Welcome to the CMC Strategy Forum
Continuous Manufacturing for 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., Biogen, Celgene Corporation, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Genentech, a Member of the Roche Group, Jazz Pharmaceuticals; MedImmune, A member of the AstraZeneca Group, Merck & Co., Inc., National Institute of Standards and Technology (NIST), Novo Nordisk A/S* and *Pfizer, Inc.* 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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Does the printed program look a little bit thinner this year? This year, we are pleased to once again offer the CASSS Mobile App for the CMC Strategy Forum January and WCBP 2019!

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- Connect and network with fellow attendees, speakers, and exhibitors
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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 Mochas and Mobile Apps: Mobile App Training on Tuesday, January 29 at 10:15 in the Cabinet Room. You can also contact Anna Lingel, CMP, Exhibitor Relations and Technology Specialist by email: alingel@casss.org or stop by the registration office in the Senate Room.

Forum Abstract

Continuous Manufacturing for Biologics

FORUM CO-CHAIRS:
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Manon Dubé, *Health Canada*
Rick Lu, *AstraZeneca*

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Continuous manufacturing has the potential to improve agility, flexibility, and robustness in manufacture of pharmaceuticals. ICH has recently decided to form an expert working group to generate a technical and scientific guideline on continuous manufacturing for global implementation. This emerging technology, however, has not been reflected in a wide adoption for manufacture of biologics, especially for the downstream manufacturing processes. This CMC Strategy Forum provides for a timely opportunity to discuss the opportunities, gaps/limitations and regulatory landscape across academics, technology innovators, biopharmaceutical companies and the regulators. The outcome of this CMC Strategy Forum will help establish expectations to facilitate implementation and improvement of continuous manufacturing for biologics.

Questions to be addressed:

- What are the business opportunities for introducing continuous manufacturing for biologics?
- What are current gaps and hurdles for implementing continuous manufacturing for biologics?
- What levels of automation in biopharmaceuticals is needed for continuous manufacturing?
- What novel analytical technologies are needed for continuous manufacturing?
- What can we leverage from our knowledge of small molecule continuous manufacturing to enable or accelerate continuous manufacturing for biologics?

CMC Strategy Forum Program Summary

Continuous Manufacturing for Biologics

Monday, January 28, 2019

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

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

08:45 – 09:00 **CASSS Welcome and Introductory Comments** in the District Ballroom
Joseph Kutza, *MedImmune, A member of the AstraZeneca Group*

CMC Strategy Forum Welcome and Introductory Comments in the District Ballroom
Andrew Chang, *Novo Nordisk Inc.*
Rick Lu, *AstraZeneca*

Workshop Session One in the District Ballroom
Session Chairs: Lindsay Arnold, *MedImmune, A member of the AstraZeneca Group* and Min Zhu, *Boehringer Ingelheim Pharmaceuticals*

Industry Perspective

09:00 – 09:25 **Industry Experiences with Small Molecule Continuous Manufacturing**
Thomas Garcia, *Pfizer, Inc., North Stonington, CT USA*

09:25 – 09:50 **Continuous Biomanufacturing: Relevant Experiences with Development, Hybrid Implementation and Emerging Opportunities**
Erik Fouts, *BioMarin Pharmaceutical Inc., Novato, CA USA*

Analytical Technologies

09:50 – 10:15 **Control of Continuous Bioprocesses: Integration of Process Analytical Technologies with Residence Time Distribution Modeling to Ensure Consistent Product Quality**
Mark Brower, *Merck & Co., Inc., Kenilworth, NJ USA*

10:15 – 10:45 **Networking Break** in the District Ballroom

10:45 – 12:00 **PANEL DISCUSSION – Questions and Answers**
Mark Brower, *Merck & Co., Inc., USA*
Manon Dubé, *Health Canada, Canada*
Erik Fouts, *BioMarin Pharmaceutical Inc., USA*
Thomas Garcia, *Pfizer, Inc., USA*
Ingrid Markovic, *Genentech, a Member of the Roche Group, USA*
Eike Zimmermann, *Boehringer Ingelheim Biopharmaceuticals, USA*

Monday, January 28 continued…

12:00 – 13:30 **Networking Lunch** in the District Ballroom

Workshop Session Two in the District Ballroom
Session Chairs: Manon Dubé, *Health Canada* and Arne Staby, *Novo Nordisk A/S*

Automation Approaches and Gaps

13:30 – 13:55 **BioPhorum Technology Roadmap (TRM Phorum): Continuous Downstream Processing for Biopharmaceuticals**
Carl Carlson, *Exyte, Boston, MA USA*

