Tuesday - Wednesday, May 17-18, 2022

VIRTUAL EVENT PQRI Workshop:

Managing Excipient and API Impact on Continuous Manufacturing

Day 1 – Tuesday, May 17, 2022 8:00 AM – 5:00 PM US ET	
7:45 – 8:00 AM	***Pre-Workshop Check Connections***
8:00 - 8:15 AM ET	***Welcome and Introductory Remarks*** David Schoneker - IPEC-Americas, Black Diamond Regulatory Consulting, Chair - PQRI Workshop Organizing Committee
Introduction of Continuous Manufacturing and Excipient/API Impact	
8:15 – 8:45 AM	***Update on Status of ICH Q13*** Sau (Larry) Lee, Ph.D., US Food and Drug Administration FDA is working with other regulatory agencies and industry to develop the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q13 guideline on continuous manufacturing of drug substances and drug products. This ICH Q13 guideline describes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing (CM). Building on existing ICH Quality guidelines, this guideline provides clarification on CM concepts and describes scientific approaches and regulatory considerations specific to CM of drug substances and drug products. This presentation will provide the latest update on the ICH Q13 development.
8:45 – 9:15 AM	***Considerations in Designing Continuous Manufacturing Processes for Biologic Drug Substance*** Venkatesh Natarajan, Ph.D., Amgen In recent years, Continuous Manufacturing (CM) has gained significant traction in the manufacture of biologic DS. This presentation will focus on considerations in designing CM processes to meet business goals.
9:15 – 9:45 AM	***Beyond ICH Q13: Applicability & Use of other ICH and IPEC Guides in Understanding Excipient Impact on CM Processes*** Joseph Zeleznik, M.A., IMCD US, Pharma While ICH Q13 will apply directly to drug active and drug product manufactured via continuous processes, other ICH Guidelines, such as ICH Q8 and Q9 will have applicability as well. Additionally, other organizations are discussing what impact excipients may have on continuous manufacture (CM) and what controls or understanding are needed to ensure success in the development and manufacture of pharmaceutical products through continuous processes. One example is IPEC-Americas and how the IPEC Guides may assist in understanding the role of excipients in CM. During this session, the various ICH and IPEC Guides will be discussed as they relate to CM and how excipients fit into the paradigm.

9:45 – 10:00 AM	**BREAK**
Regulator and Industry Input on API and Excipient Impact on CM Drugs – Risks and Mitigation?	
10:00 – 10:30 AM	***Quality Considerations in Managing Excipient and API Risks to CM: Regulatory Perspective*** Yong Hu, Ph.D., US Food and Drug Administration The presentation will discuss the impact of physical properties of excipients and APIs on continuous manufacturing process and product quality based on the Agency's experience. Considerations in managing the risk will be addressed from the viewpoints of product development, control strategies, process validation and quality systems.
10:30 – 11:00 AM	***Leveraging Raw Material and Drug Product Risk Assessments to Guide Development of Continuous Manufacturing Processes*** Wyatt J. Roth, Ph.D., Eli Lilly and Company Raw material variability is often perceived as having the potential to impact unit operation performance and residence time distributions for continuous manufacturing (CM) processes. This presentation will use case studies from a continuous direct compression process to explore which process attributes are most affected by raw material variability. The learnings from these case studies can then be used to develop raw material and drug product risk assessments that guide the development workplans for future assets that use the same CM platform.
11:00 AM – 12:00 PM	***Panel Discussion and Q&A*** Moderator: David Schoneker Panelists: Yong Hu, Wyatt Roth, Larry Lee and Christine Moore, Ph.D., (Organon)
12:00 – 12:30 PM	**LUNCH BREAK**
Impact of Material Properties and Variability on Continuous Manufacturing	
12:30 – 1:00 PM	***Understanding the Difference Between a Marginal and Robust Process – The Impact of Excipient Variability*** Bart Nitert, Ph.D., Janssen R&D A difference between batch and continuous manufacturing is the way active ingredients and excipients are added to the processing steps. While in batch all required lots are often added at once during critical process steps, thereby filtering out lot-to-lot variability, in a continuous manufacturing process, material lots are processed in a serial manner. In this presentation we will focus on how CM process design contributes to increasing process understanding and robustness towards lot-to-lot variability.

