PharmaEd's

Solubility Summit 2013

Exploring New Strategies for Optimizing Solubility & Bioavailability of Current and Future Drug Products

December 5-6, Racquet Club of Philadelphia, PA

Featured Speakers:

With Case Studies and Lessons Learned from Industry Experts!

- **Optimizing Formulation and Product Development in Early Clinical Research**
  - Presentation by Jason Vaughn, Patheon

- **Role of Small Molecule Colloid Formation on Oral Absorption**
  - Presented by Liping Zhou, Novartis

- **Nanosuspension Formulation and Process Optimization for Improved Bioavailability of Poorly Soluble Drug Compounds**
  - Presented by Indrajit Ghosh, Celgene

- **Effects of Manufacturing Process on Solid Dispersion Stability and Bio-Performance**
  - Presented by Michael Lowinger, Merck

- **Successful Formulation Strategies for Amorphous Solid Dispersions**
  - Presented by Duk Soon Choi, Roche

- **Adapting QbD Principles to Solubilization Formulation Development**
  - Presented by Marshall Crew, Agere Pharmaceuticals

And Many More! Including Special Coverage On:

* **Intellectual Property Considerations for Solid Form Drug Compounds**
* **Supersaturation & Precipitation Behavior of Poorly Soluble Drugs**
* **Rational Formulation Design for Poorly Soluble Drugs**
* **Co-Crystallization Techniques to Optimize Solubility**
* **Innovations in Discovery Pharmaceutics for Poorly Soluble Compounds**
* **Recent Developments in Lipid-Based Drug Delivery**
* **Considerations for Toxicology Formulations of Poorly Soluble Compounds**
* **Latest Formulation Strategies for Low Soluble Drugs**

Featuring Representation From:

Novartis	**GlaxoSmithKline**	**Cubist**	**Pion**
Merck	**Patheon**	**Capsugel**	**Agios**
Celgene	**Aptuit**	**Agere**	**Sirius Analytical**
Roche	**Takeda**	**Quotient Clinical**	***And More!***

PharmaED RESOURCES, Inc.

PharmaEd Resources, Inc. • 2810 Robeson Park Drive • Champaign, IL 61822
tel. 217.721.5774 • *web.* www.pharmaedresources.com

Thursday, December 5, 2013

8:00 *Complimentary Breakfast & Chairperson's Welcome and Opening Remarks*

Novel Approaches for Amorphous Solid Dispersions

8:30 **Best Practice Formulation Strategies for Amorphous Solid Dispersions**
Duk Soon Choi, Senior Research Leader, Hoffmann-La Roche

Amorphous formulation is one of the most remarkable formulation strategies to address poorly water-soluble compounds. Because of complexity and instability, however, it is still challenging to develop a robust amorphous formulation. This presentation discusses best practices in amorphous formulation development from an industry perspective, and offers case studies.

9:15 **Beyond Formulation: The Significant Influence of Process on the Stability and Performance of Solid Dispersions**
Michael Lowinger, Principal Scientist, Merck

Solid dispersion formulations provide a way to improve the bioperformance of poorly water-soluble compounds by converting the crystalline drug to a physically stabilized amorphous state in a polymer. Literature searches reveal a substantial body of work from both academia and industry focused on understanding the impact of solid dispersion composition on stability or performance of drug products. However, few published studies evaluate the impact of manufacturing process parameters on the quality attributes of drug products with the same formulation composition. This talk will examine the two main commercial process routes used to manufacture solid dispersions, spray drying and hot melt extrusion, and will provide examples in which variable manufacturing process parameters had a substantial impact on the critical quality attributes of the solid dispersions with identical formulation composition. Key Takeaways:

- There is a substantial body of work focused on understanding the impact of solid dispersion com position on stability or performance of drug products, yet very little published attention has been paid to the impact of manufacturing process on product quality for formulations of the same composition.
- Depending on process parameters selected, hot melt extrusion and spray drying process routes may result in phase separation, drug crystallization, compositional heterogeneity, degradation of drug and excipients, or dissolution changes.
- Several of these failure modes are illustrated with case study examples.