13:55 – 14:20 **Integrated Continuous Biomanufacturing Platform - Addressing Challenges in Automation Approaches and Gaps**
Marina Hincapie, *Sanofi, Framingham, MA USA*

Equipment and Facilities

14:20 – 14:45 **Advances in Next Generation Drug Substance Manufacturing of Biologics**
Ganesh Vedantham, *Amgen Limited, Juncos, Puerto Rico*

Business Case Studies

14:45 – 15:10 **iSKID: A Next-Generation Continuous Manufacturing Platform for Biologics**
Nuno Fontes, *Boehringer Ingelheim Pharmaceuticals, Fremont, CA USA*

15:15 – 15:45 **Networking Break** in the District Ballroom

15:45 – 17:00 **PANEL DISCUSSION – Questions and Answers**
Nuno Fontes, *Boehringer Ingelheim Biopharmaceuticals, USA*
Steffen Gross, *Paul-Ehrlich-Institut, Germany*
Stephen Hadley, *The Bill and Melinda Gates Foundation, USA*
Marina Hincapie, *Sanofi, USA*
Ganesh Vedantham, *Amgen Limited, Puerto Rico*
T.G. Venkateshwaran, *Merck & Co., Inc., USA*

17:00 – 17:30 **Recap of Program**
Summary Slide Presentation
Carmilia Jiménez Ramirez, *Ajinomoto Bio-Pharma Services*

17:30 – 17:45 **Closing Remarks and Invitation to the CMC Strategy Forum July 2019 "Practical Aspects of ICH Q12 Implementation"**
Andrew Chang, *Novo Nordisk Inc.*
Rick Lu, *AstraZeneca*

17:45 **Adjournment**

17:45 – 19:00 **Networking Reception** in the Chinese Room / Palm Court Ballroom

Industry Perspective and Analytical Technologies
Workshop Session One

Session Chairs: Lindsay Arnold, *MedImmune, A member of the AstraZeneca Group* and Min Zhu, *Boehringer Ingelheim Biopharmaceuticals*

The morning panel allows a valuable opportunity to engage in a discussion with regulators and industry experts on key outstanding issues, whether real or perceived, that will ultimately aid in successful implementation of continuous processing. While case studies often support the adoption of continuous manufacturing, early adopters and regulators will inevitably face the difficulty of defining universal guidances. Additionally, while recent technology innovations in PAT may give more insight into process performance, this will necessitate more complex and reactive process control. Combined with the experience of the small-molecule industry, this panel discussion looks to answer questions and alleviate fears associated with continuous bioprocessing adoption.

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Presenter's Abstracts

Industry Experiences with Small Molecule Continuous Manufacturing

Thomas Garcia

Pfizer, Inc., North Stonington, CT USA

The presentation will provide an overview for the application of continuous manufacturing to small molecules. It will include accomplishments and challenges that industry has encountered. Similarities and differences between small molecule and biologic continuous manufacturing will be presented.

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Continuous Biomanufacturing: Relevant Experiences with Development, Hybrid Implementation and Emerging Opportunities

Erik Fouts

BioMarin Pharmaceutical Inc., Novato, CA USA

The benefits of continuous manufacturing (CM) have been demonstrated for decades in industries as diverse as food, electronics, and petrochemical manufacturing. CM has the similar potential to improve agility, flexibility, robustness, quality, and reduce cost in the manufacture of pharmaceuticals. These benefits have driven many pharmaceutical manufactures to adopt CM processes for synthetic molecule products. However, the adoption of CM in the biomanufacturing space has been limited and exists primarily is in the form of a hybrid CM/batch process format. Moreover, the implementation of CM technologies has been predominantly associated with upstream processes. Today, small and pilot scale CM systems are offered by several equipment manufacturers. These tools enable the development of integrated continuous upstream and downstream processes. However, significant challenges do remain for complex biologics manufacturing, such as on-line or at-line analytical capability that allows for real time assessment of critical quality attributes spanning the operation and supporting real-time release. Another challenge is the limited understanding of the key scientific and regulatory concepts of emerging CM technology. Key to resolving this issue is a working partnership between the regulatory authorities and industry committed to creating a clear path for CM implementation. The ICH has recently formed an expert working group (EWG) to develop a technical and scientific guideline on CM for pharmaceuticals. The intent of the new ICH guidance (Q13), will be to describe key scientific and regulatory considerations, provide general guidance to regulatory agencies and industry for developing and assessing CM technologies, and promote the adoption of flexible approaches for CM implementation for a variety of modalities. Progress made by the EWG on ICH Q13 will be discussed along with examples CM implementation and development for complex biologics manufacturing to illustrate the current state, success factors, challenges, and future directions.

