PharmaED RESOURCES, Inc.

# Solubility & Bioavailability Summit 2014

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

**December 4-5, Racquet Club of Philadelphia, PA**

## Featured Speakers:

**Neil Mathias**
*Principal Scientist*
*Bristol-Myers Squibb*

**James D. Ormes**
*Assoc. Principal Scientist, Merck*

**Liping Zhou**
*Senior Scientist*
*Ipsen BioScience*

**Manuel Sanchez-Felix**
*Senior Fellow, Novartis*

**Mike Zaworotko**
*Bernal Chair*
*University of Limerick*

**Yi Gao**
*Principal Research Scientist*
*AbbVie*

**Perhaps the most critical research agenda for today's pharmaceutical industry is achieving solubility and bioavailability of poorly soluble drug candidates. The challenges are not going away, and neither are your organization's demands. Pharma Ed's Solubility & Bioavailability Summit focuses on the innovative science required to enhance bioavailability/solubility for API's in a wide range of pre-clinical, clinical, and manufacturing contexts.**

### With Comprehensive Coverage On:

- Optimizing Formulations for New Drug Product Development
- Peptide Formulation Challenges and Beyond
- De-risking New Chemical Entities for Food- and pH-Sensitivity in Early Clinical Development
- Key Formulation Considerations for Suspensions of Amorphous Dispersions
- Studying the Interplay of Dissolution, Solubility and Permeability in Formulation Development
- Re-conceptualizing Solubility & Bioavailability for Today's API Challenges
- Unique Properties of Lipid-Based Formulations & Keys of Design and Testing
- Surface-facilitated Polymorphic Transformation (SurFPT)
- Spray-dried Technologies for Amorphous Stabilization of Poorly Soluble Compounds
- Fresh Research on Co-Crystals and their Impact on Bioavailability

**And much more!**

## Featuring Representation From:

| | | | | |
|---|---|---|---|---|
| Bristol-Myers Squibb | Astra Zeneca | Kashiv Pharma | Merck | University of Limerick |
| AbbVie | Capsugel | Sirius Analytical | Agere | University of the Sciences in Philadelphia |
| Novartis | Gattefosse | H. Lundbeck | Pion | Center for Pharmaceutical Physiscs |
| Ipsen BioScience | Quotient Clinical | | | |

### What people said about last year's Summit:

***"A fantastic meeting. I was interested in so many of the talks and I met several clients— current & potential."***

**- Principal Scientist, Aptuit SSCI**

***"Stronger speakers and more in depth coverage than others on the market."***

**- Director, Emerson Resources, Inc.**

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*Pharma Ed's Solubility & Bioavailability Summit 2014 is sponsored by:*

## Thursday, December 4, 2014

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

### *Re-conceptualizing Approaches to Solubility & Bioavailability*

**8:30** **Growth of Innovation in the Solubilization Space**
***Marshall Crew, Ph.D., President and CEO, Agere Pharmaceuticals, Inc.***

In recent years, solubilization technologies have taken center stage in the drug development field. In this talk, we present an in-depth analysis of the evolution of the pharmaceutical chemical space and the growth and adoption of various solubilization platforms designed to address the growing need for enhanced bioavailability. We will also present the industry-specific economic and social drivers for adoption of solubilization technologies and thoughts on how these platforms will evolve in the next decade.

### *Case Studies—Optimizing Your Formulations for New Product Development*

**9:10** **De-risking New Chemical Entities for Food- and pH-Sensitivity in Early Clinical Development**
***Neil Mathias, Senior Principal Scientist, Drug Product Science & Technology, Bristol-Myers Squibb***

Certain new chemical entities (NCE) show sensitivity to food-intake and/or elevated gastric pH induced by diseased-state, age or pH altering medicines (antacids, proton pump inhibitors or H2 antagonists). Both scenarios can potentially alter a drug's bioperformance resulting in compromised safety and efficacy, or increased pharmacokinetic variability. The risk that a development candidate exhibits food- or gastric pH-sensitivity can be assessed in preclinical studies or early clinical development through various experimental in vitro, in vivo and in silico tools. This talk will cover the use of these tools to gauge the probability and severity of the risk and illustrate through case studies their impact on formulation and clinical development decisions.