10:00 *Mid-Morning Break and Exhibit Viewing*

10:15 **Interplay of Formulation & Process Conditions for Manufacturing Amorphous Dispersions by Melt Extrusion**
Jim DiNunzio, Associate Principal Scientist, Merck

Melt extrusion is a complex technology that relies on key aspects of the formulation and process to deliver desired critical quality attributes. This talk discusses properties for formulating amorphous solid dispersions, with a focus on the identification and application of melt solubilizing compositions to enable production at lower temperatures. Furthermore, the influence of processing conditions and related interactions cannot be overlooked when developing these systems. The complex interplay between formulation and process are presented systematically, leading to a structured development approach for extruded systems that can be particularly useful for processing high melting point compounds. Recent case studies applying these approaches are also highlighted.

11:00 **Amorphous Spray-Dried Dispersions in Early Phase Development**
Pratik Saha, PhD, Scientific Investigator, Exploratory Development Sciences, Product Development, GlaxoSmithKline

Highly solubility-limited compounds (low solubility, high dose) constitute a significant portion of the NCE portfolio. For such compounds, limited oral exposure may impact the ability to get sufficient exposure to demonstrate a safety margin or to observe dose limiting toxicity or to demonstrate efficacy. Solubility-limited compounds often fail later in the development cycle at greater expense.

- This presentation will focus on leveraging amorphous spray-dried dispersions to maximize oral exposure in early phase for solubility-limited compounds, hence enabling progression of the 'best' targets and compounds.

11:45 **Formulation Strategies for Low Soluble Drugs—An Overview**
René Holm, Divisional Director for Biologics and Pharmaceutical Science, H. Lundbeck A/S

A large proportion of new chemical entities (NCE) entering drug development possess insufficient aqueous solubility to allow sufficient and consistent absorption from conventional pharmaceutical formulation systems. This has lead to the development of a number of different pharmaceutical enabling technologies including salt formation, size reduction of NCE, stabilization of nanoparticles, complexation with cyclodextrins, solid solutions, liquid filled capsules etc.. These drug delivery systems either increase the dissolution rate or present the compound in a solubilised form, thereby

circumventing the dissolution step. The different technologies will be discussion based upon the industrial considerations related to the individual method.

12:30 *Complimentary Lunch and Exhibit Viewing*

1:30 **Co-Crystallization Techniques to Optimize Solubility**
Harry Brittain, Institute Director, Center for Pharmaceutical Physics

Many emerging drug candidates do not exhibit an acceptable degree of solubility, and workers have used a variety of formulation techniques to achieve an acceptable outcome. Quite often, a greater degree of solubilization can be achieved by modifying the substance itself, namely through the formation of a cocrystal species. Solid crystalline phases containing two cocrystallized components offer a new development pathway whereby one can potentially improve the physical characteristics (i.e., equilibrium solubility, dissolution rate, solid-state stability, etc.) of a drug substance that exhibits a profile that is less than desirable. In this lecture, the topic of pharmaceutical cocrystals will be briefly explored, and a short exposition of the solubility and dissolution rate advantages that have been realized in various systems will be provided.

These approaches will be examined as part of the scope of this presentation, and the application of each will be illustrated through the use of appropriate examples.

- What are pharmaceutical cocrystals, and how may one form them for investigational purposes?
- What techniques are suitable for the characterization of cocrystals?
- Can cocrystallization of drug substances with solubility enhancers be a viable route?
- What are the possible regulatory obstacles that might hinder the development of a plausible cocrystal, and how might one overcome those obstacles?

Leveraging QbD, Rational Formulation Design, & Nanosuspension Formulation to Improve Bioavailability of Poorly Soluble Drugs

2:15 **Formulation Design and Process Optimization of Nanosuspension Formulation for Improving the Bioavailability of Poorly Soluble Drug Compounds**
Indrajit Ghosh, Senior Manager, Global Pharmaceutical Development, Celgene

This presentation will examine the fundamentals of nanosuspension for improving the bioavailability of poorly soluble compounds. Among the topics covered include:

- This presentation will examine the fundamentals of nanosuspension for improving the bioavailability of poorly soluble compounds. Among the topics covered include:
- Selection criteria of nanosuspension formulation
- Optimization of media milling process using quality by design
- Influence of nanosuspension formulation on the *in vivo* pharmacokinetic parameters
- Future opportunities - application of nanosuspension formulation for topical delivery

3:00 *Afternoon Coffee Break and Exhibit Viewing*

Sponsored by:

Pion

3:15 **Rational Formulation Design Through Biopharmaceutics Modeling and Automation**
Chong-Hui Gu, Head of CMC, Director at Agios

Recent development in biopharmaceutics modeling and automation can enable design of formulation properties to obtain desired pharmacokinetic profile in vivo. The presentation will introduce the application of modeling to understand the controlling factors for oral absorption and the use of automation to optimize these factors in drug product. Case studies of formulation optimization to overcome issues in oral exposure will be presented.