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Control of Continuous Bioprocesses: Integration of Process Analytical Technologies with Residence Time Distribution Modeling to Ensure Consistent Product Quality

Mark Brower

Merck & Co., Inc., Kenilworth, NJ USA

In response to increased demands placed on biopharmaceutical producers to diversify portfolios and to reduce costs, bioprocesses are being intensified to allow for significant protein production in ≤2,000L single-use bioreactors. Many biopharmaceutical producers are maturing continuous bioprocessing platforms to meet these demands. At the same time specialty hardware, which was once thought to be novel and high-risk for failure, is now being proven as robust at-scale for longer production times. Some have proposed that the next step in this evolution will be fully integrated continuous bioprocessing where further efficiencies may be achieved with sophisticated automation strategies and adaptive process control to ensure consistent protein quality and patient access. To support such a vision, development efforts have been initiated in the fields of: continuous bioprocessing, process analytical technology (PAT), information technology (IT), multivariate data analysis (MVDA), residence time distribution modeling (RTD) and efforts towards real time release testing (RTRT).

This presentation will introduce PAT and Advanced Analytics approaches being developed for integration into the continuous biologics production platform at Merck. These tools can be utilized to detect process upsets in near real time and enable feedback and feed forward control algorithms in the process. In addition, RTD modeling to characterize the material flow throughout the system will also be presented. In the context of continuous bioprocessing, each unit operation will be characterized by an individual RTD which when stitched together in the overall process sequence, can be used to trace material throughout the process. These methodologies coupled with advanced data analytics will ultimately lead to dynamic product attribute control (PAC) strategies that reliably deliver protein with consistent quality enabling RTRT for biotherapeutics.

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Industry Perspective and Analytical Technologies
Workshop Session One

Panel Members:
Mark Brower, *Merck & Co., Inc., USA*
Manon Dubé, *Health Canada, Canada*
Erik Fouts, *BioMarin Pharmaceutical Inc., USA*
Thomas Garcia, *Pfizer, Inc., USA*
Rick Lu, *AstraZeneca, USA*
Eike Zimmermann, *Boehringer Ingelheim Biopharmaceuticals, USA*

The following questions will guide the panel discussion:

1. What lessons are transferable from the small molecule experience? What are hurdles unique to bioprocessing? What are benefits (unique or shared) realized by small molecule?
2. While the FDA may be receptive, acceptance of continuous manufacturing must apply at a global scale. Are there discrepancies across different regulatory agencies?
3. Increased PAT will lead to enhanced process understanding through multivariate analysis and models. Will these enhanced control strategies be required as part of a submission? Per ICH Q13, what changes will these control strategies bring to manufacturing?
4. For small molecule continuous processing, has the switch to continuous required changes in staff/workforce, both in terms of experience, capabilities, and time on the floor?
5. Which is easier: switch of a legacy project from batch manufacturing to continuous manufacturing, or complete development into a continuous manufacturing process? What additional regulatory steps would either submission require?
6. Is there a critical quality attribute measurable by PAT that would give continuous processing an edge over batch processing, from a regulatory standpoint? Is there more confidence in product quality, and is that enough of a driver to facilitate change?

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Automation Approaches and Gaps; Equipment and Facilities; and Business Case Studies
Workshop Session Two

Session Chairs: Manon Dubé, *Health Canada* and Arne Staby, *Novo Nordisk, A/S*

The afternoon panel discussion between regulators and industry representatives will focus on the more practical aspects of implementation of continuous processing, where it comes down to equipment, unit operations, and facility selection and control, and the associated automation required to make it all happen. While continuous unit operations have existed and been used for decades within the biopharmaceutical industry, the integrated solutions exploiting the full potential of continuous processing are not properly developed yet due to non-continuous nature of key unit operations, like chromatographic purification, and insufficient analytical techniques. This panel discussion will address the readiness of continuous processing with respect to facilities and automation from a regulatory as well as an industry perspective.

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BioPhorum Technology Roadmap (TRM Phorum): Continuous Downstream Processing for Biopharmaceuticals

Carl Carlson

Exyte, Boston, MA USA

BioPhorum, formally BPOG, has undertaken Technology Roadmapping (TRM) for the Biopharmaceutical Industry. TRM is a collaboration of biomanufacturers, academia, technology suppliers, architectural/engineering leaders and subject matter experts. From this collaboration, several enabling technologies and capabilities have been identified, such as Process Technology and Fully Automated Facilities, and In Line Monitoring/Real-Time Release. The Enabling Technologies have been further broken down into implementation projects like: Buffer Preparation, Continuous Downstream Processing, Harvest Clarification for Process Technology, Big Data to Smart Data, Robotic Technologies, and Plug and Play for Fully Automated Facility. This session will review the deliverables and current GAPs with potential solutions identified for Continuous Downstream Processing Project specifically and will investigate the value of Continuous Downstream Processing as discussed in the forthcoming Project White Paper (due end 1st Q 2019 on BioPhorum website). In addition, ties to other connected Implementation Projects will be identified as necessary connections to the Downstream Continuous Processing Implementation Project.