1:00 – 1:30 PM	***Understanding Raw Material Variability Impact on Continuous Manufacturing*** Stephen L. Conway, Ph.D., Merck & Co., Inc. Stephen Conway, David Goldfarb, Merck & Co., Inc, Rahway, NJ, USA. Determining the robustness of a drug product formulation and manufacturing process to variations in raw material (API and excipients) properties is an essential aspect of development of any pharmaceutical product, including those produced via continuous manufacturing (CM). At Merck, we have successfully implemented a fully integrated CM line for direct compression and coating of a pharmaceutical oral solid dosage form in a commercial environment. A qualified control strategy has enabled lot manufacture meeting all critical quality attributes. We describe implementation of a lean CM process with a risk-based control scheme appropriate for a commercial production environment and operating in parallel with the historical batch process. We demonstrate CM robustness to raw material variability. In addition – and due to inevitable evolutions in raw material sources, attributes and process improvements conducted by suppliers – we consider strategies that continue to demonstration of drug product robustness throughout the product lifecycle. While historical approaches such as QbD-driven experiments based on limited production quantities can be useful for initial CM process evaluation, they may struggle to evolve once marketing approvals have been received and commercial manufacturing commences. The realities of modern commercial manufacturing – in which rapidly changing raw materials vendors, higher volume commercial operations, and excipient manufacturing practices – can render the relatively small data sets from development studies less relevant as the much higher quantity of real-world variability encountered in the commercial lifecycle starts to dominate. We share experiences and case studies to show how a harmonized, end-to-end approach for characterizing CM raw material variability can help provide context for early, limited development experiences as production data end experience grows.
1:30 – 2:00 PM	***Leveraging Residence Time Distributions (RTDs) to Understand Ingredient and Process Impacts in Continuous Manufacturing*** Scott M. Krull, Ph.D., US Food and Drug Administration Scott M. Krull, Naresh Pavurala, Thomas F. O'Connor Office of Testing and Research, U.S. Food and Drug Administration, Silver Spring, MD Continuous manufacturing (CM) is an emerging technology in the pharmaceutical industry with potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing. Residence time distributions (RTDs) can be used to trace the flow and dispersion of material through a CM process. Development of traceability algorithms for RTDs enables prediction of how disturbances will propagate through a process, allowing for isolation/diversion of out-of-specification material. Given that RTD models used for feed-forward process control are considered medium-impact, properly accounting for the effects of material properties and process parameters in such models is critical to ensure product quality in CM processes.

2:00 – 2:30 PM	***Impact of Powder Properties on PAT Measurements in Continuous Direct Compression*** Pedro Durão, Ph.D., Hovione Properties of raw materials impact the dynamic of continuous processes by modifying particle's interaction and overall process behavior. Therefore, the dynamic characteristics of continuous process affect not only the process itself but can also have a significant impact during PAT reading, whose prediction is critical in the implementation of an adequate control strategy. Assessing the importance of blend properties in both aspects is critical to ensure the state of control and enhance yield.
2:30 – 3:00 PM	***Excipient Categorization and Risk Mitigation in Continuous Manufacturing*** Brian Carlin, Ph.D., Carlin Pharma Consulting, LLC CM provides greater insight into the impact of excipient variability facilitating Quality by Control. Model fidelity can be degraded by Special Cause Variation (SCV) so the technique of Kano Analysis has been adapted to provide a more meaningful way of categorising the excipients in a formulation, to mitigate risk of product failure. CM eliminates the confounding effect of scale-up, affords better correlation of process response and excipient variability which, together with PAT data, Multivariate analysis, and CPV may give warning of system drift in advance of SCV-related failure.
3:00 – 3:30 PM	***Multivariate Analysis: A Technique to Evaluate the Risk and Impact of Raw Material Variability*** Pauline Janssen, MSc, DFE Pharma All raw materials have some inevitable degree of variation, and it is important to understand the impact of this variation on the final product quality. Multi variate analysis (MVA) is a statistical tool that can be used to provide insights in the variability of a material, and it can be used to evaluate how batches that are used in development relate to the total expected variability.
3:30 – 4:00 PM	**BREAK**
4:00 – 5:00 PM	***Breakout Session 1 – What are the Challenges You've Experienced Related to Material Impact on CM Processes?*** *There will be two or three concurrent breakouts utilized to discuss the topic to facilitate small group discussion* Moderators: Joseph Zeleznik, Brian Carlin, Shailesh Singh Notetakers: Yong Hu, Elizabeth Tocce, Janeen Skutnik-Wilkinson
5:00 PM	***Day 1 Closing Remarks*** *- In breakout sessions*

