Welcome to the CMC Strategy Forum
The Impact of Excipients and HCPs on the Formation of Particles in Biologics

We are pleased to welcome you to the CMC Strategy Forum. The purpose of the CMC Strategy Forum is to provide a venue for biotechnology/biological product discussion. The meetings focus on relevant CMC issues throughout the lifecycle of a product and thereby foster collaborative technical and regulatory interactions. The Forum strives to share information with the regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the Forum meetings are published in an appropriate peer-reviewed journal.

Each meeting will focus on a CMC related issue such as product characterization, comparability, specifications, etc. The format of each meeting will consist of case studies and presentations by industry and/or regulatory experts to introduce the topic and the key issues of concern. Workshop sessions, which consist of panel discussions and Q&A, will then be conducted to allow for additional discussion on the technical and regulatory details of the topics. It is envisioned that the final outcome of the workshop discussions will be the development of a document to be submitted to the appropriate Regulatory Agency designees for their consideration in developing and/or clarifying good regulatory practice guidelines for biotechnology derived products.

The success of the CMC Strategy Forum will depend on your active participation in discussing and raising issues pertaining to development of biologics. We encourage you to participate wholeheartedly in the workshops that have been designed to stimulate exchange of ideas and information.

We would like to thank the speakers who are giving generously of their time and resources, and to you, for your attendance. We acknowledge the generosity of our program partners: *AbbVie Bioresearch Center, Inc.; Amgen Inc.; AstraZeneca; Biogen; Eli Lilly and Company; F. Hoffmann-La Roche Ltd.; Genentech, a Member of the Roche Group; Jazz Pharmaceuticals; Merck & Co., Inc.; National Institute of Standards and Technology (NIST); Novo Nordisk A/S; Pfizer, Inc.* and *Seqirus-A CSL Company.* We are grateful for the expert management from CASSS and the audio-visual expertise of Michael Johnstone from MJ Audio-Visual Productions. Their experience and guidance in the preparation of this Forum has been invaluable.

ACKNOWLEDGEMENTS

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The CMC Strategy Forum and WCBP 2020 Mobile App is coming in January 2020. Log on and be a part of the CMC/WCBP Community!

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Need Help?
Still not sure how to sign in and get the most out of the mobile app? Don't miss the Mobile App Training on Tuesday, January 28 at 10:15 in the Cabinet Room. You can also contact CASSS' Exhibitor and Technology Coordinator, Isolde Honoré (ihonore@casss.org) or stop by the registration office in the Senate Room.

Forum Abstract

The Impact of Excipients and HCPs on the Formation of Particles in Biologics

FORUM CO-CHAIRS:
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Excipients unquestionably play an essential role in the stabilization and formulation of biologics and vaccines. However, evolving evidence has indicated that degradation of excipient components can occur during storage. One outcome of excipient degradation is the possible formation of particles (visible and subvisible) in biologic formulations, which presents a concern from a product quality perspective. Through recent advances in analytical technologies, our capability to detect and measure low level or trace impurities has strengthened our capacity to observe and better understand excipient degradation. In particular many recent research papers and presentations have focused on the presence of certain HCPs and their impact on particle formation through degradation of polysorbates. With heightened awareness of these possibilities, companies are better prepared to address particle formation as part of the control strategy.

In this session, we intend to discuss various case studies describing mechanisms and/or pathways for particle formation resulting from excipient degradation. The analytical sciences used to interrogate and quantify particles, HCPs, and the chemical analysis of complex excipient components will be presented. Finally, expectations from regulators will be discussed as it pertains to the development and control strategies for biotherapeutics.

Some questions to be answered are as follows:

- What are some approaches and best practices on assessment and characterization of (visible and subvisible) particles?
- What are some examples and case studies for control around excipient surfactants from raw material, manufacturing controls, to final product release and stability testing?
- What are some degradation/formation mechanisms of particles that are derived from HCP or excipient sources?

