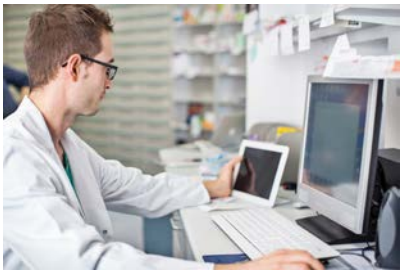
# Computer Modeling Workshop: In vitro and In vivo Studies October 23–25, 2017



# Speaker Biographies & Abstracts (listed alphabetically)

**Deirdre D'Arcy, Ph.D.**
Assistant Professor, Pharmacy
Trinity College of Dublin, School of Pharmacy and Pharmaceutical Studies
Dublin, Ireland

Dr. Deirdre D'Arcy qualified as a pharmacist in 1999. Following several years practising in hospital pharmacy she commenced research in pharmaceutical technology in 2002, completing her PhD "Use of computational fluid dynamics to investigate the relationship between hydrodynamics and dissolution" in Trinity College Dublin (TCD), Ireland, in 2007. She is currently Assistant Professor in Pharmaceutics and Pharmaceutical Technology in the School of Pharmacy and Pharmaceutical Sciences, TCD. Deirdre's research includes 2 main strands:

1: Application of computational modelling and simulation techniques in pharmacy and pharmaceutical technology. Her modelling and simulation in pharmaceutical technology has focussed on both dissolution-relevant hydrodynamic simulations and simulation of the dissolution process, using a dissolution simulation package developed in-house. This is complemented by a novel imaging tool developed in-house for dissolution visualisation, based on the principles of shadowgraph imaging.

2: Clinically relevant drug development and delivery to special populations: Deirdre is involved in several international collaborations focussed on development of dissolution and drug release testing methodologies which will support drug development for two specific populations: critically ill patients and neonates/infants. Aligned research activities include clinical pharmacokinetic studies in critically ill patients.

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**Presentation**
*Simulation and Comparison of Hydrodynamics in Compendial Dissolution Apparatuses Using Computational Fluid Dynamics (CFD)*
Tuesday, October 24, 2017, 1:00 – 1:30 p.m.

Computational fluid dynamics (CFD) is a term which covers a range of approaches used to model fluid dynamics. In this presentation, an overview of the principals of building and solving a CFD model are given. Hydrodynamic features, based on CFD models, in the paddle, basket and flow-through apparatuses are outlined, along with different modelling approaches used to generate the simulations. Specific applications such as the use of species transfer to model natural convection from dissolution in low velocity regions and the impact of the presence of a dosage form on local hydrodynamics, are described. Finally, some estimates of "in vivo hydrodynamics" are presented, illustrating the differences in in vivo and in vitro hydrodynamic environments.

**Ene I. Ette, MBA, Ph.D., FCP, FCCP, FAAPS**
President
Anoixis Corporation
Natick, MA

Dr. Ette has over 30 years of experience in academia, drug evaluation and regulation, and the pharmaceutical industry where he held several senior positions, including senior director/global head of the Clinical Pharmacology Department in Vertex Pharmaceuticals, Cambridge. He has Ph.D. (Clinical Pharmacology), MBA, M.S. (pharmacology), B.S. (pharmacology), and B.S.(pharmacy). He is a prolific author of 100 original articles in peer-reviewed journals, book chapters, numerous conference presentations and proceedings. Ette is on the editorial board of many clinical pharmacology/pharmacy journals as well as a referee for many biomedical and statistical journals. He is an invited speaker at many international clinical pharmacology/pharmacy, pharmaceutical science, and statistical meetings.

Dr. Ette is a fellow of American Colleges of Clinical Pharmacology and Clinical Pharmacy, and AAPS. He is the 2006 recipient of the American College of Clinical Pharmacy's Therapeutic Frontier Lecture Award for distinguished scientists; a special government employee of U.S. FDA (1998 to 2001, the 1999 American College of Clinical Pharmacy's prestigious Russell Miller Award, the 1996 Excellence in Review Science Award in CDER, FDA; and an adjunct applied pharmaceutical science professor at University of Rhode Island's College of Pharmacy. He was the major author of the FDA's unique *Guidance for Industry: Population Pharmacokinetics*, and senior editor of *Pharmacometrics: The science of Quantitative Pharmacology*. He is an inventor with several patents in hepatitis C therapeutics, and was the co-inventor of the shortened hepatitis C treatment duration with telaprevir. Presently, he is the president/CEO and chief scientific officer of Anoixis Corporation, a pharmacometrics service company.

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**Presentation**
*A Case for Bioequivalence Knowledge Creation*
Tuesday, October 24, 2017, 1:30 – 2:00 p.m.

**Susan Ewing**
Senior Scientist, Biopharmaceutics Group
Pfizer, Inc.
Hartford, CT

Susan Ewing is a Senior Scientist at Pfizer, Inc. in the Biopharmaceutics Group. Her current work focuses on designing dissolution experiments to enhance understanding of drug product performance. She is also involved in the development of the gCOAS oral absorption software through the Systems-based Pharmaceutics Alliance, which aims to deliver end-to-end digital design of drug products and their manufacturing processes. She has presented her work at several conferences. Her interest is to integrate experimental data, dissolution modeling and oral absorption modeling together to provide a holistic approach to drug product development. Susan also has experience in parenteral and transdermal formulation development, with publications in the area of solid state stability of freeze-dried materials. Susan holds a M.S. in Chemistry from University of Rhode Island and a B.S. in Chemistry from University of Delaware.

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**Presentation**
*Comparison Between Mechanistic Dissolution Modeling and Experimental Observations of Dissolution of Pharmaceuticals*
Tuesday, October 24, 2017, 10:30 – 11:00 a.m.