VIRTUAL EVENT

PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing

Day 2 – Wednesday, May 18, 2022 8:45 AM – 5:00 PM US ET	
8:30 – 8:45 AM US ET	***Pre-Workshop Check Connections***
8:45 – 9:15 AM	***Welcome to Day 2 and Review of Day 1 Breakouts*** David Schoneker IPEC-Americas, Black Diamond Regulatory Consulting, Chair - PQRI Workshop Organizing Committee
Risk Mitigation in Continuous Manufacturing	
9:15 – 9:45 AM	***Pre-processing API Materials to Enable Continuous Manufacturing*** Fernando J. Muzzio, Ph.D., Rutgers University
9:45 – 10:15 AM	***A CDMO Perspective on Continuous Solid Dose Manufacturing Process Development*** Douglas B. Hausner, Ph.D., Thermofisher Scientific Continuous manufacturing provides many benefits including the ability to produce large batches by running the manufacturing train for extended periods of time. This can lead to lower pricing when compared to batch but additional considerations around material handling over extended periods of time must be considered. This applies to both the active ingredients as well as the excipients. This presentation will show the approaches being taken by Thermo Fisher Scientific for continuous manufacturing of tablets and capsules as well as how materials are continuous brought into the manufacturing suite to allow for uninterrupted manufacturing of the dosage form.
10:15 – 10:30 AM	**BREAK**
10:30 – 11:00 AM	***Impact of Process Selection on Potential for Failure – How to Reduce the Potential for Failure Due to Special-Cause Variation*** R. Christian Moreton, Ph.D., FinnBrit Consulting This presentation will be focused on special cause variation and the perils of oversimplification. Ways in which the robustness of formulations and processes used in continuous manufacturing can be improved will be discussed.

Material Property Impact on CM Processes and Equipment	
11:00 – 11:30 AM	***Characterization of Powder Properties Important to Pharmaceutical Continuous Manufacturing of Tablets*** Changquan Calvin Sun, Ph.D., University of Minnesota The tablet is the most common commercial dosage form for oral drug delivery. The powder properties of a powder blend suitable for a successful continuous manufacturing (CM) of tablets must meet certain quality standards, which can be characterized using methods described in the USP. This talk covers relevant USP methods and their applications in CM of pharmaceutical tablets using a direction compression process.
11:30 AM – 12:00 PM	***Role of Excipients in Development of Continuous Dry and Wet Granulation Processes for Tablets by Applying Twin-Screw Melt Extruders*** Abu T. Serajuddin, Ph.D., St. John's University In this presentation the application of twin-screw dry and wet granulation processes to enable continuous manufacturing of tablets will be discussed. In conventional dry granulation, several unit operations, such as mixing/blending, roller compaction, milling, sieving, etc., are used that make the process non-continuous. Most of these steps can be combined into one continuous process in twin-screw dry granulation, where mixtures of drug substances and binder are extruded at high temperatures above glass transition temperatures (Tg) of binders used but below melting points of drug substances such that the granulation can occur due to the agglomeration of powders with the softened or molten binders by the force applied by the extruder. The twin-screw wet granulation is essentially like the twin-screw dry granulation, except that an additional step of adding water is incorporated. The successful implementation of continuous granulation processes using twin-screw melt extruders will usher a new era in continuous manufacturing of tablets.
12:00 – 12:30 PM	***Evaluation of High Productivity Coating Formulation in Continuous Coating Processes*** Charlie Cunningham, Colorcon Inc. This presentation will highlight the performance of a new high productivity film coating system in continuous, semi-continuous and continuous-cycled tablet film coating processes. The effect of process conditions on coated tablet color uniformity and appearance will be discussed. Coated tablet throughput rates will also be compared between the different coating machine technologies.
12:30 - 1:00 PM	**LUNCH BREAK**