CMC Strategy Forum Program Summary

The Impact of Excipients and HCPs on the Formation of Particles in Biologics

Monday, January 27, 2020

07:30 – 17:00 **Registration** in the Senate Room

07:30 – 08:30 **Breakfast** in the Palm Court Ballroom

08:30 – 08:45 **CASSS Welcome and Introductory Comments** in the District Ballroom
Mark Schenerman, *CMC Biotech-MAS Consulting*

CMC Strategy Forum Welcome and Introductory Comments in the District Ballroom
Taro Fujimori, *AbbVie Bioresearch Center, Inc.*

Analytics for Particle Detection in Biologics and Excipient Degradation Mechanisms
Workshop Session One in the District Ballroom
Session Chairs: Fiona Cornel, *Health Canada* and Vincent Corvari, *Eli Lilly and Company*

08:45 – 08:50 **Introduction**

08:50 – 09:15 **Visible Particles from Polysorbate Degradation – Cases & Perspectives**
Felix Nikels, *Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany*

09:15 – 09:40 **Multi-company Assessment of Submicron Particles in Biotech Products**
Mario Hubert, *Celgene Corporation, A Bristol-Myers Squibb Company, Summit, NJ USA*

09:40 – 10:05 **Mechanisms of Surfactant Degradation: Focus on Enzymatic Hydrolysis**
Lihua Huang, *Eli Lilly and Company, Indianapolis, IN USA*

10:05 – 10:30 **New Aspects on the Degradation Mechanisms of Polysorbate Complex Reaction Pathways of a Complex Surfactant**
Christian Schõneich, *University of Kansas, Lawrence, KS USA*

10:30 – 11:00 **Networking Break** in the District Ballroom

11:00 – 12:15 **PANEL DISCUSSION – Questions and Answers**
Lihua Huang, *Eli Lilly and Company, USA*
Mario Hubert, *Celgene Corporation, A Bristol-Myers Squibb Company, USA*
Atanas Koulov, *Lonza AG, Switzerland*
Michael Lewis, *Janssen Pharmaceutical R&D, LLC, USA*
Felix Nikels, *Boehringer Ingelheim Pharma GmbH & Co. KG, Germany*
Rachel Novak, *CDER, FDA, USA*
Christian Shõneich, *University of Kansas, USA*

Monday, January 28 continued…

12:15 – 13:45 **Networking Lunch** in the District Ballroom

Mitigation Strategies of Particle Formation and Regulatory Perspectives
Workshop Session Two in the District Ballroom
Session Chairs: Ewa Marszal, *CBER, FDA* and Jennifer Sexton, *Genentech, a Member of the Roche Group*

13:45 – 13:50 **Introduction**

13:50 – 14:15 **Excipients and Biotechnology Product Quality Attributes: A Regulator's Perspective on Reducing the Interfacial Tension**
Ashutosh Rao, *CDER, FDA, Silver Spring, MD USA*

14:15 – 14:40 **Mitigation Strategies to Polysorbate-derived Particles: A Holistic Approach**
Kishore Ravuri, *F. Hoffmann-La Roche Ltd., Basel, Switzerland*

14:40 – 15:05 **Polysorbate Degradation Case Studies: Characterization and Mechanism Elucidation, Consequences and Mitigation Measures**
Atanas Koulov, *Lonza AG, Basel, Switzerland*

15:05 – 15:30 **Control Strategies for Particles Arising from HCP-mediated Degradation of Polysorbate: A Regulatory Perspective**
Paula Russell, *Health Canada, Ottawa, ON Canada*

15:30 – 16:00 **Networking Break** in the District Ballroom

16:00 – 17:15 **PANEL DISCUSSION – Questions and Answers**
Atanas Koulov, *Lonza AG, Switzerland*
Linda Narhi, *USA*
Ashutosh Rao, *CDER, FDA, USA*
Kishore Ravuri, *F. Hoffmann-La Roche Ltd., Switzerland*
Paula Russell, *Health Canada, Canada*
Wendy Weinberg, *CDER, FDA, USA*

17:15 – 17:45 **Forum Recap**
Karen Rutherford, *Genentech, a Member of the Roche Group*
Ageliki Tzovolos, *Genentech, a Member of the Roche Group*

17:45 – 18:00 **Closing Remarks and Invitation to the CMC Strategy Forum July 2020 *"Phase Appropriate GMPs and CMC Considerations for Expedited Program Development"***
Jason Starkey, *Pfizer, Inc.*

18:00 **Adjournment**

18:00 – 19:15 **Networking Reception** in the Palm Court Ballroom / Promenade Foyer

Analytics for Particle Detection in Biologics and Excipient Degradation Mechanisms
Workshop Session One

Session Chairs: Fiona Cornel, *Health Canada* and Vincent Corvari, *Eli Lilly and Company*

Excipients are essential for the stabilization, manufacturability and physiological compatibility of injectable biologics. In recent years, reports have documented the potential for a key stabilizing excipient, polysorbate, to degrade in biologic formulations where the protein is expressed by mammalian cell culture. Additionally, an increased focus on analytical analysis of polysorbate has further exposed the degree of degradation by other mechanisms such as oxidation.