This content includes:

- The implementation of in vitro biorelevant dissolution and precipitation methods to screen for bioperformance risks for NCEs
- The use of In vivo and in silico methods to analyze underlying mechanisms
- Case studies highlighting strategies to mitigate the risk

**9:50** **Optimizing Formulation to Maximize Drug Absorption from Solution Formulations**
***Wenzhan Yang, Senior Scientist, Pharmaceutical Development, Astra Zeneca***

Solution formulations are not all made equal. The type of excipients as well as the level of excipients in solutions can have either positive or negative impact on oral absorption of drug molecules. In this presentation, considerations and evaluation tools in selecting and optimizing solution formulations in order to maximize the oral absorption of drug molecules will be illustrated with case studies.

**10:30** *Networking Break and Exhibit Viewing*

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**10:55** **Understanding Key Oral Absorption Parameters Preclinically by Ultilization of IntelliCap Capsule in Combination with Physiological-Based Absorption Modeling**
***Manuel Sanchez-Felix, Senior Fellow, Novartis Institute for BioMedical Research***

During the preclinical phase a wealth of in vivo data can be generated using different formulations (i.e., solution, suspensions, solid dispersion, etc.), doses, compound solid states (i.e., salts, amorphous form, polymorphs) while determining exposure in species that have different GI physiology. These variables are far greater than in the clinical phase and should in theory enable the development and validation of a reasonable absorption model that can be used to determine the key physicochemical parameters for the compound that impact exposure and contribute to the design of the drug product required to support human phase I studies. Un-

fortunately, there is a lack of confidence in the models developed during the preclinical phase. This presentation will decribed some recent in-vivo studies in dogs that Ultilized the IntelliCap Capsule in combination with physiological-based modeling that provided some new insights that can be used to help improve dog in-vivo studies for the design of formulations for humans.

11:35 **Studying the Interplay of Dissolution, Solubility and Permeability in Formulation Development**
***Konstantin Tsinman, Ph.D., Director, Science and Research, Pion Inc.***

Development strategy for insoluble compounds requires not only measurements of the solubility enhancement from formulations but also the assessment for the effect formulations having on permeability. An introduced dissolution-permeability (μFLUX) measurement platform allows simultaneous monitoring for both effects enabling in vitro setup for early in vivo predictive dissolution - absorption testing. Among other topics the presentation will highlight:

- Combining dissolution and permeability assays for better formulation design and more realistic IVIVC;
- Studying if solubility enhancement in the bio-relevant media leads to the same gain in the absorption and bioavailability;
- Understanding the supersaturation behavior of amorphous formulations in bio-relevant media;
- Monitoring in real time the free API fraction released from nanoparticles and predicting absorption enhancement from nanoparticle formulations;
- Developing of predictive in vitro method to monitor powder/formulation dissolution and concomitant precipitation processes in dynamically changing biorelevant media;
- Demonstrating case studies with poor soluble compounds.

12:15 *Networking Lunch and Exhibit Viewing*

## *Critical Issues— The Challenge of Peptides*

1:30 **Peptide Formulation Challenges and Beyond**
***Liping Zhou, Senior Scientist, Ipsen BioScience***

Peptide drugs are getting more and more attractive in the pharmaceutical industry due to their specificity and safety. Peptides are not small molecules, nor are they small proteins. Their special physiochemical properties make them even more challenging to formulate. It is essential to set up peptide specifications and implement them within the teams that are more accustomed to working with small molecules. The early assessment of both physical and chemical stability liabilities will ensure a successful transformation of a peptide drug substance into a peptide drug product.

Intravenous (IV) has been the main route of administration for peptide drugs; however alternative administration routes are of high interest due to the patient centricity, improved efficacy, decreased toxicity, and many other advantages. The first oral peptide drug product is now granted by the FDA and EMA earlier this year. A key for this success is the usage of permeability enhancer. The challenges and opportunities with permeability and solubility enhancement to improve bioavailability will also be discussed.