Mechanistic mathematical models are an integral part of predictive dissolution modeling and a mainstay in modeling of oral absorption of drugs. Understanding of the impact of the underlying assumptions of dissolution models is essential for comparison between predictions and experimental observations. Mechanistic models contain many simplifying assumptions (spherical particles, instant saturation at aqueous boundary layer, uniform hydrodynamics, log-normal particle size distributions, etc.) and thus may not be truly predictive of experimental data. Confidence in mechanistic dissolution modeling forms the basis for more complex models, such as for dissolution within oral absorption models, especially for BCS class II compounds where dissolution may be the rate limiting step in the absorption process.

This presentation investigates whether mechanistic dissolution models align with observations of experimental dissolution data of pharmaceuticals. Comparisons between model based predictions and experimental data are presented for API powder dissolution data and tablet dissolution data. Additionally insights on changes in particles size distributions during dissolution and SEM images of particles undergoing dissolution are presented. Opportunities to expand the capability of current mechanistic models are highlighted through comparison with experimental data.

**Humberto Ferraz, Ph.D.**
Professor, Department of Pharmacy
University of San Paulo
San Paulo, Brazil

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**Presentations**
*In silico Simulations of Intrinsic Dissolution*
Tuesday, October 24, 2017, 11:00 – 11:30 a.m.

**Nikoletta Fotaki, MSc, Ph.D.**
Reader (Assoc/Full Professor) in Pharmaceutics, Department of Pharmacy and Pharmacology
University of Bath
Bath, UK

Dr Nikoletta Fotaki is a UK registered Greek Pharmacist, with an MSc in Toxicology and a PhD in Biopharmaceutics-Pharmacokinetics. She participated in several research projects in the School of Pharmacy of the University of Athens and in Hoffman La Roche (USA) before her academic appointment at the University of Bath. She has also worked in the National Organisation for Medicines in Greece. Her expertise and research are focused on PBPK modeling, drug absorption, development of in vitro and in silico screening tools for predicting in vivo performance in normal and in special populations (i.e. paediatrics, disease states), biorelevant dissolution methods, dissolution imaging, development of IVIVC, formulation development, animal models for the prediction of absorption, methods for reduction/ replacement of animal experimentation, biowaivers, dissolution testing, design of BA/BE studies, pharmacokinetics. She is a reviewer and scientific advisor of several scientific journals, an Associate Editor for AAPS Open and member of the editorial board of Dissolution Technologies and DiePharmazie. She is an Associate Fellow of the Higher Education Academy and has been involved in the evaluation of several research proposals. She is also an Adjunct Associate Professor in the University of Waterloo (Canada) and in King's College (London, UK). She is a member of several scientific societies and the chair of the IVRDT Focus Group of AAPS. She has organised and moderated sessions and has been an invited speaker at several conferences and seminars.

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**Presentation**
*Challenges in Physiologically Based Pharmacokinetic Modeling for the Prediction of In vivo Performance After Oral Administration*
Wednesday, October 25, 2017, 9:30 – 10:00 a.m.

During drug development, many new compounds (around 40%) fail in the late clinical phases because of pharmacokinetic problems. Therefore, the successful prediction of human pharmacokinetics during pre-clinical research is of great importance. Physiologically based pharmacokinetic modeling (PBPK) approaches as a mechanistic quantitative platform for prediction of potential human absorption/bioavailability and for formulation development are used. The challenges in the development of PBPK models related to the type and quality of in vivo predictive in vitro data for the successful prediction of in vivo performance after oral administration will be discussed through the presentation of case studies.

**David Good, Ph.D.**
Senior Research Investigator
Bristol-Meyers Squibb
New Brunswick, NJ

David is a Principal Scientist at Bristol-Myers Squibb in the Drug Product Science and Technology (DPST) Biopharmaceutics group in New Brunswick, NJ. His professional interests include PBPK modeling and simulation to support formulation development from preclinical to commercial stages. He currently is responsible for in silico biopharmaceutics assessments of small molecules and therapeutic proteins. Additionally, David has material science research interests related to the rational design of supersaturating drug forms. David has been with BMS since 2010 and has held several roles in oral solid dosage form and biologics development including modeling and simulation. Prior to joining BMS David received his doctoral degree in Pharmaceutics from the University of Michigan.

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**Presentation**
*Applications of Modeling in Quantitative Biopharmaceutics to Bridge Formulation and Clinical Performance*
Monday, October 23, 2017, 10:30 – 11:00 a.m.

**Guenther Hochhaus, Ph.D.**
Professor, Pharmaceutics
University of Florida
Gainesville, FL

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**Presentation**
*Predicting Deposition and Absorption Rate for Orally Inhaled Products Based on Dissolution Data and a PK Simulation Model*
Tuesday, October 24, 2017, 3:30 – 4:00 p.m.

**Maziar Kakhi, Ph.D.**
Staff Fellow
U.S. Food and Drug Administration
Silver Spring, MD

Dr. Maziar Kakhi obtained his Bachelor's degree in mechanical engineering in 1990 and his Ph.D. in 1994 from Imperial College, University of London (UK). He has over eleven years of industrial experience in the automotive and process/chemical engineering sectors (based in Austria and Germany respectively), in areas related to combustion, complex fluid flow analysis, chemical reaction engineering and software development. Since 2005 he has been working at the FDA as a principal investigator focusing on the application of mathematical modeling techniques to the hydrodynamics in dissolution apparatuses, IVIVC modeling, and statistical sampling methods for large sample sizes. He has also worked with the Division of Biopharmaceutics as a primary reviewer.

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**Presentation**
*Advances and Challenges of Modeling and Simulation Studies in Regulatory Submissions*
Wednesday, October 25, 2017, 11:00 – 11:30 a.m.

Modeling and Simulation (M&S) studies are generally appearing with greater frequency in regulatory submissions. Their value in cost-saving, achieved by more informed decision making and reduction of otherwise redundant experiments during the drug development process, is clearly recognized. Due to advances in underlying mechanistic understanding and its incorporation into commercially available software tools, the scope of M&S' intended purpose (or context of use) in submissions is impacting regulatory decision more and more significantly.

