development of monoclonal antibodies in the last phases of clinical development. He also serves on the editorial board of the European Journal of Pharmaceutics and Biopharmaceutics and was recently appointed to the USP's Expert Panel on Excipient Performance. In addition to a patent, Dr. Demeule has published numerous paper and book chapters on topics related to the formulation of biopharmaceuticals, surfactants and analytical ultracentrifugation; he also edited the book "Biobetters" in collaboration with Dr. Amy Rosenberg.

Behavior of Surfactant During Processing - UF/DF, filter adsorption

Surfactants are usually required excipients to ensure stability and manufacturability of proteins. However, surfactants also pose specific challenges during development, manufacture and control. The Surfactants' interaction with filter materials and their behavior of micellar formation are key considerations for processing, such as ultrafiltration/diafiltration (UF-DF) and filtration using sterilizing-grade filters. Surfactants are best avoided prior UF-DF steps, or, if unavoidable, their concentration must be carefully monitored and controlled. Sterilizing-grade filters need to be specifically evaluated for surfactant interaction (adsorption), and the choice of filter is usually the most critical element. Surfactant adsorption by filters also needs to be considered for product flush of filters.

Hanns-Christian Mahler, Lonza

Since September 2015, Dr. Mahler is leading the Drug Product services organization at Lonza AG, a leading service provider for the Pharma and Biotech industry. His highly skilled and experienced team was built in Basel during 2016, and provides formulation, manufacture and analytical services with current focus on parenteral dosage forms including for a variety of modalities such as biologics, drug conjugates, peptides and small molecules.

Prior this position, he led the department Pharmaceutical Development & Supplies, Biologics EU at Roche, Basel, Switzerland from 2010 to 2015 and as Head of Formulation R&D Biologics, Roche, Basel, from 2005 to 2010. From 2000-2005, Dr. Mahler worked at Merck KGaA, Darmstadt, Germany as Principal Formulation Scientist, Lab Manager for Protein Formulation Development and Clinical Trial Manufacturing and CMC Team leader.

Dr. Mahler studied Pharmacy at the University of Mainz, Germany, holds in Ph.D. in Toxicology from the Institute of Pharmacy, University of Mainz. Dr. Mahler obtained his venia legendi (german Habilitation) from the University Frankfurt/Germany in 2010 and is adjunct faculty at the universities of Frankfurt (Germany), and Basel (Switzerland). He was elected AAPS Fellow in November 2013, nominated extraordinary Professor in November 2015 and received the PDA Distinguished Service Award 2018.

Control of PS80 Degradation During Bioprocessing

Polysorbates are the most widely used non-ionic surfactants to prevent interface-induced protein adsorption, protein aggregation or particulate formation. Polysorbate 80 (PS80) is one of the most commonly used surfactants in therapeutic proteins formulations. PS80 degradation can occur through different mechanisms including autoxidation, hydrolysis of the fatty acid ester bond by lipase, and others. PS80 degradation may impact therapeutic protein quality and shelf life of the drug product. This presentation demonstrates several control strategies in bioprocessing to minimize PS80 degradation including (i) optimization of medium components in upstream cell culture processes, (ii) applications in downstream processing to remove impurities that can possibly cause PS80 degradation, (iii) mitigation of analytical challenges in PS80 degradation measurement during process development, and (iv) analytical characterization of the species causing PS80 degradation. This presentation highlights several case studies and provides a holistic overview of PS80 degradation control strategy in bioprocessing.

Jie Chen, Ph.D., Bristol-Myers Squibb

Jie Chen is a senior scientist and group leader in Biological Development organization in Bristol-Myers Squibb. Dr. Chen earned her Ph.D. in Chemical Engineering from Rensselaer Polytechnic Institute. After graduation, she joined Millipore working on chromatography resin development and Shire in downstream process development. She has great experience in process development and characterization.