## *Methodology & Technology Spotlight— SurFPT, and Automated Instrumentation for Solubility*

2:15 **Surface-facilitated Polymorphic Transformation (SurFPT) Revealed through Molecular Dynamics Simulations and Physicochemical Characterization of Acetominophen**
***Yi Gao, Principal Research Scientist, AbbVie***

Rapid polymorphic conversion of acetaminophen (APAP) in solution, from metastable orthorhombic Form II to the stable monoclinic Form I, is well-known. The mechanism is believed to be solution-mediated phase transformation (SMPT) but with little experimental evidence. The present study was undertaken to understand this phenomenon from both thermodynamic and kinetic perspectives. Reliable apparent solubility of Form II was measured, for the first time, in 0.15 M aqueous NaCl solution at 37 °C. The solubility ratio of Form II over Form I, 1.27 ± 0.04, is quite low, which translates to a relatively low thermodynamic driving force for the conversion. Further solution crystallization experiments at supersaturation levels equal to or much greater than Form II solubility did not result in any crystallization in 10 days. Therefore, fast conversion is not possible through SMPT. To explore alternative mechanisms, molecular dynamics (MD) simulations were conducted to investigate the molecular level dissolution behavior and the solid state differences between the two polymorphs. The MD simulations reveal very different behavior. Form II exhibits a much higher rate of H-bond breakage, leading to the accumulation of a large number of disordered APAP molecules on the crystal surface. This thick disordered molecular layer provides a high local acetaminophen concentration which could be responsible for the fast crystallization of Form I. This was further supported by the observations made, using polarized light microscopy and powder X-ray diffractometry, when monitoring Form II crystals coming into contact with NaCl solution. We thus concluded that the hydrated surface layer is the "catalyst" for the facile phase conversion. This new mechanism, termed as SurFPT (surface-facilitated

phase transformation), is much more effective in promoting polymorphic transformation than the well-known SMPT.

**2:55** *Networking Break and Exhibit Viewing*

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**3:20** **Novel Automated Instrumentation for Biorelevant Dissolution and Solubility**
***Jon Mole, Executive Vice President, Sirius Analytical***

This presentation will reveal recent advances in automated instrumentation that achieve several benefits for the industry, including:

- In Vivo predictive dissolution methodology; biphasic dissolution to model GI dissolution and absorption.
- In Vitro methods show how APIs and formulations behave in presence of simulated gastric and intestinal pH and biorelevant media (FaSSIF and FeSSIF); the quest for IVIVC.
- Monitoring precipitation from supersaturated solutions and studying the effect of precipitation inhibitors.

**4:00** **Roundtable: Future Trends in Drug Formulation**
***Marshall Crew, Agere***
***Manuel Sanchez-Felix, Novartis***
***Liping Zhou, Ipsen***
***Neil Matthias, Bristol-Myers Squibb***

**4:40** *End of Day One*

## Friday, December 5, 2014

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

### *Research Spotlight—Bioavailability & Cocrystals*

**8:30** **The Impact of Pharmaceutical Cocrystals upon API Solubility and Bioavailability**
***Michael Zaworotko, Bernal Chair of Crystal Engineering Science Foundation of Ireland Research Professor***

This presentation will examine coformer libraries especially for ionic cocrystals, present some case studies of pharmaceutical cocrystals, and offer an overview of publically disclosed information on bioavailability of cocrystals. Key takeaways include:

- Coformer properties do not translate to cocrystals in a predictable manner
- Bioavailability studies should use standardized protocols
- Cocrystals can be used to modulate bioavailability of high solubility APIs and well as low solubility APIs

**9:10** **Enhancement of the Dissolution Rates of Poorly-Soluble Drug Substances through Cocrystal Formation**
***Harry G. Brittain, PhD, FRSC, Center for Pharmaceutical Physics***

A variety of approaches can be used to enhance the dissolution rate of a drug substance when needed, such as reduction in the particle size distribution of the drug, use of its amorphous (rather than crystalline) form, use of a suitable salt form, or the inclusion of complexing agents or surfactants as formulation additives. Quite often, an increase in the dissolution rate can achieve an increase in the overall bioavailability for drug substances that are readily absorbed by the body. Recently it is being shown that 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 drug substances.