This talk will briefly present the M&S landscape at the FDA and examine a select number of regulatory disciplines which are relevant to the themes of this Workshop. The focus will be primarily on the areas of application for M&S in regulatory submissions, typical deficiencies found therein and guidance documents intended to assist with their preparation and planning. Several regulatory case studies will be discussed which highlight typical contexts of use for M&S and the corresponding deficiencies found during the review process. It is hoped that by presenting these examples, industry stakeholders gain a more informed perspective of 'what to watch out for' when planning M&S as part of their drug development and submission processes.

**Edmund Kostewicz, Ph.D.**
Senior Scientist
Institute for Pharmaceutical Technology, Goethe University
Frankfurt, Germany

Edmund Kostewicz received a Bachelor of Science from the University of Adelaide (Australia) in 1992, Honors Degree from Flinders University (Australia) in 1993 and his PhD was awarded from the University of South Australia (Australia) in 1997. Following the completion of his PhD, he held a Postdoctoral position at the Institute of Pharmaceutical Technology at the Goethe University in Frankfurt for a period of 3 years. Thereafter, he held a position as Research Scientist within the Department of Biopharmaceutics at AstraZeneca (Mölndal) Sweden prior to taking on the position as Project Coordinator within the Centre for Drug Candidate Optimisation at Monash University in Melbourne, Australia. In 2009, Edmund accepted his current position back in the Institute of Pharmaceutical Technology at Goethe University in Germany.

Edmund's research interests lie in the use of different *in vitro* and *in vivo* tools for predicting oral drug absorption in humans. Not only has he worked extensively with the use of animal models (such as dog and swine) but also in the use of various *in vitro* tools to predict oral drug absorption in humans. He has a particular interest in evaluating gastrointestinal supersaturation and precipitation and the use of physiologically based pharmacokinetic modeling to predict oral drug absorption.

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**Presentation**
*Translating In vitro Data to In vivo Predictions – Is PBPK Modeling the Missing Link?*
Monday, October 23, 2017, 1:30 – 2:00 p.m.

As the prevalence of poorly-soluble compounds in contemporary drug discovery pipelines has increased considerably, formulation approaches that enhance supersaturation or minimize gastrointestinal (GI) precipitation within the GI environment are becoming more widely adopted for enhancing bioavailability. As the options for delivering poorly soluble drugs have become more innovative, predictive and reliable *in vitro* tools combined with appropriate physiology based pharmacokinetic (PBPK) modelling, is needed for the reliable evaluation of formulation behaviour.
Given that the supersaturation and precipitation behaviour of drugs in the GI tract can be influenced by a plethora of GI physiological, drug and formulation properties, it is experimentally challenging to capture all of GI factors in the *in vitro* model to evaluate supersaturation and precipitation. Consequently, an in vitro model capturing the "average" physiology, or in certain cases the extremes that can be anticipated, be utilized under controlled conditions.

Supersaturation and precipitation data for ketoconazole (KTZ) using Nizoral® 200mg tablets was collected using the transfer model[1] which utilizes an USPII dissolution apparatus containing two biorelevant compartments simulating the stomach and intestine. Data from the transfer model (including precipitation rate and degree of supersaturation) were coupled to a physiologically based pharmacokinetic (PBPK) model constructed using Stella® software. The disposition kinetics of KTZ were taken from the literature to predict the plasma profile in humans.

The results from the transfer model suggested the precipitation of KTZ in the duodenal compartment. These results were inconsistent with the previous finding by Psachoulias et al 2011[2], where KTZ only demonstrated very limited to no precipitation in the intestinal lumen in humans within the same dose range. By combining the results obtained from the transfer model into the PBPK model, where the high permeability of KTZ is considered, not only was there a high degree of similarity with the simulated profile to the actual *in vivo* plasma profile in humans, but the PBPK model also predicted the lack of precipitation occurring in the intestinal compartment. Thereby, whilst the *in vitro* model over predicted the amount of precipitation, PBPK modeling was required to more appropriately evaluate the significance of these *in vitro*

findings to the *in vivo* situation.

These findings suggest the importance of integrating *in vitro* data in a PBPK model to accurately predict their significance *in vivo*. In the design of an *in vitro* test simulating the gastrointestinal (GI) tract, whilst it is impossible to consider all of the GI physiological parameters (including regional differences and inter-subject variability), this physiologically variability including the permeability of the drug, needs to be considered by the PBPK model using a mechanistic framework for the handling of *in vitro* data to simulate the PK profile.


1. Ruff A, Fiolka T, Kostewicz E (2017) Eur. J. Pharm. Sci.42-55
2. Psachououlias D, Vertzoni M, Goumas K, Kaliras V, Beato S, Butler J, Reppas C (2011) Pharm Res 28 3145-3158

**Raimar Löbenberg, Ph.D.**
**USP Affiliation:**
Member, BDSHM and NBDS - General Chapters Joint Subcommittee

Professor, Pharmacy & Pharmaceutical Studies
University of Alberta
Alberta, Canada

Dr. Löbenberg holds a BSc in pharmacy from the Johannes Gutenberg-University in Mainz, Germany. He received his PhD in pharmaceutics from the Johann Wolfgang Goethe-University in Frankfurt in 1996. He joined the University of Alberta in 2000.

His research interests are in Biopharmaceutics to predict the oral performance of drugs and botanicals and inhalable nanoparticles to treat lung diseases like cancer or tuberculosis.

He is founder and director of the Drug Development and Innovation Centre at the University of Alberta.

He was president of the Canadian Society for Pharmaceutical Sciences 2014 & 2015

He is member of the United States Pharmacopeia Dietary Supplement Expert Committee.

He is Vice Chair of the Specialty Committee of Traditional Chinese Medicine in Pharmaceutics of the World Foundation of Chinese Medicine Science.

He is member of the Health Canada Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology.

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**Presentation**
*Clinical Relevant Product Specifications: Understanding In vitro and In vivo Data Using In silico Approaches*
Tuesday, October 24, 2017, 9:00 – 9:30 a.m.

