The Cortona Conference:
Advances in Pharmaceutical Innovation
and Manufacturing Control

September 28 – 1 October, 2014
Centro Convegni Sant’Agostino, Cortona, Italy
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Monday, 29 September, 2014

**DAY ONE – AM** Session Chair: Mel Koch

**Plenary**

8:30 a.m. **Registration**

**Plenary Session – Mel Koch, CPAC, APL, University of Washington, Seattle, WA, USA**

9:00 a.m. **Conference Logistics and Introduction**
Bob Zutkis, IFPAC, USA

9:05 a.m. **Session and Speakers Introduction**
Mel Koch, CPAC, APL, University of Washington, Seattle, WA, USA

9:15 a.m. **Pharmaceutical Manufacturing: Challenges and Opportunities – Industry Perspective**
Moheb Nasr, GSK, USA

9:45 a.m. **Pharmaceutical Manufacturing: Challenges and Opportunities – Regulatory Perspective**
Evdokia Korakianiti, EMA, UK and Jean-Louis Robert, Laboratoire National de Sante, (EMA), Dudelange, Luxembourg

10:15 a.m. **Break**

**Manufacturing Innovation Session**
Chair: Mel Koch, CPAC, APL, University of Washington, Seattle, WA, USA

10:45 a.m. **Pharmaceutical Manufacturing Innovation – Opportunities and Challenges**
Mark Buswell, Global Head of Advanced Manufacturing Innovation, GSK. UK

11:15 a.m. **Development & Manufacturing Innovation: An Industry Case Study**
Michael O’Brien, Pfizer, Peapack, NJ, USA

11:45 a.m. **Combination Products and Medical Devices – Product Development and Regulatory Landscape Challenges – The Lucentis Case**
Thomas Fischer, Novartis, Basel, Switzerland

12:15 p.m. **Panel Discussion**

1:00 p.m. **Lunch**
DAY ONE – PM  Session Chair: Patricia Hurter
Process Control, Modeling and Chemometrics

2:00 p.m.  Process Control, Modeling and Chemometrics Session
            Chair: Patricia Hurter, Vertex Pharmaceuticals, Boston, MA, USA

2:10 p.m.  Control Strategy Implementation Including RTRT for A Fully
            Continuous Drug Product Manufacturing Process
            Kelly A. Swinney, Hayden Thomas and David Nadig, Vertex
            Pharmaceuticals Inc., Boston, MA, USA

2:40 p.m.  Model Implementation and Management for Real-Time Release- Case
            Study
            Nathan Pixley, Merck

3:10 p.m.  Model Maintenance: Using Simulations to Set Action Limits and Identify
            Robust Models
            Barry M. Wise and Robert T. Roginski, Eigenvector Research, Inc.,
            Wenatchee, WA, USA

3:40 p.m.  The Use of NIR Spectroscopy and Process Environmental Data to
            Monitor the Coating of Multiparticulate Beads in a Fluid Bed
            Stephen Hoag, Department of Pharmaceutical Science, University of
            Maryland, Baltimore, MD, USA

4:10 p.m.  Break

4:20 p.m.  Modeling and Chemometrics for Process Control (TBA)
            Evdokia Korakianiti and Dolores Hernán, EMA, UK

4:50 p.m.  Continued Process Verification, CPV – Cost-effective Quality Assurance
            Petter Mörée, Director, GPM, Umetrics, Malmö, Sweden

5:10 p.m.  Panel Discussion

5:30 p.m.  Close

6:15 p.m.  Departure for evening Event/Evening Cocktail Event – Piazza Garibaldi
            Hosted by the University of Georgia, College of Arts and Sciences,
            School of Art, and the UGA Cortona Program

Table Top Exhibit and Posters – 10:00 a.m. – 4:30 p.m.
Set up 8:00-10:00 a.m.
DAY TWO – AM  
Session Chairs: Evdokia Korakianiti, Jean-Louis Robert and Moheb Nasr  
Continuous Manufacturing  

Registration  

8:30 a.m.  
Continuous Manufacturing Session  
Chairs: Evdokia Korakianiti, EMA, UK, Jean-Louis Robert, Laboratoire National de Sante, (EMA), Dundelange, Luxembourg and Moheb Nasr, GSK, USA  

8:40 a.m.  
Technologies and Approaches for Synthesis Work-Up and Isolation of Drug Substance  
Alastair Florence, University of Strathclyde, UK  

9:10 a.m.  
Implementation of Continuous Drug Product Manufacturing  
Hayden Thomas, VP, Vertex Pharmaceuticals, Boston, MA, USA  

9:40 a.m.  
Equipment and Analytical Companies Perspective on Continuous Manufacturing  
Craig Johnston, CMAC, UK  

10:10 a.m.  
Achieving Excellence in Continuous Manufacturing  
Fernando Muzzio, Marianthi Ierapetritou, Rohit Ramachandran, Amanda Rogers, and Ravendra Singh, Rutgers University, Piscataway, NJ, USA  

10:40 a.m.  
Break  

11:10 a.m.  
Pharmaceutical Manufacturing Supply Chain, Time for Change  
Clive Badman, GSK, UK  

11:40 a.m.  
Integrated Continuous Manufacturing of Pharmaceuticals: from Synthesis to Pills without Pause  
Salvatore Mascia, Continuus Pharmaceuticals, Inc., Boston, MA, USA  

12:10 p.m.  
CM - An Industry Perspective on Implementation Opportunities and Current Challenges  
Markus Krumme, Novartis, Basel, Switzerland  

12:40 p.m.  
Panel Discussion  

1:15 p.m.  
Lunch  

Poster Session – 10:30 a.m. – 4:30 p.m.  
Table Top Exhibit and Posters – 10:30 a.m. – 4:30 p.m.
Tuesday, 30 September, 2014