In this lecture, the use of suitable cocrystallizing agents as means to improve the dissolution rate of various drug substances will be developed, and illustrated through several examples derived from recent research.

- What types of cocrystallization agents should be considered for the formation of fast-dissolving products?
- What are the fastest routes to prepare cocrystals, and how does one determine if a cocrystal product has formed?
- How much dissolution rate enhancement can be expected for a successful, fast-dissolving cocrystal product?

What formulation route would be most appropriate for such cocrystal products?

**9:50** *Networking Break and Exhibit Viewing*

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## *Formulation in Pre-Clinial and Clinical Contexts*

10:15 **Solubility Modulation Via Ion Pair Formation**
***Duk Soon Choi,***
***Vice President, Kashiv Pharma***

Many drug molecules are either weak base or weak acid. Bioavailability of such molecules can be modulated by proper salt formation or using ion pairing. Selection of counter ion is critical in obtaining the desired biopharmaceutical properties. In this presentation, the basics of ionic equilibria, salt form selection strategy in preclinical stage, and the use of various counter ions to modulate solubility and to control release profile will be presented.

10:55 **Real-time Flexibility to Change Formulation Platforms and Compositions in Early Clinical Trials**
***Kieran Crowley, Senior Director Translational Pharmaceutics, Quotient Clinical***

For molecules with challenging biopharmaceutic properties, including poor solubility, decisions on technology selection and quantitative compositions including dose often have to be made weeks or months prior to clinical dosing, meaning the ability for "within-study" responses to emerging safety, PK or PD data is extremely limited if not prohibitive. A Translational Pharmaceutics platform with integrated GMP manufacturing and clinical testing can circumvent these challenges as drug products are manufactured and dosed in a clinical study in timeframes as short as 24 hours. By taking advantage of approved formulation design spaces and bracketing strategies, the development team has "real-time" freedom to rapidly screen multiple technologies and then optimize product compositions based on human clinical data, starting with the very first-in-human (FIH) study. This approach can significantly de-risk development programs by avoiding complete dependence on in silico, in vitro or preclinical models to pre-define the formulation choice. The presentation will cover the following topics:

- The solubility challenge and options available to the development team
- Incorporating a formulation design space within a clinical program to give real-time flexibility in dose and composition of drug products
- Benefits and applications across the development life-cycle including first-in-human studies and downstream formulations
- Case studies - poorly soluble molecules, enabled formulations flexible CMC strategies and clinical protocols

11:35 **Key Formulation Considerations for Suspensions of Amorphous Dispersions to Support Clinical and Preclinical Studies**
***James D. Ormes, Associate Principal Scientist, Discovery Pharmaceutical Sciences, Merck***

Aqueous suspensions of amorphous dispersions are becoming a common tool to enhance oral exposures of poorly soluble compounds in the preclinical and early clinical setting. The preparation of an aqueous suspension of an amorphous dispersion provides a simple way to deliver amorphous dispersions in animal and early clinical studies.

Several critical design attributes need to be considered when preparing a suspension of an amorphous dispersion. First, the physical properties of the drug substance need to be considered, specifically the potential rate of crystallization of the drug substance in aqueous media. Second, the polymer type and drug loading of the amorphous dispersion can have an impact on formulation properties including physical stability and the maximum suspension concentration. Third, the processing parameters associated with manufacture can have an impact on the particle properties of the suspended particle. Lastly, the complex interplay between the amorphous dispersion, and the suspension vehicle components, such as pH-modifying agents, surfactants and polymers can affect the physical stability and bioperformance of the formulation.