One consequence of polysorbate degradation is the formation of low solubility, free fatty acids which may precipitate and form particulate matter. This session aims to discuss 1) the approaches to particle analysis and control strategy based on industry perspectives and multi-company analysis of biotech products; and 2) the many mechanisms for polysorbate degradation with a focus on HCP mediated hydrolysis and complex reactions that may occur to degrade surfactants.

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Presenter's Abstracts

Visible Particles from Polysorbate Degradation – Cases & Perspectives

Felix Nikels

Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany

Polysorbate degradation is usually associated with the formation of particles in the subvisible size range. Here we show examples for visibe particles associated with polysorbate degradation and give insights to the underlying degradation mechanism.

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Multi-company Assessment of Submicron Particles in Biotech Products

Mario Hubert

Celgene Corporation, A Bristol-Myers Squibb Company, Summit, NJ USA

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Mechanisms of Surfactant Degradation: Focus on Enzymatic Hydrolysis

Lihua Huang

Eli Lilly and Company, Indianapolis, IN USA

Residual host cell proteins (HCPs) in biopharmaceuticals manufactured using cell-based expression systems can present potential safety risks to patients or compromise product stability. Recent publications have confirmed that polysorbate instability in protein formulation can be related to specific residual HCPs, such as lipases and/or esterases. Several Chinese hamster ovary (CHO) polysorbate hydrolysis enzymes that co-purified with the molecules of interest have been identified in recent years. Recombinant or commercially available sources of the identified enzymes have been evaluated for polysorbate hydrolysis in solutions or protein formulations. The results have demonstrated a direct impact on polysorbate stability even when the levels of the enzymes are as low as < 0.1 ppm, thus presenting a significant challenge to their detection, monitoring and removal. It has also been found that polysorbate is generally stable if none of the identified CHO enzymes is detected (< 0.05 ppm) in protein drug substance. Furthermore, polysorbate hydrolysis identified in several commercial mAb drug products were also possibly related to those identified enzymes.

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New Aspects on the Degradation Mechanisms of Polysorbate Complex Reaction Pathways of a Complex Surfactant

Christian Schõneich

University of Kansas, Lawrence, KS USA

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Analytics for Particle Detection in Biologics and Excipient Degradation Mechanisms
Workshop Session One

Panel Members:
Lihua Huang, *Eli Lilly and Company, USA*
Mario Hubert, *Celgene Corporation, A Bristol-Myers Squibb Company, USA*
Atanas Koulov, *Lonza AG, Switzerland*
Michael Lewis, *Janssen Pharmaceutical R&D, LLC, USA*
Felix Nikels, *Boehringer Ingelheim Pharma GmbH & Co. KG, Germany*
Rachel Novak, *CDER, FDA, USA*
Christian Shõneich, *University of Kansas, USA*

The following questions will guide the panel discussion:

1. Which subvisible particulate matter and visible particle analysis techniques are recommended for characterization and which are more suitable for quality control and why? During what stage of development should these analyses be applied?
2. During the development of a product, what are the key analytical elements for detecting and characterizing subvisible and visible particulate matter resulting from degradation of polysorbate? Should the analysis strategy include developmental stability studies?
3. What methods are/can be used for quantification of polysorbate and polysorbate degradation products? How can the degradation mechanism be discerned?
4. What are the mechanisms of protein aggregation during the hydrolytic and oxidative degradation of polysorbates?
5. Is there a propensity for formulations containing histidine to have increased potential for polysorbate oxidation?
6. Discuss experience with sources/excipients with higher potential for heavy metals that may contribute to polysorbate oxidation.
7. Are accelerated study method/condition(s) recommended to screen formulations for hydrolysis and oxidation potential of polysorbate?

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Mitigation Strategies of Particle Formation and Regulatory Perspectives
Workshop Session Two

Session Chairs: Ewa Marszal, *CBER, FDA* and Jennifer Sexton, *Genentech, a Member of the Roche Group*

Surfactant excipient components such as polysorbates are commonly used to facilitate the manufacture and stabilization of biologics. However, reported degradation of polysorbates may lead to the formation of non-proteinaceous and proteinaceous particulate matter in drug products that are visible and subvisible in nature. Mitigation of such a problem requires:

- Understanding of surfactant degradation, and surfactant/protein aggregation mechanisms
- Addressing related risks during product development and when changes to the process are planned post-approval
- Implementation of an appropriate in-process and drug product control strategy

This session will focus on the product and process design and control strategies planned to mitigate surfactant degradation. These strategies are designed to limit surfactant degradation, particle formation, and ensure that products containing surfactant excipient components remain safe and efficacious throughout their lifecycle.