DAY TWO – PM  Session Chair: Gordon Muirhead
Knowledge and Data Management

2:00 p.m.  Knowledge and Data Management Session
            Chair: Gordon Muirhead, GSK, UK

2:10 p.m.  Leveraging Real-Time Analytics: Reducing Variation-From Supplier to Annual Product Review
            Jim Petrusich, Vice President, Northwest Analytics, Manufacturing Intelligence for Intelligent Manufacturing, Portland, OR, USA

2:40 p.m.  Knowledge and Data Management: Pharmaceutical Industry Perspective
            Nicola Walker, Product Quality Infomatics Director, GSK, UK

3:10 p.m.  Implementing Knowledge and Data Management Strategies to Address Business Challenges across Pharmaceutical Sciences, Pfizer
            Phil Levett, Director, Head of Pfizer’s Pharmaceutical Sciences Global Knowledge Management Office, Sandwich, UK

3:40 p.m.  Group Photo

4:00 p.m.  Break

4:30 p.m.  Analyser Device Integration: The Power of Data for Increasing Process Understanding
            Marco Banti, ABB SpA Process Automation Division, Control Technologies BU, Sesto San Giovanni (Milan)-Italy (TBD)

5:00 p.m.  Panel Discussion

5:30 p.m.  Close

8:00 p.m.  Gala Dinner - Town Centre

Table Top Exhibit – 10:30 a.m. – 4:30 p.m.
Wednesday, 1 October, 2014

**DAY THREE – AM Interactive** Session Chairs: Eric S. Ahuja & John V. Lepore

8:00 a.m.  **Interactive Session: Global Harmonization**
Eric S. Ahuja and John V. Lepore, Merck, USA

Wednesday, 1 October, 2014

**DAY THREE – AM** Session Chairs: Sarah Pope Miksinski and Ferdinando Aspesi

**Quality by Design and Analytical QbD**

9:00 a.m.  **Quality by Design and Analytical QbD Session**
Chairs: Sarah Pope Miksinski, OPS, ONDQA, CDER, FDA, Silver Spring, MD, USA and Ferdinando Aspesi, Novartis, Parsippany, NJ, USA

9:10 a.m.  **Implementation of Risk-Based Approaches to Control Strategy Design: Challenges and Opportunities**
Lynne A Krummen, VP, Global Technical Regulatory, Biologics, Genentech a member of the Roche group, South San Francisco, CA, USA

9:40 a.m.  **QbD/PAT Reality in Pharmaceutical Production – Case Examples from API and DP Manufacturing**
Lorenz Liesum, Novartis Pharma AG, Basel, Switzerland

10:10 a.m.  **Analytical Quality by Design at Vertex**
Kelly A. Swinney, Justin Pritchard, Chun Cai and David Nadig, Vertex Pharmaceuticals Inc. Boston, MA, USA

10:40 a.m.  **Break**

11:00 a.m.  **Technology Transfer in the QbD Framework**
Eric S. Ahuja and John V. Lepore, Merck, USA

11:30 a.m.  **QbD & PAT – In the Generic Industry**
Simona Dicapua, Director, Technology and Design, Teva Pharmaceuticals, Israel

12:00 p.m.  **Real Time Release as part of a Control Strategy - A QbD Perspective by EMA/EU**
Dr. Jobst Limberg, Bundesinstitut f. Arzneimittel und Medizinprodukte, Bonn, Germany

12:30 p.m.  **EMA-FDA Pilot Program and Regulatory Perspective on QbD for Analytical Methods**
Sarah Pope Miksinki, FDA, Silver Spring, MD, USA

1:00 p.m.  **Panel Discussion**

1:20 p.m.  **Lunch**

Table Top Exhibit – 10:30 a.m. – 1:00 p.m.
Wednesday, 1 October, 2014

DAY THREE – PM Session Chairs: Roger Nosal & Jagota Nirdosh
CMC Lifecycle Management

2:00 p.m.  CMC Lifecycle Management
Chairs: Roger Nosal, Pfizer, Peapack, NJ, USA and Jagota Nirdosh, Roche, S. San Francisco, CA, USA

2:10 p.m.  A Global Perspective of Managing Change through a Product Lifecycle: Opportunities & Challenges for Innovation
Julie L. Williams, Ph.D., FRPS, Pfizer

2:40 p.m.  The Progression of Control Strategy through the Product Lifecycle
Sander van den Ban, GSK, UK

3:10 p.m.  Managing Supply Chain Diversity during the Lifecycle of a Product: Reducing the Risk of Variability of Raw Materials & Excipients
Brian Carlin, FMC BioPolymer, Ewing, NJ, USA

3:40 p.m.  Break

4:00 p.m.  Managing Supply Chain Diversity during the Lifecycle of a Product: Leveraging Knowledge through Collaboration
Kevin Hool, Ph.D., Vice President R&D, United States Pharmacopeia, Rockville, MD, USA

4:30 p.m.  Using Comparability Protocols for Making Post-Approval Changes to QbD Products
Hayden Thomas and Stephanie Krogmeier, Vertex Pharmaceuticals, Boston, MA, USA

5:00 p.m.  Panel Discussion
Nirdosh Jagota, Moderator, Julie Williams, Sander van den Ban, Brian Carlin, Hayden Thomas, Kevin Hool, Evdokia Korakianiti, Dolores Hernán and Sarah Pope Miksinski

• What does effective lifecycle management look like to regulators/inspectors?
• What are the perceived technical & regulatory challenges to ensuring robust lifecycle management of change?
• Is there a need to increase collaboration between industry and regulators to effectively demonstrate lifecycle management of change?
• Are there regulatory incentives to improve lifecycle management?