Analytical Toolbox for Characterization and Control of Surfactants in Biopharmaceuticals

Surfactants – mainly polysorbate 20 and 80, and to a lesser extent poloxamer – are added as excipients to biopharmaceutical formulations in order to protect the contained therapeutic proteins from interfacial stress. As a critical excipient the surfactant in the formulation has to be controlled, i.e. analyzed, quantitatively. The analytical methods HPLC-FMA, HPLC-ELSD and HPLC-CAD are routinely used for this purpose. Because the surfactants contain structural elements that are prone to hydrolytic and oxidative degradation it is also necessary to apply qualitative analytical methods. HPLC-FMA, shallow gradient HPLC-ELSD and CAD, as well as HPLC-MS are such stability indicating methods.
The presentation will elaborate in detail on the mentioned control techniques as well as on others (free fatty acid analysis, particle analysis by spectroscopies and mass spectrometry, etc.) which can be used for root cause investigations in the case of surfactant degradation.

Michael Jahn, Ph.D., Lonza

Dr. Michael Jahn is leading the group Forensic Chemistry at Lonza's Drug Product Services in Basel, Switzerland, since 2016. During his previous 11 years in industry (Ciba Expert Services, Novartis) Michael was setting up and leading analytical laboratories specialized in trace analysis and structure elucidation. In his current position Michael and his group are supporting Lonza's customers from the (Bio) Pharmaceutical Industry in the focus areas excipient / surfactant analysis, extractables / leachables assessment, particle identification / spectroscopy / imaging, protein characterization by MS, and trace analysis / structure elucidation.

Surfactant Analytics in Biopharmaceutical Development – Case studies

The attendees will develop an understanding of how to investigate the root cause of polysorbate degradation using advanced analytical techniques to distinguish between the main degradation routes. They will also become familiar with approaches to assessing lipase activity to guide process improvements.

Zhihua Liu, Ph.D., Bristol-Myers, Squibb

Zhihua Liu is a Senior Research Investigator at Bristol Myers-Squibb within the Parenteral Science and Technology group. He leads scientific efforts to generate in-depth knowledge of biologic and small molecule parenteral drug products and processes through the development of innovative analytical strategies and methods. Dr. Liu is an expert in surfactant analysis with an emphasis on novel analytical methods for the determination of polysorbates and polysorbate degradants which he has used to further understand polysorbate degradation mechanisms. Before joining BMS, Dr. Zhihua Liu obtained his Ph.D. degree in organic chemistry from the University of Arizona and conducted his post-doctoral training in chemical biology at Princeton University.

Regulatory Perspective on Surfactant Monitoring and Control

Session description unavailable.

Ashutosh Rao, Ph.D., U.S. Food and Drug Administration

Biography unavailable.

Surfactant Control Strategy (1)

Session description unavailable.

Atanas Koulov, Ph.D., Lonza

Biography unavailable.

Surfactant Control Strategy (2)

Session description unavailable.

Robert Kopf, Roche

Robert Kopf works as a principal scientist at Pharma Technical Development Europe - Biotech Analytics (PTDE-A) in Basel, Switzerland for 13 years. Robert started his career in 1981 as an apprentice at Hoffmann- La Roche Grenzach, Germany. Later he studied analytical chemistry at the Fachhochschule Reutlingen, Germany. During his whole career he was involved in HPLC method development and validation for small and large molecules. His special interest is the development of multi-dimensional chromatography. He currently heads the GLP dose formulation analysis - and the excipient testing lab for large molecules.

Organizing Committee Biographies

Satish K. Singh, Ph.D., Lonza

Satish Singh is the Head of Drug Product Process Development, in the Drug Product Services group at Lonza AG., where he is responsible for drug process development and characterization capabilities for the newly established group. Prior to joining Lonza in September 2016, Satish was Research Fellow and Group Leader at Pfizer's BioTherapeutics Pharmaceutical R&D unit. Satish has more than 25 years of experience in the industry and has deep expertise in all aspects of (bio)pharmaceutical Drug Product development. His experience includes ophthalmics and parenterals, encompassing primarily biologics but also small molecules, and he has been involved in the submission of several BLAs and INDs. Satish has a strong technical background, complemented by an appreciation for regulatory challenges and the evolving regulatory landscape. He has more than 80 scientific publications and is involved in various professional groups within AAPS and USP where he is a member of the USP<788> Expert Panel. He obtained his B.Tech from the Indian Institute of Technology, New Delhi, and an M.S. and Ph.D. in Chemical Engineering from Kansas State University. He holds the position of Adjunct Professor at the Dept. of Physical Pharmaceutical Chemistry at Uppsala University, Sweden and was selected Fellow of AAPS in 2017.

Atanas Koulov, Ph.D., Lonza

Biography unavailable.