**Margareth Marques, Ph.D.**
Principal Scientific Liaison
U.S. Pharmacopeia
Rockville, MD

Principal scientific liaison at the Science Department at the United States Pharmacopeia. Scientific liaison to the USP Expert Committee on Dosage Forms working on general chapters for performance tests (dissolution/drug release), and for some pharmaceutical dosage forms (products applied to the skin, ophthalmic products, etc.), responsible for the USP general chapters on osmolality, titrimetry, and UV/Vis spectrophotometry. Dr. Marques is also responsible for developing specifications for reagents, test solutions, buffer solutions, etc., used in USP – NF monographs. She manages the USP database on chromatographic columns, the USP database on dissolution methods and the USP web site on column equivalency. She has a B.Sc. and an M. Sc. both in Pharmacy by the University of Sao Paulo, Brazil. She has a Ph. D. in Analytical Chemistry by the State University of Campinas, Brazil. She managed analytical laboratories at Ciba-Geigy, Sandoz, and Astra.

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**Workshop Report/Closing Remarks**
Wednesday, October 25, 2017, 12:30 – 12:35 p.m.

**John Mauger, Ph.D.**
**USP Affiliation:**
Member, General Chapters-Dosage Forms Expert Committee

Professor, Pharmaceutical Chemistry
University of Utah
Salt Lake City, UT

John W. Mauger is currently professor of pharmaceutics and pharmaceutical chemistry at the University of Utah where he also serves as Associate Vice President for Health Sciences. His educational background includes a B.S. degree in pharmacy (Union University, Albany College of Pharmacy) and M.S. and Ph.D. degrees in pharmaceutics (University of Rhode Island). John's association with USP includes membership on expert committees and service as a member of the USP Board of Trustees where he also served as chair. His research interests include solubility properties of pharmaceutical active ingredients and the application of physicochemical hydrodynamic principles to standards related to dissolution testing. He is an elected fellow of the American Association for the Advancement of Science.

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**Presentation**
*USP Revision Process*
Monday, Octobert 23, 2017, 8:30 – 9:00 a.m.

**Amitava Mitra, Ph.D.**
Clinical Development
Sandoz, Inc.
Princeton, NJ

Amitava Mitra currently works in Clinical Development at Sandoz, he has previously worked in the Biopharmaceutics group at Merck & Co. Amitava graduated with a PhD in Pharmaceutical Sciences from University of Maryland, Baltimore in 2006.

Amitava's main research interests include pharmacokinetics, biopharmaceutics, PBPK modeling & simulation of oral and alternate drug delivery systems and IVIVC. He has interacted with global regulatory authorities on these topics. Amitava has published more than 30 research and review articles in peer-reviewed journals and has also authored book chapters on the topics of modeling & simulation, oral and alternate drug delivery, fixed dose combinations, and general biopharmaceutics. He has 19 podium presentations in national & international conferences. Amitava has been previously involved in cross-organization (industry, academia and regulatory) consortium, OrBiTo, which are related to development and improvement of analytical and computational tools.

Amitava is currently the Chair of AAPS Oral Absorption Focus Group, member of the AAPS Year-round Theme Task Force on Predictive Modeling and Clinical Pharmacology Track Leader on 2018 AAPS PharmSci 360 Scientific Programming Committee.

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***Presentation***
*Prediction of Formulation Bioperformance and Bioequivalence by Incorporating Dissolution Data in PBPK Models*
Monday, October 23, 2017, 3:00 – 3:30 p.m.

The Physiologically Based Pharmacokinetic (PBPK) Modeling is a widely-used *in silico* tool in the pharmaceutical industry to predict oral drug absorption rate and extent, to simulate clinical pharmacokinetic profiles and also to support Regulatory submissions. Such models can provide valuable insights to address various aspects of challenges in the biopharmaceutics area. In vitro dissolution data are key inputs in these models to guide formulations development and also to assess if formulations would be bioequivalent. In this session, selected cases of the application of PBPK modeling will be discussed with the focus on guiding formulation development efforts, including drug-drug interactions (DDIs) with acid-reducing agents, evaluation of API PSD on formulation bioperformance of a BCS class-2 drug, solid dispersion formulation bioperformance, prediction of bioequivalence for IR and CR formulations.

**Jim Mullin**
Principal Scientist
Simulations-Plus, Inc.
Lancaster, CA

James Mullin is a Principal Scientist and Product Manager of DDDPlus and MembranePlus™, two in silico software tools to predict in vitro dissolution and permeability & clearance mechanisms/kinetics. James has 13 years of experience in computational modeling in the pharmaceutical industry, spending 10 years at Bend Research before joining Simulations Plus in 2014. In his most recent research, James developed models for the Artificial Stomach and Duodenum and Biphasic dissolution test, as well as, active transport and metabolism in suspended, plated, and sandwich hepatocytes. In addition to the development of computational models, James also contributes to several FDA & EMA collaboration grants for Simulations Plus and trains scientists on the use of mechanistic modeling & simulation technology.

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**Presentation**
*Computer Modeling and Biphasic Dissolution*
Wednesday, October 25, 2017, 11:30 a.m. – 12:00 p.m.

**Jasmina Novakovic, Ph.D.**
Scientific Leader
Apotex, Inc.
Toronto, Ontario, Canada

Jasmina is a pharmacist by training, holding PhD degrees in Analytical Chemistry (Charles University, Prague) and Pharmaceutical Chemistry (University of Belgrade, Serbia). Since 2007, she has been a Scientific Leader at Apotex Inc. (Toronto, Canada), covering multidisciplinary areas of research with a special focus on modeling and simulations to support product development and regulatory approval. Jasmina actively contributes to the scientific community by delivering presentations/webinars, reviewing and commenting on regulatory guidance documents, as well as by serving as a USP expert committee member since 2015. Prior to joining Apotex, Jasmina was a Post-Doctoral Fellow (2000-2003) and a Research Associate (2004-2007) at the Faculty of Pharmacy, University of Toronto.