5:30 p.m.  Close

Table Top Exhibits – 10:30 a.m. – 1:00 p.m.
Tear down – 1:00 p.m. – 4:00 p.m.
POSTERS

Establishment of Continuous Sono-crystallisation process for Lactose in a Multi-orifice OBR
Humera Siddique, Ian Houson and Alastair Florence, CMAC

Use of In-die Powder Densification Parameters in the Implementation of Process Analytical Technologies for Tablet Production on Industrial Scale
Marco Cespia, Diego R. Perinellia, Luca Casettarib, Giulia Bonacucin aa, Giuseppe Caporiccic, Filippo Rendinac and Giovanni F. Palmieria* a School of Pharmacy, University of Camerino, via S. Agostino 1, 62032 Camerino (MC), Italy. b Department of Biomolecular Sciences, University of Urbino, Urbino, Italy c Janssen-Pharmaceutical Company of Johnson & Jonhson, via C. Janssen, Borgo S. Michele, Latina, Italy

Application of Quality by Design Principles to Analytical Methods
Kimber Barnett, Pfizer
CORTONA 2014 EXHIBITORS

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Pharmaceutical Manufacturing
Conference Logistics and Introduction  
Bob Zutkis, IFPAC, USA

Session and Speakers Introduction  
Mel Koch, CPAC, APL, University of Washington, Seattle, WA, USA

Pharmaceutical Manufacturing: Challenges and Opportunities – Industry Perspective  
Moheb Nasr, GSK, USA

Pharmaceutical Manufacturing: Challenges and Opportunities-Regulatory Perspective  
Evdokia Korakianiti, EMA, UK and Jean-Louis Robert, Laboratoire National de Sante, (EMA), Dudelange, Luxembourg

Pharmaceutical Manufacturing Innovation – Opportunities and Challenges  
Mark Buswell, Global Head of Advanced Manufacturing Innovation, GSK, UK

Biography:  
Mark Buswell is the Head of Advanced Manufacturing Technologies at GSK and is leading the implementation of the GSK Manufacturing Technology Roadmap that aims to transform pharmaceutical manufacturing. Mark joined GSK in 2002 and has held roles in R&D and manufacturing in process development and engineering, innovation and sustainability. He has a PhD in Chemical Engineering from University of Cambridge and an MBA from Cranfield University. He is married with 3 children

Development & Manufacturing Innovation: An Industry Case Study  
Michael O’Brien, Pfizer, Peapack, NJ, U.S.A

Biography:  
Michael K. O’Brien, Executive Director, is the head of the PTx Pharmaceutical Sciences Technology & Innovation (T&I) Group and is a member of the Pharmaceutical Sciences Executive Leadership Team.  
Michael earned his Bachelors of Science degree from Ohio Wesleyan University, and in 1989 received his Ph.D. in Organic Chemistry from Case Western Reserve University under the guidance of Prof. Anthony J. Pearson. He joined Hercules Inc. in 1989, where as a member of a multi-disciplinary team in the Aerospace division, he investigated the use of organic materials for unique optical applications. 
In 1992 he joined Rhone-Poulenc Rorer / Aventis Pharma as a Research Scientist and in 1999 he became the US Head of Chemical Process Research. There he championed the use of automated parallel chemistry technologies as an integral tool in process research and development.
In 2001 Michael joined Wyeth Research Chemical Development in Pearl River where he was the Assistant Vice President of the Synthesis Research & Development group overseeing Process Chemistry, the Chemical Engineering Technologies group (CET) and the high throughput process screening group. Michael joined Pfizer in 2010 after the Wyeth acquisition. As the T&I Head, he directs a group that oversees a range of functions, including informatics, technology strategy / technology development, and the leveraging of internal innovation & science to develop external networks focused on the delivery of horizon 2/3 technology advances.

Abstract:  
The Pharmaceutical Industry is now at the point where it is viable and practical for continuous/semi-continuous processing equipment and process intensification technologies to replace traditional Drug Product and API large-scale manufacturing operations. These advances have led to dramatic reductions in size while enabling true modularity. Furthermore, reduced footprint in combination with more flexible operations has enabled processing trains to be enclosed in dramatically smaller, autonomous, GMP compliant suites. Since these self-contained processing entities are environmentally isolated, the need to ‘brick and mortar’ processing trains into a traditional factory infrastructure is largely obviated.
Some of the anticipated benefits of the above evolving paradigm:
• Elimination of the uncertainty and reduction of the costs associated with development to manufacturing and site to site technical transfers.
• Enablement of an uninterrupted process knowledge chain that that begins in development and is continually expanded upon over the course of the products life.
• Make rapid deployment of facilities, cost effective cloning, and re-deployment options a reality
• Improve reliability of supplies and confidence in quality among regulatory authorities.

As our industry develops transformational strategies regarding the development & manufacturing paradigm of the future, the understanding of current approaches is fundamentally important. This presentation will discuss the ongoing development and implementation of an Oral Solid Dose manufacturing platform at Pfizer together with the transformational concepts that are driving this program.

Combination Products and Medical Devices – Product Development and Regulatory Landscape
Challenges – The Lucentis Case
Thomas Fischer, Novartis, Basel, Switzerland

Abstract:
Lucentis is a biological product treating AMT (wet age-related macular degeneration) via intravitreal injection. Novartis is working on innovative drug delivery devices which are submitted as part of a combination product submission. The focus of this development lies on a read-to-use presentation which reduces also the risk of iatrogenic infections. The rapidly changing regulatory environment in different geographical areas in the world are affecting the development activities.