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Integrated Continuous Biomanufacturing Platform - Addressing Challenges in Automation Approaches and Gaps

Aleksandar Cvetkovic, Shawn Barrett, Marcus Fiadeiro, Lin Huang, Jagdish Tewari, Dhanuka Wasalathanthri, Marina Hincapie

Sanofi, Framingham, MA USA

Integrated Continuous Biomanufacturing (ICB) provides significant benefits and strategic advantages for therapeutic protein production through process intensification, simplification and automated integration. Reduction in capital, operating expenses and improvements in product quality and consistency will come from reduced human/operator workload and fewer quality-control demands. The benefits and advantages, when combined should lead to greater efficiency, improvements, increased productivity and process economics. Dramatic reductions in cost of goods manufactured and improvement of productivity can be achieved as demonstrated by integrating intensified perfusion culture with multi-column capture. It is increasingly important to define right level of automation and control required for ICB process. For the most of the reported continuous process developments, automated control stops at ensuring synchronized liquid flow rates through all integrated unit operations. Reduction in need for human/operator and quality-control intervention remains a gap in development of continuous bioprocesses despite recent progress made in real time process analytic technology (PAT). Therefore, we are developing reliable model-scale setups with integrated unit operations, PAT, data collection & monitoring where process development and trouble-shooting can be performed concurrently with testing and implementation of automation control strategies. Potential automation approaches and gaps for continuous biomanufacturing processes will be discussed.

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Advances in Next Generation Drug Substance Manufacturing of Biologics

James Weidner; Art Hewig; Ganesh Vedantham

Amgen Limited, Juncos, Puerto Rico

We are in the midst of amazing innovations in biology, which is fueling development of new modalities to help address unmet medical needs. Our manufacturing paradigm needs to effectively accommodate this diversity in clinical pipeline. As a result, we are developing new tools that will allow for greater efficiencies ranging from efficient control of product attributes to advanced manufacturing operations to meet the need for speed to clinic/market, quality, and for easier global expansion/access. The talk will highlight lessons learned from our first to our second implementation of advanced commercial manufacturing operations. This presentation will also highlight some of the technologies that Amgen - and the industry, in general – are developing in the areas drug substance manufacturing operations.

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iSKID: A Next-Generation Continuous Manufacturing Platform for Biologics

Nuno Fontes

Boehringer Ingelheim Pharmaceuticals, Fremont, CA USA

Continuous manufacturing combined with single-use technology present an attractive opportunity for improving the flexibility, cost, and speed-to-market for biotherapeutics. Boehringer-Ingelheim has been actively developing a next-generation continuous manufacturing platform based on a highly intensified dynamic perfusion-based cell culture system integrated with a hybrid downstream process based on a combination of conventional high-throughput batch and novel continuous unit operations. Here we discuss our strategic vision, along with the challenges and opportunities associated to how the biologics development and manufacturing industry will evolve towards a progressive adoption and implementation of continuous manufacturing.

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Automation Approaches and Gaps; Equipment and Facilities; and Business Case Studies
Workshop Session Two

Panel Members:
Nuno Fontes, *Boehringer Ingelheim Biopharmaceuticals, USA*
Steffen Gross, *Paul-Ehrlich-Institut, Germany*
Stephen Hadley, *The Bill and Melinda Gates Foundation, USA*
Marina Hincapie, *Sanofi, USA*
Ganesh Vedantham, *Amgen Limited, Puerto Rico*
T.G. Venkateshwaran, *Merck & Co., Inc., USA*

The following questions will guide the panel discussion:

1. Would regulatory requirements for documentation of continuous processes and facilities exceed those of batch processes?
2. What is the level of documentation required for substitution of release/specification analyses with in-process analyses?
3. Continuous processing has been used at the unit operation level for decades for many types of biopharmaceutical proteins, e.g. therapeutic enzymes – why is the difficulty in implementation and need for regulation suddenly a huge discussion topic?
4. What lessons are transferable from the other industries, like the dairy/beer/industrial enzymes industry where continuous processing is implemented throughout?
5. Is the industry really ready to change to continuous processing? – are the equipment, facility and automation solutions sufficiently developed? – opinions from industry regulatory authorities are sought including potential differences between US, Europe and RoW.

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