Information from Other Industries	
1:00 – 1:30 PM	***Learnings from Modeling of Continuous Manufacturing of Excipients*** Kevin Thurow, IFF Pharma Solutions Digitally enabled manufacturing is the future for both excipient and pharmaceutical products. Process modeling is an important part of the digital transformation. Modeling, especially of continuous processes, may aid in providing consistent quality of product, costs savings and improved throughput. Not all models are equal, and it is important to understand the benefits and limitations of the models beforehand and as they are being used. This talk will highlight practical considerations for approaching and implementing models, and the learnings from examples in excipient manufacturing that could be leveraged in the pharmaceutical industry.
The Need for Novel Materials and Processes	
1:30 – 2:00 PM	***The Need for Novel, Co-processed or Modified Excipients Designed for Purpose in CM Processes*** Krizia M. Karry, Ph.D., BASF A survey was recently completed to understand what CM formulators and process engineers look for in terms of material properties. Their answers were varied, and unsurprisingly no current excipient fulfilled all requirements. Considering the *wants* and *can*, multifunctional coprocessed excipients were investigated. A case study highlighting differences between blends formulated with coprocessed excipients vs. individual excipients in terms of "wanted" material properties, CM process robustness, sampling errors, and PAT accuracy/precision will be presented.
2:00 – 2:30 PM	***Recent Advances in Co-processed APIs and Proposals for Enabling Commercialization of These Transformative Technologies*** Raimundo Ho, Ph.D., AbbVie Inc. (IQ Co-processed API Working Group) This presentation will provide the academic/industry perspective on opportunities of co-processed APIs to address the need for innovative routes to manage API physical properties, with a few case studies highlighted. Regulatory landscape and proposals to enable translation of technologies in pharmaceutical industry will also be presented.

2:30 – 3:00 PM	***Atomic Layer Coating Technology for Enhancing Processability & Enabling Continuous Manufacturing for Challenging APIs*** Shivkumar Chiruvolu, Ph.D. and Suneel Rastogi, Ph.D., Applied Materials Cohesive, high aspect ratio needle-like, low bulk density, poorly flowing active pharmaceutical ingredients (APIs) are increasingly prevalent in development pipelines of pharmaceutical companies. The poor particle and bulk level properties pose a challenge during pharmaceutical manufacturing processes. Engineering the particle surface by applying a thin nanometer scale coating can address these processability challenges. In this presentation, the application of atomic layer coating (ALC) technology adapted from semiconductor industry to coat APIs is reported. ALC is demonstrated to be a viable strategy to address the poor flowability and bulk properties of high surface area, cohesive, needle-like APIs, without impacting the other critical API and drug product attributes.
3:00 – 3:30 PM	**PANEL DISCUSSION:** ***What Types of Materials and Processes Might Be Needed to Support CM Developments Over the Next 5 to 10 Years?*** Moderator: Sebastian Escotet, Ph.D., Merck and Co., Inc. Panelists: Thomas O'Connor, Ph.D., US Food and Drug Administration Krizia M. Karry, Ph.D., BASF Fernando J. Muzzio, Ph.D., Rutgers University Abu T. Serajuddin, Ph.D., St. John's University
3:30 – 3:45 PM	**BREAK**
3:45 – 4:45 PM	***Breakout Session 2 – What Types of Characterization Techniques and Novel Excipients are Needed to Enhance CM Going Forward?*** *There will two or three concurrent breakouts utilized to discuss the topic to facilitate small group discussion.* Moderators: Krizia Karry, Priscilla Zawislak, Kathy Ulman Notetakers: Chris Moreton, Edmond Biba, Sebastian Escotet
4:45 – 5:00 PM	***Review of Day 2 and Closing Remarks*** David Schoneker IPEC-Americas, Black Diamond Regulatory Consulting, Chair - PQRI Workshop Organizing Committee