12:15 ***Networking Lunch and Exhibit Viewing***

## *Spotlight on Lipid-Based Formulations and Excipient Phys-chem Properties*

1:25 **Unique Properties of Lipid-Based Formulations & Keys of Design and Testing**
***Eduardo Jule, Senior Manager, Formulation and Pharmaceutical Development, Capsugel***

A substantial number of drugs in development display poor water solubility, which often results in poor or variable bioavailability. Lipid based formulation is a technology platform primarily used for bioavailability enhancement of such poorly soluble drugs, though other benefits such as food effect or variability reduction have been evidenced. In addition, novel applications such as low dose/high potency delivery (through uniform solutions that further minimize exposure hazard) or abuse deterrence (through controlled substance suspension in non-crushable lipidic matrices) have been explored, and lipid multiparticulates have opened the gates to taste and odor masking, as well as controlled release.

Smart formulation and product development is achieved through:

- Technology Selection – simulation tools, 30+ years of experience in drug delivery, and 1,000+ compounds

formulated into spray-dried dispersion and lipid based formulations enable expert platform selection based on drug physical, chemical and biological parameters;

- Design – in-depth analysis of biopharmaceutical properties lead to clever excipient selection, tailored for each and every new drug; concept formulation identification is assisted by in silico tools such as the Lipid Expert System®, a proprietary database of experimentally generated phase diagrams;
- Develop – concepts identified through the expert system are developed, optimized into formulation candidates and tested using standardized LFCS guidelines to evaluate key performance criteria dispersion and digestion. These in vitro tests have proven effective predictive tools, enable selection of lead formulations, and help reduce an overreliance on in vivo testing.
- Manufacture – lipid based formulations can be conveniently scaled up and filled in soft capsules, or filled and sealed (through fusion or banding technologies) in 2-piece hard capsules in a variety of materials, sizes and colors. Liquid filled soft and hard capsules are reference dosage forms with extensive commercial precedence, which Capsugel strives to continuously optimize.

**2:05** 

## Lipid-Based Systems For Improving Oral Drug Delivery: Impact Of Excipient Phys-chem Properties

***Vincent Jannin, PharmD, PhD, HDR, Pharmaceutical Project Director, Gattefossé SAS, France***

Lipid-based systems can be effective drug delivery systems for poorly water-soluble drugs, provided they are designed with careful selection of the excipients, based on their role in the delivery system and in relation to the drug properties.

Key considerations in the selection of lipid-based excipients must be:

- The ability to dissolve the drug in the dosage form to avoid the solid-to-liquid phase transition process in the gastrointestinal tract.
- The interaction of lipid excipients and their metabolites with endogenous lipids to maintain the drug in solution within colloidal structures.
- The ability to modulate drug absorption by inhibition of intestinal efflux transporters, fluidization of the intestinal epithelium or promotion of lymphatic transport.

**2:45**

## Spray-dried Technologies for Amorphous Stabilization of Poorly Soluble Compounds

***Kamal Jonnalagadda, Associate Professor, University of the Sciences in Philadelphia***

Aqueous drug solubility & dissolution rate can play a critical role in the commercial feasibility of drugs belonging to the Biopharmaceutical Classification System (BCS) Class II. Both solubility and dissolution can be enhanced by the production of high energy amorphous particulate systems. Chemical purity is not compromised when trapping a drug in its amorphous state; however, stability and shelf-life can be affected significantly. Spray drying is a rapid way of preparing amorphous formulations. The process is relatively simple, practical, and scalable after process optimization using statistical designs. In this presentation, the use of spray drying will be discussed as a means of stabilizing specific BCS Class II drugs in the solid (amorphous) state.

**3:30** ***Close of Program***

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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!

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## VENUE INFORMATION:

| | |
|---|---|
| Dates: | December 4-5, 2014 |
| Venue: | The Racquet Club of Philadelphia |
| Venue Address: | 215 South 16th Street<br>Philadelphia, PA 19102 |
| Venue Phone: | (215) 735-1525 |
| Hotel Room Block: | Radisson Blu Warwick |
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