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**Presentation**
*In Silico Modeling and Simulations to Support Development and Bioequivalence Assessment of Generic Drug Product*
Wednesday, October 25, 2017, 8:30 – 9:00 a.m.

A generic drug product is defined as comparable to a Reference Listed Drug (RLD) product in dosage form, strength, route of administration, quality and performance characteristics, as well as in its intended use.

The objective for a generic product development is to design a formulation/process that results in the performance equivalent to that of the reference (innovative) product. For drugs formulated as solid oral dosage forms, *in vitro* dissolution/release testing with *in vivo* predictive power plays a crucial role towards achieving this objective.

At the development stage, *in silico* modeling is a tool to bridge the gap between *in vivo* absorption/dissolution profile and *in vitro* dissolution/release target performance (*in vivo-in silico-in vitro*), and to predict *in vivo* performance for the test product against the target (*in vitro-in silico-in vivo*).

The links between *in vivo-in silico-in vitro* parameters/processes are bi-directional, with *in silico* modeling and simulations playing a central role. A general methodology for linking *in vivo-in silico-in vitro* processes comprises modeling to (a) reveal *in vivo* absorption profile of the RLD, (b) identify *in vitro* dissolution/release profile reflective of *in vivo* absorption and (c) suggest dissolution test conditions with *in vivo* predictive potential. Once the generic drug product is available for testing, *in vitro-in silico-in vivo* parameters/processes are linked to assess bioequivalence for the generic drug product against the target prior to pilot bio-study by incorporating *in vitro* dissolution/release profiles into *in silico* modeling to simulate *in vivo* PK profiles for the formulations of interest.

The applicability of the bi-directional interplay between *in vivo- in silico- in vitro* parameters/processes is illustrated by providing examples of a BCS 2 drug formulated as an immediate release (IR) capsule and a BCS 1 drug formulated as an extended release tablet.

**Devendra Pade, Ph.D.**
Senior Research Scientist
Simcyp Limited (a Certara Company), Blades Enterprise Center
Sheffield, UK

Devendra Pade, PhD is a Senior Research Scientist at Simcyp (a Certara Company). He received his PhD in Prediction of Oral Drug Absorption and Pre-Clinical Pharmacokinetics from The University of Texas at Austin under the guidance of Dr. Salomon Stavchansky. Since joining Simcyp in 2009, he has worked on various projects in PBPK modelling with a major interest in oral drug absorption and development of animal PBPK models. He has been a project lead for multiple Simcyp projects including simulation of pharmacokinetics in Bariatric Surgery patients. Prior to joining Simcyp, Deven has also worked with Watson Pharmaceuticals (now Actavis/Allergan) on orally inhaled respiratory drug products.

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**Presentation**
*Mechanistic Oral Absorption & PBPK Modelling to Understand Formulation Behavior & Preclinical Pharmacokinetics*
Monday, October 23, 2017, 2:30 – 3:00 p.m.

**Alan Parr, Ph.D.**
**USP Affiliation:**
Vice Chair, Compounding Expert Committee

Managing Member
BioCeutics, LLC
Emerald Isle, NC

Dr. Parr has worked in the field of Pharmaceutical Sciences for 33 years. This time period covers work done while in graduate schools and post-doc (work with many pharmaceutical companies in which I employed novel methods to radiolabel pharmaceutical dosage forms and drug delivery systems for scintigraphic imaging studies. I was responsible for designing and executing pharmacokinetic studies that were designed to better understand the in vivo behavior of dosage forms and what formulation and GI factors affected the oral bioavailability of drugs) and well as working in large pharma (Glaxo, GlaxoWellcome and GlaxoSmithKline). Dr. Parr's roles in big pharma including included formulation scientist, formulation manager, and Director of Biopharmaceutics and responsibilities ranged from development of formulations from the early development phase all the way through to the scale up of commercial size batches for the marketplace. Specific activities during this time period included physical property characterization, formulation screening, formulation development, manufacture of clinical supplies, transfer of product to production and overall project management. He was intimately involved with the creation, review and submission of regulatory documents to the US Food and Drug Administration, including Investigational New Drug (IND) applications, New Drug Applications (NDA) and Marketing Authorization Applications (MAA), as well as foreign filings. Since June of 2015 Dr. Parr as served as consultant to numerous small pharmaceutical companies and has serve as principle investor for 2 NIH grants where his primary responsibility was to file an IND for an NCE that was being developed. Dr. Parr earned his Pharm.D. degree from the University of Nebraska College of Pharmacy and his Ph.D. from the University of Kentucky College of Pharmacy.

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**Presentation**
*Bridging In silico with In vivo for Better Drug Development*
Monday, October 23, 2017, 9:00 – 9:30 a.m.

In the early years pharmaceutical scientists considered the gastrointestinal (GI) tract as somewhat of a black box. They put their formulations into it and got bioavailability data out of it, but in many cases they could not explain their data. Early attempts to explain unusual results focused on ways to affect the physical chemical properties (e.g., reduction of particle size, amorphous versus crystalline drug) of the drug to improve its oral bioavailability. In many cases improvements were observed, but the reason for the improvement was not immediately known. In recent years an extensive amount of work has been done to better understand the GI tract and how formulations behave within the GI tract by using various In vivo tools (e.g., Gamma Scintigraphy, Regional absorption studies, etc.) The application of these tools generates additional knowledge giving the pharmaceutical scientist a better understanding of how their drug and delivery systems work In vivo.

Additionally, modeling tools have been developed to better understand observed PK results and predict future PK results. These models have shown great promise and their application in the development process continues to be expanded. As with In vivo studies, PK modeling has room for improvement to derive the maximum benefit on product development.
This presentation will cover the impact of combining In vivo tools with modeling tools to lead to more efficient drug development process.