Panel Discussion

Vendor Presentations (TBA)

Control Strategy Implementation Including RTRT for A Fully Continuous Drug Product Manufacturing Process
Kelly A. Swinney, Hayden Thomas and David Nadig, Vertex Pharmaceuticals Inc., Boston, MA, USA

Biography:
Kelly has over ten years of experience in the pharmaceutical industry working in the United States and Europe focused CMC activities. Her experience spans from pre-clinical development through marketing authorization in the areas of analytical chemistry, process analytical technology (PAT), solid state chemistry and pre-formulation development. Currently at Vertex, she leads the PAT group focused on in process control and real time release testing for continuous manufacturing. In this role, her team’s responsibilities include RTRT strategy development, method development and validation, PAT technology development and implementation, and GMP manufacture support. Kelly holds a BS degree in Chemistry from James Madison University and a PhD in Chemistry from Texas Tech University.

Abstract:
Presented will be the implementation of a PAT enabled control strategy for a continuous tableting manufacturing line. In-process controls, real time decision making for process control and product segregation, and real time release testing will be discussed.

Model Implementation and Management for Real-Time Release- Case Study
Nathan Pixley, Merck

Model Maintenance: Using Simulations to Set Action Limits and Identify Robust Models
Barry M. Wise and Robert T. Roginski, Eigenvector Research, Inc., Wenatchee, WA, USA

The Use of NIR Spectroscopy and Process Environmental Data to Monitor the Coating of Multiparticulate Beads in a Fluid Bed
Stephen Hoag, Department of Pharmaceutical Science, University of Maryland, Baltimore, MD, USA

Modeling and Chemometrics for Process Control (TBA)
Evdokia Korakianiti and Dolores Hernán, EMA, UK

Continued Process Verification, CPV – Cost-effective Quality Assurance
Petter Mörée, Director, GPM, Umetrics, Malmö, Sweden

Abstract:
The data collected for CPV should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. As the data to be collected consists of single values, multivariate data (NIR), at line data, streams of online data and multivariate data in real time, the task for the
IS/IT personnel is challenging. In addition to these data, start and stop of phases and processes and lag times between process steps need to be collected and stored.

Multivariate Data Analysis has now reached a state where correctly stored data can be handled almost regardless of the complexity of the data. This means that CPV reports for batches and sets of batches can be prepared in real time (minutes delay). In addition the same data can be used for online out of trend monitoring, online prediction of quality and online control of batches. In summary, the above results in cost-effective quality assurance. Practical examples from Umetrics customers will be demonstrated.

Panel Discussion

Vendor Presentations (TBA)

Technologies and Approaches for Synthesis Work-Up and Isolation of Drug Substance
Alastair Florence, University of Strathclyde, UK

Implementation of Continuous Drug Product Manufacturing
Hayden Thomas, VP, Vertex Pharmaceuticals, Boston, MA, USA

Biography:
Hayden Thomas is Vice President of Formulation Development at Vertex Pharmaceuticals Inc., Boston, MA. His department consists of materials assessment, formulation design, and continuous manufacturing in support of dosage form design and process development from early clinical development up to commercial manufacturing. Dr. Thomas is currently focused on the implementation of a drug product continuous manufacturing platform to enable the clinical and commercial production of a breakthrough therapeutics. Prior to joining Vertex, Dr. Thomas worked at Pfizer where he held leadership positions in preformulation, formulation, and chemical development groups. He has a Ph.D. in Pharmaceutical Chemistry.

Equipment and Analytical Companies Perspective on Continuous Manufacturing
Craig Johnston, CMAC, UK

Achieving Excellence in Continuous Manufacturing
Fernando Muzzio, Mariamthi Ierapetritou, Rohit Ramachandran, Amanda Rogers, and Ravendra Singh, Rutgers University, Piscataway, NJ, USA

Biography:
Fernando Muzzio is a Distinguished Professor of Chemical Engineering at Rutgers University. For the last 23 years, pharmaceutical product and process design has been Professor Muzzio’s main research and educational focus. His research interests comprise continuous manufacturing, powder mixing, powder flow, segregation, compaction, mixing and flow of liquids and suspensions, capsule filling, tablet dissolution, and tablet coating. In the last ten years, his main research focus has been the development of continuous systems for solid dose manufacturing.

Professor Fernando Muzzio is also the director of the National Science Foundation Engineering Research Center on Structured Organic Particulate Systems. The center, which has an budget in excess of $8 million per year, focuses on pharmaceutical product and process design, with special emphasis on continuous manufacturing, particle engineering, and personalized medicine. FDA and 45 companies are currently members of the center.

Professor Muzzio is a frequent advisor and lecturer at FDA events. In 2010 he was appointed a voting member of the FDA committee on Pharmaceutical Sciences and clinical pharmacology. Professor Muzzio has been funded numerous times by FDA to perform regulatory science research, and is a Principal Investigator in three currently active grants from FDA on using PAT to assess blend uniformity, continuous manufacturing training, and on the use of flowsheet models for continuous risk assessment of manufacturing processes.

Professor Muzzio is also the president of Mixing Consultants Inc, a specialty consulting company focused on providing scientific and technical support in the general applications of mixing science and technology, and the Chief Scientific Officer of Acumen Biopharma, a specialty consulting firm specializing in pharmaceutical IP litigation.