4:00 **Adapting QbD Principles to Solubilization Formulation Development**
Marshall Crew, President, Agere Pharmaceuticals

Best practices in other industries show that designing for quality and manufacturability from the earliest stages can significantly impact the quality and manufacturability of a product, and also reduce time-to-market and overall product costs. Leveraging these concepts, we present a modern approach to solubilization that is a QbD-based design platform with extensions to address the materials science needs of formulation design. The platform is augmented by comprehensive modeling and automated analyses similar to the best-practice approaches used by other industries dealing with similarly complex design, such as in consumer electronics design. The combination of QbD constraints and mechanistic based modeling enables a faster, more efficient formulation process that promises to minimize costly iterations and re-formulation as a drug product enters the clinic.

4:45 **Considerations for Formulating Poorly Soluble Compounds for Toxicology Studies**
Mitch Friedman, Senior Director, Toxicology, Takeda Pharmaceuticals

In this talk we will consider the differences between the development of a formulation for toxicology studies vs. clinical studies. We will consider the implications of different salt forms, the use of novel excipients and of course route of administration. We will couple this with consideration of the compound's ADME/PK characteristics and how these can be affected by formulation as well.

5:30 *End of Day One*

Friday, December 6, 2013

8:00 *Complimentary Breakfast & Chairperson's Opening Remarks*

Morning Workshop—Patent Law Opportunities & Solid Form Drug Compounds

8:30 **Understanding How Intellectual Property Provides Opportunities When Solubility Challenges Exist with Crystalline and Amorphous Solid Forms**
Eyal Barash, JD, Chief Patent Counsel to Aptuit, and Dr. David Engers, PhD, Director, Commercial Operations, Aptuit

In this workshop, the basics of patent law will be introduced in the context of the inherent properties of both crystalline and amorphous solid forms. In addition, the workshop will address scientific options for addressing solubility challenges by modifying the physical form of drug substances. More specifically, the workshop will address:

- The patentability of salts, polymorphs, cocrystals and other solid forms in the US and in Europe—similarities and key differences and how scientists can prepare their patent attorneys for success
- Using data to describe solid forms: industry best practices and traps for the unwary
- The science behind cocrystals and amorphous dispersions and what to expect from the unexpected
- Patents in Practice—recent case law on enforcing and defending solid form patents in the United States

10:30 *Mid-Morning Break and Exhibit Viewing*

Sponsored by:

aptuit
Uncommon Expertise. Exceptional Results.

Remodeling Product Development in Early Clinical Research

10:45 **Stepwise Preformulation and Formulation Development to Maximize Clinical Success**
Jason Vaughn, Director of Formulation and Product Development, Patheon

A strategic plan is necessary in order to increase the speed of taking a new API into the clinic for First in Human studies as well as for streamlining formulation development while keeping a project on budget. Rapid early development strategies must include a thorough definition of the target product profile. Physico-chemical properties such as aqueous solubility and hygroscopicity should also be understood prior to formulation development. Formulation approaches should be kept simple and when solubility and bioavailability challenges arise integrated solutions must be considered. Benefits of this talk include:

- Understanding the Target Product Profile
- Importance of Physico-chemical Properties
- Formulation Approaches for Phase I Studies
- Dealing with Solubility Limitations

11:30 **Translational Pharmaceutics™ — A New Platform to Overcome Solubility Challenges in Early Clinical Research**
Peter Scholes, Chief Scientific Officer, Quotient Clinical