**James Polli, Ph.D.**
Professor
University of Maryland School of Pharmacy
Baltimore, MD

Dr. James E. Polli is Professor and Ralph F. Shangraw/Noxell Endowed Professor in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy. He received a B.S. in Pharmacy from the Philadelphia College of Pharmacy and Science and a Ph.D. (pharmaceutics) from the University of Michigan. He is also co-Director of the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI; www.cersi.umd.edu), an FDA-funded collaborative agreement with the Agency, and Director of the online MS in Regulatory Science program (www.pharmacy.umaryland.edu/regulatoryscience). His two main research interests are 1) maximizing oral bioavailability through formulation and chemical approaches and 2) developing public quality standards for oral dosage forms. He has published in the areas of dissolution, drug intestinal permeability, transporter substrate requirements, prodrug design, oral bioavailability, in vitro - in vivo correlation, and bioequivalence. Dr. Polli is a fellow of the American Association of Pharmaceutical Scientists, an Editorial Board member of several journals, an Editor of Pharmaceutical Research, and a member of the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee. He teaches professional pharmacy students and graduate students, and has served as advisor to 19 Ph.D. graduates.

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**Presentation**
*Oral IVIVC Simulation*
Tuesday, October 24, 2017, 8:30 – 9:00 a.m.

**Dennis Sandell, Ph.D.**
**USP Affiliation:**
Member, General Chapters-Statistics Expert Committee

Director
S5 Consulting
Lund, Sweden

Dr. Sandell holds a Ph.D. in Mathematical Statistics (1990, U. of Lund, Sweden). He has worked for AstraZeneca, Amgen and Siegfried Pharma Development GmbH in both specialist and management roles and is currently an Adjunct Professor at the Department of Pharmaceutics, University of Florida.

Dr. Sandell is a world leading expert in the area of CMC statistics, especially related to development, registration and commercial manufacture of inhalation products. He has a special interest in and long experience of in-vitro bioequivalence evaluations as well as correlating in-vitro data with results from pharmacokinetic studies (IVIVC). He has deep experiences from of a wide range of innovator and generic DPIs, MDIs, nasal sprays and nebulization products, as well as different add-on devices.

Dr. Sandell has 80 publications and frequently presents at international conferences. He has participated in different industry collaborations such as IPAC-RS, EPAG, PQRI and PhRMA and is a currently a member of the USP Statistics Expert Committee, chair of the USP Large N Expert Panel and member of the USP Data Analysis Subcommittee.

In May 2010 Dr. Sandell started the consulting firm S5 Consulting, providing CMC statistical support, general inhalation development advice, regulatory writing, due diligence assistance and acts as an expert witness.

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**Presentation**
*Development of a Multivariate Model for Simulation of Cascade Impactor Data*
Tuesday, October 24, 2017, 3:00 – 3:30 p.m.

**David C. Sperry, Ph.D.**
Research Advisor
Eli Lilly and Company
Indianapolis, IN

Dr. Sperry is a Research Advisor in Small Molecule Drug Development at Lilly Research Laboratories. He obtained a B.S. degree in chemistry from Indiana University, Bloomington, IN and a Ph.D. degree in chemistry from the University of Rochester, Rochester, NY. After receiving his degree, he took a postdoctoral research scientist position at Pharmacia & Upjohn where he developed an Artificial Stomach Duodenum model and studied its utility in drug development. Shortly thereafter, he accepted a research scientist position at Pharmacia (later Pfizer), working in the area of in vitro methods and biopharmaceutics. He then moved to Bausch and Lomb where he developed commercial ophthalmic formulations for late stage molecules. In 2007, Dr. Sperry joined Lilly Research Laboratories, where he created a group focusing on in vitro drug product performance techniques and predictions of in vivo performance. In 2013, Dr. Sperry joined a computational modeling group at Lilly. He now supports product development by using existing and creating new models to predict product performance and oral absorption of small molecule drug formulations.

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**Presentation**
*Predicting Product Performance: Integrated In vitro Dissolution and In vivo Absorption Modeling*
Monday, October 23, 2017, 11:00 – 11:30 a.m.

Predicting in vivo product performance has, for many years, relied heavily on in vitro methodology. As recently as 15 years ago, in vitro tests would often be used - on their own - to predict the performance of formulations. Since this time, the field has evolved significantly, with the development and wide-spread use of mechanistic models of drug release, dissolution, absorption and pharmacokinetics. Now, the state-of-the-art product development paradigm utilizes both in vitro data as well as computational models of product performance and absorption to determine the impact of formulation and material properties on in vivo performance. Several commercial tools are available that are in broad use to perform these modeling tasks. But, custom models that are built in-house are still often employed when needed.

In this presentation, we will cover several approaches and examples that utilize both in vitro tools as well as in silico models. The models are used to enable a better understanding of in vitro results: predict in vitro dissolution and understand mechanisms of in vitro release. The models are also used to predict in vivo absorption and pharmacokinetic profiles. In some cases, the models are ultimately used to produce design criteria or justify specifications. The models presented will include both commercial products as well as custom models.

**David Turner, Ph.D.**
Principal Scientist
Simcyp Limited (a Certara Company)
Sheffield, UK

Dr. Turner is a Principle Scientist at Simcyp Limited located in Sheffield, UK with lead responsibility for the oral absorption modelling team. His first degree was in Biochemistry after which he obtained an MSc in Computer Science. He obtained his PhD in 1996 from Sheffield University in Cheminformatics and QSAR Modelling. Subsequently, he worked as a Postdoctoral Researcher in the same group for several years developing spectral descriptors for QSAR modeling and molecular similarity scoring. From 1999 he spent three years in the Computational Drug Discovery Group at Synt:em SA, a biopharmaceutical company based in Nîmes, France, involved mainly in early discovery virtual screening projects. He joined Simcyp Limited in late 2004 where his main responsibilities currently lie with the physico-chemical aspects of the development of the Simcyp Population-based ADME Simulator particularly the PBPK oral absorption and tissue distribution models and QSAR model development. He is currently Principal Investigator on a two-year US FDA funded grant for the development of PBPK Modelling tools for handling Supersaturating Drug Products.