Abstract:
One important difference between batch and continuous processes is that while batch processes are intrinsically time-dependent, continuous processes operate in a small neighborhood around a desired, typically steady, set point condition. Thus, development of integrated predictive models for continuous processes is much more feasible than for batch processes. Very importantly, as it has been demonstrated in the chemical and petrochemical industries (among others), once such models are developed and validated, it is possible to use them to systematically design and optimize continuous processes, to design and implement optimal control methods, to examine process robustness and determine the feasible operating space, and to collect and use massive amounts of information during manufacturing to dynamically optimize system performance.
In this talk, I will introduce an integrated modeling platform that seeks to achieve the outcomes described above. I will describe how this platform can be linked to raw and intermediate material property databases in order to create a growing capability for developing new products and new processes, and how such integrated models can be interfaced to the process control platform in order to achieve real time process optimization. In the new manufacturing paradigm enabled by such tools, the system predicts, monitors, and controls the quality of the product instantaneously, providing not only greatly improved operational capabilities, but greatly reduced manufacturer and patient risk.

**Pharmaceutical Manufacturing Supply Chain, Time for Change**

Clive Badman, GSK, UK

**Biography:**

Dr. Clive Badman OBE Vice President, Pre-Competitive Activities GlaxoSmithKline

Clive Badman took up the position of Vice President, Pre-Competitive Activities, in R&D, in October 2013 having previously been responsible for the supply chain for clinical trials worldwide and the scale up and transfer of products into manufacturing.

Clive joined Beecham Pharmaceuticals in 1978 and has held positions of increasing responsibility in Development and Production both at site and in central functions before moving to R&D in 2002.

From October 2013 he also took on a role in the Business Engagement Group at Strathclyde University where he is a Visiting Professor and Chairman of CMAC (Continuous Manufacturing and Crystallisation).

Clive has a BSc and PhD in Chemistry from Dundee University. He was awarded an OBE in 2012 for services to the Pharmaceutical Industry

**Abstract:**

The pharmaceutical world is changing with less blockbusters and more niche products. The introduction of stratified and personalised medicines adds to this picture. It is likely that much of the existing manufacturing architecture will not be adequate for the future. The paper examines Continuous Manufacturing and the many benefits it will bring to future supply chains.

**Integrated Continuous Manufacturing of Pharmaceuticals: from Synthesis to Pills without Pause**

Salvatore Mascia, Continuus Pharmaceuticals, Inc., Boston, MA, USA

**Abstract:**

The development of novel manufacturing technologies has the potential for reaping the full benefits of continuous manufacturing. Moreover, their integration into an end-to-end continuous manufacturing solution, including both chemical and pharmaceutical operations (i.e. integrated continuous manufacturing, ICM) can open a new manufacturing paradigm for this industry. This vision employs concepts of continuous flow, end-to-end integration, a systems approach, and an integrated control strategy. The first ICM pilot plant, developed at the Novartis-MIT Center for Continuous Manufacturing, demonstrated that pharmaceuticals can be produced continuously in a fully integrated manner with automated control. In this way, raw materials can be transformed into finished tablets without interruption (24 hours a day), with the active ingredient being synthetized in situ without isolation.

**CM - An Industry Perspective on Implementation Opportunities and Current Challenges**

Markus Krumme, Novartis, Basel, Switzerland

**Biography:**

Markus Krumme is Head of the Continuous Manufacturing Unit at Novartis Pharma in Basel since 2011. There he is leading all activities around CM, technology development, equipment development and process development both with internal and a variety of external resources.

Prior to joining Novartis he was working as Vice President Research & Development with LTS Lohmann Therapy Systems Corp in NJ, USA for eight years and before that as Department Head R&D Oral Systems with LTS AG in Germany. During his tenure at LTS he was driving the Thin Film development from a concept, formulation, analytical, process, packaging and equipment development perspective. When he started at LTS, Thin films did basically not exist as dosage form, just as an idea. When he left, Thin films were an established dosage form with visibility to authorities, customers and several products in the market and LTS being the market leader in that business.

Prior to LTS he was a lecturer at the University of Tübingen in Pharmaceutical Technology with a research interest in formulation and engineering aspects of solid dosage forms, like sensor and test instrument designs, high speed data acquisition & control and theoretical simulations of material properties. He has a PhD in Pharmaceutical Technology from the Free University Berlin.
**Abstract:**

The presentation gives an overview of what CM is, what the unique characteristics are, what the consequences of these characteristics are for development and Technical operations, what the impact on portfolio development may be and where chances and challenges are in a big pharma environment.

Based on an unusual definition of CM three key commercial drivers for implementations are derived and verified on a real portfolio. Various implementation scenarios are discussed and effects on the key performance of organisations are evaluated. Several unique characteristics are worked out and in a deductive way used to navigate the main obstacles and drive an implementation in a rational way avoiding dogmatic pitfalls.

**Panel Discussion**

**Leveraging Real-Time Analytics: Reducing Variation-From Supplier to Annual Product Review**
Jim Petrusich, Vice President, Northwest Analytics, Manufacturing Intelligence for Intelligent Manufacturing, Portland, OR, USA

**Knowledge and Data Management: Pharmaceutical Industry Perspective**
Nicola Walker, Product Quality Infomatics Director, GSK, UK

**Implementing Knowledge and Data Management Strategies to Address Business Challenges across Pharmaceutical Sciences, Pfizer**
Phil Levett, Director, Head of Pfizer’s Pharmaceutical Sciences Global Knowledge Management Office, Sandwich, UK

**Abstract:**

The Knowledge Management Office in Pfizer Pharmaceutical Sciences is responsible for effectively managing our data and knowledge to reduce our business risk, enhance the value of our knowledge assets and to optimize the flow of data and knowledge across our business with a vision to becoming a more effective learning organization.

**Panel Discussion**

**Interactive Session: Global Harmonization**
Eric S. Ahuja and John V. Lepore, Merck, USA

Global Harmonization

Goals of this Strategy Session

Determine if there is broad support for advancing "working solutions" to address current state issues. Identify how best to make progress to drive more global harmonization and address the pain points felt by industry and regulators, what high level working solutions might look like, potential barriers and seek engagement and commitment from key stakeholders in the pharmaceutical community to collaborate following this session to develop an actionable plan for 2015 and beyond.