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Presenter's Abstracts

Excipients and Biotechnology Product Quality Attributes: A Regulator's Perspective on Reducing the Interfacial Tension

Ashutosh Rao

CDER, FDA, Silver Spring, MD USA

Surfactants and other excipients are an integral component of many biotechnology drug products. Consequently, optimal formulation and control of excipients are key aspects of an overall control strategy by drug manufacturers aimed at consistent product quality, safety, and efficacy. Evolving evidence suggests that certain surfactants are susceptible to degradation and particulate formation in protein formulations; although, the root cause, biochemical drivers of degradation, and impact to the product and patient remain unresolved questions. The regulatory basis for expectations on the quality and analysis of excipients during drug development is primarily derived from 21 CFR 211.84(6)(d)(2), which states that "*Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.*" The overall control strategy and other information submitted by the drug developer is generally expected to address unreasonable and significant risk of illness or injury to human subjects as well as to provide sufficient information to allow regulators to assess potential risk to human subjects. This presentation will cover (1) the current scientific and regulatory rationale for using and controlling surfactants in protein formulations, (2) a pragmatic overview of the risk from surfactant degradation, (3) orthogonal strategies for controlling surfactant, host cell proteins, and related product quality attributes such as particulates in therapeutic proteins, (4) the types of studies that generally support the safe use of surfactants in protein formulations, and (5) the desired state of surfactant and related product quality attributes.

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Mitigation Strategies to Polysorbate-derived Particles: A Holistic Approach

Kishore Ravuri

F. Hoffmann-La Roche Ltd., Basel, Switzerland

Polysorbate degradation in biologics drug product leads to formation of insoluble free fatty acid particles in Drug Product. The root cause to this issue has been identified to be the presence of enzymatic host cell proteins which can co-purify along with the therapeutic protein. The current talk will discuss on aspects of assessing the risk of both degradation as well as FFA particles. It will further focus on mitigation strategies to these particles based on case studies at various stages of CMC development.

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Polysorbate Degradation Case Studies: Characterization and Mechanism Elucidation, Consequences and Mitigation Measures

Atanas Koulov

Lonza AG, Basel, Switzerland

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Control Strategies for Particles Arising from HCP-mediated Degradation of Polysorbate: A Regulatory Perspective

Paula Russell

Health Canada, Ottawa, ON Canada

Polysorbate is a common excipient included in the formulation of biotherapeutic proteins and is responsible for mitigating stress-induced protein aggregation that can occur during manufacture and storage. Degradation of polysorbate can be a product quality concern for biologics as it can result in particle formation. Degradation has increasingly been linked to some purification processes and the residual host cell proteins. This presentation will discuss the regulatory perspective regarding control strategies for particle formation resulting from degradation of polysorbate. The talk will include some case studies involving different approaches to mitigate the risk associated with particle formation.

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Mitigation Strategies of Particle Formation and Regulatory Perspectives
Workshop Session Two

Panel Members:
Atanas Koulov, *Lonza AG, Switzerland*
Linda Narhi, *USA*
Ashutosh Rao, *CDER, FDA, USA*
Kishore Ravuri, *F. Hoffmann-La Roche Ltd., Switzerland*
Paula Russell, *Health Canada, Canada*
Wendy Weinberg, *CDER, FDA, USA*

The following questions will guide the panel discussion:

1. What is the impact of polysorbate degradation on the product quality?
2. How well do we understand the impact of surfactant raw material quality and grade on degradation and particle formation? What raw material testing should be routinely performed for polysorbates?
3. What factors could be considered during development of the manufacturing process and how should the product and in-process intermediates be characterized to minimize the risk of surfactant degradation? How should in-process controls be designed?
4. How do we measure mitigation effectiveness? Are there models to predict particle formation under real time stability conditions?
5. What are the regulator expectations for mitigation – is complete remediation of particle formation required? Is there a regulatory path forward if non-proteinaceous visible particulate matter is present due to free fatty acid precipitation resulting from polysorbate degradation?
6. What drug product protein and surfactant attributes should be tested to control particles? Should the specifications depend on the observed stability (or instability) of a surfactant? How should the acceptance criteria be set? What additional supportive information would be helpful in setting acceptance criteria?
7. How should an investigation be performed if a product containing surfactant unexpectedly develops particles on stability?

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