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**Presentation**

*Population-Based PBPK and IVIV_E of Dissolution and Precipitation: Current Status and What Next?*

Wednesday, October 25, 2017, 10:30 – 11:00 a.m.

There has and continues to be a significant rise in the use of Physiologically-based pharmacokinetic (PBPK) modelling tools within the pharmaceutical industry, not only as an aid for internal decision making but also as part of regulatory submissions. Population PBPK involves consideration, not only of an average representative subject, but by design is able to anticipate population variability. A key component of extrapolating to different individuals is the use of mechanistic models able to capture the impact of the known variability of physiological and anatomical system parameters that, for the gut, includes luminal pH and bile salts, buffer capacity, gastric emptying and so on. The presentation focusses on modelling tools relevant to biopharmaceutics that can be used to extract from and/or confirm parameters from the modelling of appropriate *in vitro* experiments, including USP 2 paddle dissolution and dynamic transfer experiments for handling supersaturating drugs. This process has been dubbed *in vitro-in vivo* extrapolation (IVIV_E) of dissolution and precipitation. Consideration is paid to some of the limitations and assumptions of these approaches.

**Maria Vertzoni, Ph.D.**
Faculty of Pharmacy
National and Kapodistrian University of Athens
Athens, Greece

Dr. Maria Vertzoni has been recently elected as Assistant Professor of Pharmaceutical Technology and Biopharmaceutics at the Department of Pharmacy, National and Kapodistrian University of Athens (UoA), Greece. She received her Bachelor in Chemistry from UoA in 1994, her Master of Science in Analytical Chemistry in 1999, her Ph.D in Pharmaceutical Sciences in 2004 from the same University and her Master of Science in Medical and Pharmaceutical Statistics from Athens University of Economics and Business in 2016. Dr Vertzoni teaches Pharmaceutical Analysis to the graduate students of the Department of Pharmacy. Her research interests focus on the physicochemical characterization of intraluminal environment, oral absorption characteristics of highly lipophilic compounds and analysis of drugs in biorelevant media and in biological fluids. She is coauthor of two book chapters and more than 60 peer reviewed papers.

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**Presentation**
*In vitro Evaluation of Dissolution and PBPK Modeling to Understand the Impact of Absorption of High Dose Low Solubility Drugs from the Lower Intestine*
Tuesday, October 24, 2017, 9:30 – 10:00 a.m.

Dissolution in the lower intestine is of interest in cases of orally administered active pharmaceutical ingredients (APIs) with extended and/or delayed absorption kinetics. Relevant scenarios include immediate release products of highly dosed APIs and modified release drug products. In recent years our knowledge on the conditions prevailing in the lower intestine has been increased and the evaluation of colonic absorption using middle – out PBPK modelling approaches has been possible. For passively absorbed APIs, colonic absorption could be based mostly on drug dissolution characteristics in the region. Recently, media simulating the contents of lower intestine i.e. distal ileum and proximal colon under conditions simulating the bioavailability and bioequivalence studies in the fasted and in the fed states and in vitro two-stage single-compartment model for evaluating dissolution characteristics in the lower intestine have been proposed. This approach evaluates the impact of dilution of ileal contents as they empty into the proximal colon and the potential precipitation of weak acids, due to the decrease of the pH in the proximal colon, particularly apparent in the fed state. To evaluate the importance of specific luminal characteristics within a specific region of intestinal lumen various levels of simulation of luminal composition can be considered. For example, Level I biorelevant media reflect luminal pH and buffer capacity whereas Level II biorelevant media take additionally into account luminal bile components and osmolality. In addition, the importance of solid particles [i.e. of Level III simulation] was evaluated. For the evaluation of the impact of passive absorption from the lower intestine on the overall absorption process, in vitro data collected under conditions simulating the environment in the upper gastrointestinal lumen and under the conditions simulating the environment in the lower intestinal lumen could be coupled with physiologically based oral absorption modelling to simulate the overall drug absorption process. The impact of the absorption from the lower intestine could then be evaluated by eliminating the relevant process from the model.

**Herbert Wachtel, Ph.D.**
Senior Principal Scientist
Boehringer Ingelheim
Frankfurt, Germany

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**Presentation**
*Combining in vitro Mouth-Throat Deposition Measurements, Cascade Impactor Data and Computational Fluid Dynamics (CFD) Simulations*
Tuesday, October 24, 2017, 4:00 – 4:30 p.m.

Purpose. Computational fluid dynamic simulations are accessible to an increasing number of users. Combined with growing computer power, quickly evolving commercial programs (e.g. ANSYS Fluent) and/or public domain programs can speed up inhaler device development. However, input data for successful simulations is required. A viable combination with bench testing is proposed, embracing inhalers under test, mouth throat models, breathing simulator, cascade impactor (e.g. NGI) and/or filter. The quantitative determination of the amount of active pharmaceutical ingredient is the basis for any modeling of dose to the lung or even regional deposition predictions.

Research methodology. The critical step of aerosol generation and the effects of the mouth throat passage are captured using bench testing. For that purpose, flow profiles have been acquired which are reproduced using a lung simulator. At the throat outlet either a filter or a mixing inlet with cascade impactor is situated. Thus the modeled dose to the lung and its size distribution can be determined at the outlet of the mouth throat model. A range of mouth throat models (e.g. Alberta throat) and age-dependent as well as disease-dependent flow profiles are available for specific predictions. At the outlet of the throat the experimental data are fed into computational fluid dynamic (CFD) simulations. The required throat and lung geometries were either built according to literature data or segmented from CT or MRT data.