Problem Statement: The practical application of the ICH Q8, 9, 10 and 11 framework across all ICH regions and other worldwide health authorities continues to evolve within industry and the regulatory community. Despite this, no clear best practices have emerged, and in fact, some practices have become more diverse as a result of:

1. Inconsistent interpretation and application of existing guidance and supporting documents
2. Inconsistent expectations as to the sufficiency criteria to achieve a given regulatory outcome
3. Inconsistent and unpredictable business outcomes driving churn at regulator-industry interface
4. Unaligned understanding of residual risk and its implication across all stakeholder groups

When QbD was in its formative stages, industry and regulators were highly engaged in determining how the new framework could benefit our shared service to the patient. As pilots have come and gone, and with more case studies entering the public domain, a more accurate view of the situation is now possible. We are at a crossroads and given the current business environment, failure to recognize and address these inconsistencies in a timely manner and within a global framework will further delay or even threaten ever realizing the value of QbD to stakeholders, especially the patient. The fragmented nature of trade groups, along with the multitude of pair-wise company-regulator interactions with health authorities, the latter often done in the highly pressurized context of a specific product approval, is contributing in part to the diversity of approaches, and exacerbates the current situation. In addition, many of the well-intended efforts by industry consortia, etc, have led to solutions in a snapshot of time that often failed to gain enduring global acceptance.

Important Components of a Desired Path Forward- a starting point

1. Inclusion: Broad participation by the global pharmaceutical community- regulators and industry.
2. Communication:
   a. Expectations on interpretation of standards requires dialog between stakeholders to ensure common understanding and alignment, and enable regulator confidence in quality
   b. Communication pathways across regulatory regions for specific applications can be enhanced to ensure timely and transparent resolution of issues, and above project matters, so fewer issues require resolution in the pressurized context of single project approvals.
   c. Preparation of a clear, consistent narrative of processes that articulate the level of technical understanding by industry is an urgent need
3. Clarity of expectations
   a. Regulatory commitments.
   b. Level of detail
   c. Change management

Implementation of Risk-Based Approaches to Control Strategy Design: Challenges and Opportunities
Lynne A Krummen, VP, Global Technical Regulatory, Biologics, Genentech a member of the Roche group, South San Francisco, CA, USA

Abstract:
The Quality by Design initiative has allowed the opportunity to use systematic risk-based approaches to develop modern product control strategies and define design spaces for well-characterized processes. Full implementation of QbD concepts facilitates risk-based life-cycle management of products, and ensures a sustained level of product quality. To realize this overarching goal, QbD concepts must be fully integrated into process and product development and the manufacturer's Quality Management System (QMS). This presentation will overview the challenges encountered by Genentech and Roche during development of QbD approaches for biotech products, the strategies that have led to global approvals of a QbD-based control strategies, including process-wide design space, and discuss implications of QbD implementation for lifecycle management.

QbD/PAT Reality in Pharmaceutical Production – Case Examples from API and DP Manufacturing
Lorenz Liesum, Novartis Pharma AG, Basel, Switzerland

Abstract:
After an introduction covering the conclusion and lesson learned from the first QbD projects at Novartis, two case studies will presented from API manufacturing.

In both case studies, a drying process is monitored by using in one example a classical NIR instrument and in the second a soft sensor model based on multivariate statistics. Furthermore a case study on Content Uniformity (CU) by NIR will be presented and how the new EMA NIR guidance and the Pharm. Eur. 2.9.47 for large sample sizes were incorporated.

Analytical Quality by Design at Vertex
Kelly A. Swinney, Justin Pritchard, Chun Cai and David Nadig, Vertex Pharmaceuticals Inc. Boston, MA, USA

Abstract:
Presented will be quality by design guided PAT IPC and RTRT method development and life cycle management. The presentation will discuss the development of robust methods/chemometric models, method validation, transfer, and model maintenance. Additionally, RTRT verification for batch release will be presented.
Technology Transfers in the QbD Framework
John Lepore and Eric Ahuja, Merck Sharp and Dohme Corp, Global Science Technology and Commercialization, Rahway, New Jersey and West Point, Pennsylvania, USA

Abstract:
The pharmaceutical community continues to advance the practical application of ICH Q8, Q9, Q10 and Q11 that define Quality by Design to process and product development and supply. The integration and implementation of Quality by Design practices in the drug development and manufacturing processes have encompassed a wide range of knowledge- and technology-based approaches. Historically, process knowledge would have transferred across a single point, a handoff, on the critical path to product registration. Currently, we use the QbD approach, augmented with Lean-Six Sigma methodology to drive an integrated approach to product and process development, technology and knowledge transfer and continual improvement over the product life cycle. These approaches also are the corner stone for PAI readiness and process validation including continuous process verification over the product lifecycle.

This presentation will focus on the transfers of real examples of innovative, risk based control strategies that involve the use of predictive modeling and process analytical technology (PAT) including technology/knowledge transfer. The examples shared will cover practical experiences in technology and knowledge transfer operating within the QbD framework. It will include application and implementation of advanced control strategies to both drug substance and finished products that have been approved by regulatory agencies. Challenges will be discussed and first experiences in operational use including the benefits realized will also be shared.

QbD & PAT – In the Generic Industry
Simona Dicapua, Director, Technology and Design, Teva Pharmaceuticals, Israel

Abstract:
QbD and PAT strategy with focus on the generic industry will be summarized. A case study of PAT, the Parsum technology for real time monitoring of granulation processes will be presented. This technique can be used in wet and dry granulation processes as a mean for faster and more efficient process development, as well as improving process control. The rationale, advantages and limitations of this technique will be covered.