A conventional drug product optimization process involves iterative rounds of screening multiple formulation prototypes in preclinical species to identify a limited number of "lead" systems to progress into human clinical PK studies. This process is time consuming and expensive, costing over $1.5m and taking over 18 months. The RapidFACT™ approach, underpinned by a Translational Pharmaceutics™ platform, integrates formulation development, GMP manufacture and clinical to optimize drug products with significantly shorter timelines and reduced associated expenditure compared to traditional paradigms. The approach allows products to be manufactured and investigated in a clinical study in timeframes as short as 24 hours. Candidate formulations can be rapidly screened, selected and validated on the basis of human clinical data. This significantly improves the precision by which an optimal drug product that matches the desired target product profile can be identified. Coverage includes:

- The solubility challenge and limitations of conventional development paradigms
- Novel CMC and regulatory strategies to enhance flexibility and precision in rapid clinical evaluation of formulation prototypes
- RapidFACT™ - effective screening and optimization of drug product formulation technologies

- Emerging innovations in First-in-human programs for BCS Class II/IV compounds
- Case studies - poorly soluble molecules and enabled formulations

12:15 *Complimentary Lunch and Exhibit Viewing*

Critical Issues—Overcoming Colloid Formation in Drug Delivery

1:15 **Role of Small Molecule Colloid Formation on Oral Absorption**
Liping Zhou, Principal Scientist, Novartis

Many small molecules are known to form aggregation in aqueous solution at micromolar concentrations. These aggregates nonspecifically inhibit proteins by sequestration and partial denaturation and are a major source of false positives in high-throughput screening. There is a developing theory that molecules are forming colloidal aggregate in the gastric-intestinal track that may affect both solubility/permeability; thus impact both absorption and distribution in vivo. A few related models have been published including aggregate absorption via lymphatic pathway as well as applying surfactant to interrupt the colloid formation to increase absorption. It has also been observed that the aggregation formation is linked to compound-lipid interaction. The mechanism of action by far remains challenging to address. This presentation will focus on the current measurement and understanding of aggregation effect to pharmacokinetic and discuss its potential impact on formulation as well as drug delivery.

2:00 **Reducing Development Timelines and Cost with a Lipid Expert System**
Eduardo Jule, Senior Manager, Pharmaceutical Development, Capsugel

Today, formulation scientists are faced with the challenge of identifying the most suitable drug delivery platform, but also developing and validating robust systems that address the challenges posed by increasingly complex drug candidates, in ever shortening timelines. Among these platforms, lipid-based formulations have become a well-established strategy to improve the bioavailability, reduce the food effects or even the absorption variability of poorly soluble compounds. Capsugel has developed an expert system approach based on experimental data that generates phase diagram output packages and provides unique formulation development support as well as increased speed to market.

2:45 *Afternoon Coffee Break & Exhibit Viewing*

3:00 **Discovery Pharmaceutics: Challenges, Opportunities, and Innovation**
You Seok (Tim) Hwang, Senior Scientist, Cubist Pharmaceuticals

Discovery pharmaceutics plays pivotal roles in advancing drug candidates from research to development by enabling candidate selection and identifying novel delivery approaches upfront to maximize a NCE's (New Chemical Entity) therapeutic potential and its fit with intended clinical applications. In this presentation, case studies and a general perspective will be discussed to highlight the challenges, opportunities, and potential for innovation that Discovery Pharmaceutics possesses.

- Creating an Effective Discovery Pharmaceutics Team
- Strategies to Enhance Productivity
- Enabling Candidate Selection
- Novel Delivery Approaches

Investigating Supersaturation & In Situ Concentration Monitoring of Low Soluble Drugs

3:45 **Experimental Methods for Investigating & Modifying Dissolution, Supersaturation & Precipitation Behavior of Poorly Soluble Drugs**
Jon Mole, Executive Vice President, Sirius Analytical, Inc.

This presentation will discuss some of the parameters responsible for intestinal precipitation and supersaturation of orally administered drugs and describe novel in-vitro experimental tools and procedures for improved understanding of these phenomena. These experiments may provide evidence for an enhanced absorption window over a particular pH range, thereby allowing poorly soluble compounds to be "promoted" to BCS class I that would otherwise lie in class II if thermodynamic solubility values were applied.