Results and benefits. The combination of bench testing and CFD results in a better understanding of inhaler operation and fate of the generated aerosol in the lung. While air flow can be captured in the device at high precision, modeling the aerosol generation still is demanding and requires future research. For that reason bench testing combining the device under test and a suitable mouth throat model provides faster access to quantitative data. This holds for liquid and dry powder inhalers. They face challenges in the numerical descriptions of droplet break-up and the interaction of powder particles, respectively. Applying CFD deposition in the mouth throat region seems to strongly depend on the turbulence model selected. Therefore the experimental determination is favored. Considering lung deposition, alternatives to radio labelling studies are rare. The first few branching generations may be replicated in vitro, however CFD can in principle calculate the particle's fate until landing. Performing such modeling gives a visual impression of the limitations of today's computer tomography in humans. In addition the required assumptions on boundary conditions in the lung are clarified. In spite of their limitations the advantage of this modeling approach is the reproducibility which can be used for comparison and optimization of inhalers without need for patients or healthy volunteers.

**Hu Wang, Ph.D.**
**USP Affiliation:**
Member, Use of Enzymes in the Dissolution Testing of Gelatin Capsules Expert Panel

Senior Scientist
Merck
Rahway, NJ

Dr. Hu Wang is a senior scientist in Merck & Co. and a USP expert panel member. Supporting Merck's new product launch, from solid dosages to oral suspensions, he has been actively involved in *in vitro* and *in vivo* modeling and simulations. Applying the state-of-the-art software available, he is currently expanding the use of M&S specifically for pediatric anti-bacterial agents. Dr. Wang publishes in the area of Nrf2 signal transduction, bioanalysis, pharmacokinetics/pharmacodynamics, and druggability. He obtained his Ph.D. in Pharmaceutics from Rutgers, The State University of New Jersey.

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**Presentation**
*Dissolving a Drug In vitro and In vivo via In silico-A Case Study*
Monday, October 23, 2017, 1:00 – 1:30 p.m.

Modeling and simulations turned out to be an effective and cost-saving tool in the drug development in various disciplines. This presentation showcased a study by establishing an in silico model for in vitro dissolution testing and then applying the model for the prediction. The study is then expanded to the in vivo area in establishing a population pharmacokinetic model, optimizing, and qualifying the model for larger scale clinical trials. The study concludes with the similarities and contracts of the model buildings in these two different disciplines.

**Jane Weitzel**
**USP Affiliation:**
Member, General Chapters-Statistics Expert Committee

Independent Consultant
Manitoba, Canada

Jane Weitzel has been working in analytical chemistry for over 40 years for pharmaceutical and mining companies. She is currently a consultant specialising in laboratory management systems and ISO/IEC 17025, an auditor, and an educator. Jane has applied Quality Systems and statistical techniques, including the evaluation and use of measurement uncertainty, in a wide variety of technical and scientific businesses. She has obtained the American Society for Quality Certification for both Quality Engineer and Quality Manager.

For the 2010 – 2015 cycle, Jane was a member of the USP Reference Standards committee and Expert Panel on Method Validation and Verification. In 2014 she was pointed to the Chinese National Drug Reference Standards Committee and attended their inaugural meeting in Beijing. Jane is a member of the USP's Expert Committee on Statistics and the Expert Panel on Method Validation and Verification For the 2015 – 2020 cycle.

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**Presentation**
*Modeling and Measurement Uncertainty*
Monday, October 23, 2017, 9:30 – 10:00 a.m.

**Ryan Yamagata**
**USP Affiliation:**
Member, Bioassay General Chapter Expert Panel

Principal Statistician
GSK Vaccines
Rockville, MD

Ryan Yamagata is the Principal Statistician in Technical R&D, CMC Statistical Sciences for GSK Vaccines in Rockville, MD. Prior to joining GSK, Ryan was a consultant working with small biotech and medical device companies, and has also worked for MedImmune/Astra Zeneca, Shire, and Wyeth. He has over 15 years of experience supporting preclinical and clinical studies, translational science, and CMC activities (formulation, process and method design space characterization and optimization, process and method validation and transfer, stability). Ryan has an MS in Statistics from Brigham Young University and a BS in Mathematics from BYU-Hawaii.

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**Presentation**
*Using In silico Simulation to Aid Development of In-vivo Assay for Vaccine Potency Assessment*
Wednesday, October 25, 2017, 9:00 – 9:30 a.m.

The development and optimization of an analytical method can be a complex and time consuming process. The complexity is compounded when developing an in-vivo immunogenicity potency assay for a multi-component vaccine. This presentation reviews how experimental results can be simulated in-silico to assess method performance, determine assay acceptance criteria, and optimize the mathematical modeling.

**Xinyuan (Susie) Zhang, Ph.D.**
Pharmacologist, Office of Clinical Pharmacology (OCP), CDER
U.S. Food & Drug Administration
Silver Spring, MD

Dr. Xinyuan (Susie) Zhang currently is a pharmacologist in the Office of Clinical Pharmacology (OCP) in CDER. Prior to joining OCP, Dr. Zhang was a Scientific Lead for absorption modeling in the Office of Research and Standards (ORS)/ Office of Generic Drugs (OGD)/ CDER, where she was a key contributor to establishing the quantitative methods and modeling program. She has published numerous research and review articles focusing on physiologically based pharmacokinetic and absorption modeling and simulation and its application in regulatory sciences. She received her Ph.D. from the University of Michigan, Ann Arbor.

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**Presentation**
*Physiologically Based Pharmacokinetic and Absorption Modeling and Simulation–Case Studies*
Tuesday, October 24, 2017, 2:00 – 2:30 p.m.

Physiologically based pharmacokinetic (PBPK) and absorption modeling and simulation have been used extensively recently in drug product development and regulatory science. This presentation will provide a brief overview of physiologically based pharmacokinetic and absorption modeling and simulation and its application in bioequivalence (BE) assessment followed by two case examples. In the first case example, the established models were used to evaluate BE in special populations, potential risks associated with wide dissolution specification, and the sensitivity of pharmacokinetic (PK) metrics to the change of critical formulation factors. In the second case example, PBPK absorption modeling and simulation were conducted to systemically evaluate the in vivo relevance of in vitro dissolution for osmotic pump extended release drug products, and explore the impact of changes in major physiological parameters, and in vivo release on PK metrics.