Real Time Release as part of a Control Strategy - A QbD Perspective by EMA/EU
Dr. Jobst Limberg, Bundesinstitut f. Arzneimittel und Medizinprodukte, Bonn, Germany

EMA-FDA Pilot Program and Regulatory Perspective on QbD for Analytical Methods
Sarah Pope Miksinki, FDA, Silver Spring, MD, USA

Biography:
Sarah Pope Miksinski, Ph.D., is the Acting Director of the Office of New Drug Quality Assessment. She obtained her B.A. from Earlham College (1994), her doctorate in Organic Chemistry from Oklahoma State University (1999), and completed a postdoctoral fellowship from NIH (NIDA, 2000-2002). Sarah joined FDA approximately 12 years ago, serving initially as a Chemistry Reviewer for reproductive/urologic drugs. Since that time, she has held additional positions within ONDQA including Chemistry, Manufacturing and Controls Lead as well as Branch Chief and Division Director. Sarah’s areas of technical expertise include the characterization of complex drug substances/products, manufacture of injectable dosage forms, and spectroscopic methodology.

Auxiliary -
As an undergraduate, Sarah’s initial career aspirations involved professional performance (violin, piano, dance). She moved into the organic chemistry field only after taking an introductory chemistry class to meet general education requirements. She maintains her focus on the arts to this day, and still attends regular ballet classes.

In her free time, Sarah enjoys skiing, spending time with her husband (Ted) and 4-year-old son (Adam), and running. She is looking forward to her next 5k race in mid-October.

Panel Discussion
A Global Perspective of Managing Change through a Product Lifecycle: Opportunities & Challenges for Innovation
Julie L. Williams, Ph.D., FRPS, Pfizer

Biography:
Julie Williams leads a Pfizer global regulatory team, based in Asia, Middle East, Europe, US and Latin America, which provides knowledge on regional regulatory requirements, supports and prosecutes submission strategies and ensures product conformance. Julie is a pharmacist, recently recognized as a Fellow of the Royal
Pharmaceutical Society Faculty for advanced professional practice. Prior to joining Pfizer, Julie worked in the research and development of biotechnology products and vaccines, for United Biomedical, in New York, and Fidia Advanced Biopolymers, in Padova, Italy. Julie lives in Sandwich, UK with her husband and two sons.

Abstract:
Global Perspective of Managing Change through a Product Lifecycle: Opportunities & Challenges for Innovation”. Dr. Williams’ presentation will give an overview of typical changes through a product lifecycle, will discuss regulatory challenges particularly in Emerging Markets and will highlight the importance of effective change and knowledge management to ensure compliance. This presentation will set the scene for the following presentations in the session.

The Progression of Control Strategy through the Product Lifecycle
Sander van den Ban, GSK, UK

Managing Supply Chain Diversity during the Lifecycle of a Product: Reducing the Risk of Variability of Raw Materials & Excipients
Brian Carlin, FMC BioPolymer, Ewing, NJ, USA

Managing Supply Chain Diversity during the Lifecycle of a Product: Leveraging Knowledge through Collaboration
Kevin Hool, Ph.D., Vice President R&D, United States Pharmacopeia, Rockville, MD, USA

Abstract:
Regulatory changes as well as existing regulatory requirements place real stress on the pharma supply chain and the manufacturing quality work processes. Often these stresses are not unique to a specific manufacturer or company, and reaction to them can permit implementation and/or collaboration that can lower overall cost, and also better leverage the underlying benefits that drive product quality. This presentation will illustrate how any pharma manufacturer and/or supplier can find a collaborative pathway that can lead to the above mentioned benefits. Past case studies will be presented to illustrate this opportunity and showcase current efforts as well as on how to create new collaborative efforts with industry, FDA, USP and other stakeholders on product quality lifecycle management challenges. The Product Quality Research Institute was created in the late 1990’s for just that purpose. PQRI is an organization that is a consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development.

Using Comparability Protocols for Making Post-Approval Changes to QbD Products
Hayden Thomas and Stephanie Krogmeier, Vertex Pharmaceuticals, Boston, MA, USA

Abstract:
A review of post approval requirements and comparability protocols will be presented followed by a discussion on the post approval management of QbD submissions and the use of comparability protocols to reduce the post approval burden globally, encourage continual improvement, and increase assurance of quality through the lifecycle.

Panel Discussion
Nirdosh Jagota, Moderator, Julie Williams, Sander van den Ban, Brian Carlin, Hayden Thomas, Kevin Hool, Evdokia Korakianiti, Dolores Hernán, and Sarah Pope Miksinski

- What does effective lifecycle management look like to regulators/inspectors?
- What are the perceived technical & regulatory challenges to ensuring robust lifecycle management of change?
- Is there a need to increase collaboration between industry and regulators to effectively demonstrate lifecycle management of change?
- Are there regulatory incentives to improve lifecycle management?

Close
Establishment of Continuous Sono-crystallisation process for Lactose in a Multi-orifice OBR
Humera Siddique, Ian Houson and Alastair Florence, CMAC
(Poster)

Biography:
My name is Humera Siddique. I am working as a research associate in Centre for Continuous Manufacturing and Crystallisation, Strathclyde University. I am chemical engineer by background. I did my masters in process engineering. My PhD was on the development of compaction resistant organic solvent nanofiltration membranes for continuous processes. I finished my PhD in April 2013 from Imperial College London.
Currently I am working on the establishment of continuous crystallisation process using process analytical tools and model predictive control, which will enable the crystalliser to reach optimum performance quickly and efficiently.