Ionizable pharmaceutical compounds, in particular weak bases, can be completely or partially solubilized in the stomach at low pH, where they will form ionized species. At higher pH in the intestine, they are susceptible to precipitation because of the lower solubility of the neutral species. However, under some conditions the neutral form of some poorly soluble compounds can remain supersaturated in solution. If a poorly soluble API can be supersaturated for a sufficient length of time, the higher concentration in solution may lead to an increased fraction absorbed into the systemic circulation, and an increase in efficacy.

- Solubility measurement using titration with real-time mass and charge balance analysis to determine concentration in the presence of precipitate
- Using solid dispersions & formulation additives to enhance solubility and supersaturation

- Applying this knowledge in small-scale dissolution studies with solubility enhancement and simulated absorption
- Surface Dissolution Imaging and real-time particle size & shape measurement to enhance mechanistic understanding of dissolution, solubility & precipitation.

4:30 **Applications of *In Situ* Concentration Monitoring in the Development of Low Soluble Drugs: Release from Nanoparticles, Supersaturation of Amorphous Forms and Dissolution-Permeability Studies for Better IVIVC**

Konstantin Tsinman, Director of Science and Research, Pion, Inc.

This presentation demonstrates the benefits of *in situ* concentration monitoring for multiple applications essential during the drug development phase. Among others, the case studies include:

- Integrated dissolution-permeability assay with dynamic concentration assessment in both donor and receiver compartments;
- The investigation of the extent and the rate of supersaturation for amorphous formulations in the buffers and bio-relevant media;
- A novel method for in situ measurements of free API being released from nanoparticles;

Estimation of effective particle sizes from powder dissolution profiles.

5:15 ***Close of Program***

Solubility Summit 2013 sponsored by

aptuit
Uncommon Expertise. Exceptional Results.

Pion

Patheon
Performance the World Over

Drug Development & Delivery

PharmaED RESOURCES, Inc.

PharmaEd Resources, Inc. • 2810 Robeson Park Drive • Champaign, IL 61822

About your conference destination:

The Racquet Club of Philadelphia is located in the heart of downtown Philadelphia, adjacent to beautiful Rittenhouse Square. From the conference venue, you can access many points of interest in Philadelphia including Independence Hall, the Kimmel Center, the Avenue of the Arts, numerous shops, and excellent restaurants!

Registration Information

Register for the conference using one of three options:
Online: www.pharmaedresources.com Phone: (217) 721-5774
Mail: 2810 Robeson Park Drive, Champaign, IL 61822

Please Complete the Following

FIRST NAME: _____

LAST NAME: _____

TITLE: _____

COMPANY: _____

ADDRESS: _____

ADDRESS: _____

CITY: _____ STATE: _____

ZIP: _____ COUNTRY CODE: _____

OFFICE PHONE: _____

MOBILE PHONE: _____

FAX: _____

E-MAIL: _____

VENUE INFORMATION:

Dates:	December 5-6, 2013
Venue:	The Racquet Club of Philadelphia
Venue Address:	215 South 16th Street Philadelphia, PA 19102
Venue Phone:	(215) 735-1525
Hotel Room Block:	Radisson Plaza Warwick
Hotel Address:	220 South 17th Street Philadelphia, PA 19103
Reservations:	(800) 967-9033
Hotel Telephone:	(215) 735-6000

Please register me for:

Solubility Summit, 2013:

Exploring New Strategies for Optimizing Solubility & Bioavailability of Current and Future Drug Products

Standard registration: $1,595
Early bird Special: Register by September 12th and take $500 off!
Early bird: Register by November 1st and take $300 off!
Call for government or academic discount

PAYMENT METHOD

CREDIT CARD REGISTRATION:

☐ CREDIT CARD ☐ VISA ☐ MASTERCARD ☐ AMEX

NAME: _____

CARD #: _____

EXPIRATION: _____ / _____

SIGNATURE: _____

BILLING ADDRESS: _____

CHECK REGISTRATION:

To pay by check, please provide a purchase order below. Please note that all payments must be received five (5) days prior to the conference to ensure space. Attendees will not be admitted to the conference without full payment.

PURCHASE ORDER #:

PLEASE NOTE:

PharmaEd Resources does not offer refunds. However, if you cannot attend after registering, we are happy to apply your registration fee to another PharmaEd Resources event, or transfer your registration to a colleague. Notice of cancellation must be received at least 5 days prior to the event.