Workshop Organizing Committee

David Schoneker, Chair – Workshop Org. Committee; Black Diamond Regulatory Consulting, LLC, IPEC Americas
Edmond Biba, USP
Brian Carlin, Carlin Pharma Consulting
George Collins, Vanderbilt Minerals, LLC
Sebastian Escotet, Merck and Co., Inc.
Tom Farrell, Colorcon Inc.
Dede Godstrey, PQRI Secretariat
Yong Hu, FDA
Krizia Karry, BASF
Chris Moreton, FinnBrit Consulting
Himanshu Patel, BASF
Shailesh Singh, Merck
Janeen Skutnik-Wilkinson, Biogen
Elizabeth Tocce, IFF
Katherine Ulman, KLU Consulting
Priscilla Zawislak, International Flavors and Fragrances (IFF)
Joseph Zeleznik, IMCD US Pharma

Workshop Faculty

Brian Carlin, Ph.D., Owner, Carlin Pharma Consulting LLC
Shivkumar Chiruvolu, Ph.D., Senior Director, Business Development, Applied Materials
Stephen L. Conway, Ph.D., Merck & Co., Inc.
Charlie Cunningham, Technical Director – North America Region, Colorcon Inc.
Pedro Durão, Ph.D., PAT Scientist, Hovione
Sebastian Escotet, Ph.D., Merck & Co., Inc.
Douglas B. Hausner, Ph.D., Senior Manager, Continuous Manufacturing Business Development, Thermo Fisher Scientific
Raimundo Ho, Ph.D., Principal Research Scientist, AbbVie Inc.
Yong Hu, Ph.D., Branch Chief, Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ/CDER/U.S. Food and Drug Administration
Pauline Janssen, MSc, Product Application Specialist, DFE Pharma
Krizia M. Karry, Ph.D., Head of Global Technical Marketing – Pharma Solutions, BASF Corp.
Scott M. Krull, Ph.D., Chemical Engineer, US Food and Drug Administration
Sau (Larry) Lee, Ph.D., Deputy Director of Science, Office of Pharmaceutical Quality (OPQ)/CDER/U.S. Food and Drug Administration
Christine Moore, Ph.D., Executive Director, Organon
Chris Moreton, Ph.D., Partner, FinnBrit Consulting
Fernando J. Muzzio, Ph.D., Rutgers University
Venkatesh Natarajan, Ph.D., Principal Engineer, Amgen
Bart Nitert, Ph.D., Principal Scientist Oral Solids Development, Janssen R&D, Johnson & Johnson
Thomas O'Connor, Ph.D., Deputy Director, Office of Testing and Research, OPQ/CDER/U.S. Food and Drug Administration
Suneel Rastogi, Ph.D., Product Marketing Director, Applied Materials
Wyatt J. Roth, Ph.D., Senior Director, Eli Lilly and Company
David R. Schoneker, President/Owner, Black Diamond Regulatory Consulting, LLC
Abu T. Serajuddin, Ph.D., Professor of Industrial Pharmacy, St. John's University
Shailesh K. Singh, Ph.D., Executive Director, Merck & Co., Inc.
Changquan Calvin Sun, Ph.D., Professor, Department of Pharmaceutics, University of Minnesota
Kevin Thurow, Global Improvement Leader, IFF Pharma Solutions
Katherine Ulman, Owner and Primary, KLU Consulting, LLC
Priscilla Zawislak, Global Regulatory Affairs Advocacy Manager, International Flavors and Fragrances (IFF)
Joseph Zeleznik, MA, Technical Director, North America, IMCD US Pharma