Abstract:
Crystallisation at production scale is typically a poorly understood unit operation with little application of first principles aspect of crystallisation in its design, optimisation and control. Aim of this study was establishment of a systematic approach to develop a crystallisation process from batch to continuous process using process analytical tools. In this study experimental study has been conducted to evaluate the feasibility of a continuous sono-crystallisation process for alpha lactose monohydrate (LMH) in a multi-orifice oscillatory baffle crystalliser to achieve consistent product with a narrow particle size distribution. Kinetic and thermodynamic parameters were investigated for lactose crystallisation using FBRM and mid IR. Optimisation of the kinetic parameters, cooling profile and sonication for seeding was performed in batch stirred tank and batch oscillatory baffled crystalliser. Mixing and flow characterisation of continuous oscillatory baffled crystalliser (COBC) was performed in the COBC to achieve plug flow conditions and results indicated the capability of this system to run for 1-5 hours crystallisation process under plug flow conditions. The results show that continuous crystallization offers significant advantages in terms of process, and operation, and delivers the optimum yield and particle size distribution of LMH in 2.5-4 hours compared to the 13-20 hours in a batch process. Continuous crystallisation was performed at a throughput of 356g.h⁻¹ for 12 hours without any fouling or blockage in the system.

Use of In-die Powder Densification Parameters in the Implementation of Process Analytical Technologies for Tablet Production on Industrial Scale
Marco Cespia, Diego R. Perinellia, Luca Casey, Giulia Bonacucinaa, Giuseppe Caporiccic, Filippo Rendinac and Giovanni F. Palmieria* a School of Pharmacy, University of Camerino, via S. Agostino 1, 62032 Camerino (MC), Italy. b Department of Biomolecular Sciences, University of Urbino, Urbino, Italy c Janssen-Pharmaceutical Company of Johnson & Jonhson, via C. Janssen, Borgo S. Michele, Latina, Italy

Abstract:
The use of process analytical technologies (PAT) to ensure final product quality is by now a well established practice in pharmaceutical industry. To date, most of the efforts in this field have focused on development of analytical methods using spectroscopic techniques. This work evaluated the possibility of using the parameters derived from the processing of in-line raw compaction data (the forces and displacement of the punches) as a PAT tool for controlling the tableting process. To reach this goal, two commercially available formulation were used, varying the quantitative composition and compressing these “varied mixtures” on a fully instrumented rotary pressing machine. The Heckel yield pressure and the compaction energies, together with the tablets hardness and compaction pressure, were selected and evaluated as discriminating parameters in all the prepared formulations.

The apparent yield pressure, as shown in the obtained results has the necessary sensitivity to be effectively included in a PAT strategy to monitor the tableting process. Additional (experiments) investigations were performed to understand the criticalities and the mechanisms beyond this (ese) performing parameter(s) and the associated implications.
Specifically, it was discovered that the efficiency of the apparent yield pressure depends on the nominal drug title, the drug densification mechanism and the error in pycnometric density.
Application of Quality by Design Principles to Analytical Methods
Kimber Barnett, Pfizer

Abstract:
The same QbD principles applied to the design of manufacturing processes are applicable to the design of analytical methodology. Pfizer is routinely applying these principles to method development practices by using an analogous science and risk based approach. The approach starts with the identification of method requirements which enables selection and development of an appropriate technique. Risk assessments are conducted to identify parameters that could potentially impact method performance. Subsequent experiments are conducted to understand and control sources of variability. Ultimately, this leads to the implementation of a robust measurement system for routine use as well as in support of process evaluation and improvement. The greatest value in applying these concepts lies in enhanced understanding of sources of variability and their control. Examples that illustrate these concepts will be provided.
CORTONA PROGRAM UPDATES

Monday, 29 September, 2014

DAY ONE – PM Session Chair: Patricia Hurter
Process Control, Modeling and Chemometrics

New Speaker added
2:10 p.m.  Control Strategy Implementation Including RTRT for A Fully Continuous Drug Product Manufacturing Process
Henrik Rasmussen, Kelly A. Swinney, Hayden Thomas and David Nadig, Vertex Pharmaceuticals Inc., Boston, MA, USA

Tuesday, 30 September, 2014

DAY TWO – AM Session Chairs: Evdokia Korakianiti, Jean-Louis Robert and Moheb Nasr
Continuous Manufacturing

New Speaker added
9:10 a.m.  Implementation of Continuous Drug Product Manufacturing
Patricia Hurter and Hayden Thomas, VP, Vertex Pharmaceuticals, Boston, MA, USA

Tuesday, 30 September, 2014

DAY TWO – PM Session Chair: Gordon Muirhead
Knowledge and Data Management

New Title
2:10 p.m.  Leveraging Real-Time Analytics: Reducing Variation-From Supplier to CPV/APR
Jim Petrusich, Vice President, Northwest Analytics, Manufacturing Intelligence for Intelligent Manufacturing, Portland, OR, USA

Wednesday, 1 October, 2014

DAY THREE – AM Session Chairs: Sarah Pope Miksinski and Ferdinando Aspesi
Quality by Design and Analytical QbD

New Speaker added
10:10 a.m.  Analytical Quality by Design at Vertex
Henrik Rasmussen, Kelly A. Swinney, Justin Pritchard, Chun Cai and David Nadig, Vertex Pharmaceuticals Inc. Boston, MA, USA

Wednesday, 1 October, 2014

DAY THREE – PM Session Chairs: Roger Nosal & Jagota Nirdosh
CMC Lifecycle Management

New Speaker added
4:30 p.m.  Using Comparability Protocols for Making Post-Approval Changes to QbD Products
Elaine Morefield, Hayden Thomas and Stephanie Krogmeier, Vertex Pharmaceuticals, Boston, MA, USA