

USP Workshops

→ Exploring the science of drug absorption

October 15-16, 2018

Understanding oral drug absorption and formulation behavior via in silico, in vitro and translational strategies.



Final Agenda

DAY ONE: Monday, October 15, 2018

Translational Strategies: Human-Canine Oral Bioavailability Predictions

Moderator: Albert E. Jergens, DVM, Ph.D., DACVIM, *Professor & Associate Chair for Research and Graduate Studies, College of Veterinary Medicine, Iowa State University*

- 8:00 – 8:45 a.m.** **Registration & Coffee**
- 8:45 – 9:00 a.m.** **Introduction to the Two One-Day Workshops: Why These Topics?**
Marilyn Martinez, Ph.D., *Senior Scientist, U.S. Food & Drug Administration, Center for Veterinary Medicine*
- 9:00 – 9:30 a.m.** **Characterization of GI Fluids Content, Viscosity, Volume in Dogs and Humans: Comparison Under Fasted and Fed Conditions**
Christos Reppas, Ph.D., *Department of Pharmacy, National and Kapodistrian University of Athens*
- 9:30 – 10:00 a.m.** **Examples of Dissolution Differences When Using Canine vs Human Biorelevant Media: Working to Optimize In Vitro Methods That Support the Translation of In Vivo Oral Drug Product Dissolution in Dogs vs Humans**
Maria Vertzoni, Ph.D., *Department of Pharmacy, National and Kapodistrian University of Athens*
- 10:00 – 10:30 a.m.** **Morning Break**
- 10:30 – 11:10 a.m.** **In Silico Modeling of Oral Drug Absorption in Dogs vs Humans: Differences in GI Tract Physiology of Humans and Dogs (intestinal transporters, gut metabolism, absorptive surface area)**
Devendra Pade, Ph.D., *Senior Research Scientist, Certara UK Limited (Simcyp Division), Blades Enterprise Center*
- 11:10 – 11:30 a.m.** **ECCS as a Tool for Facilitating Interspecies Extrapolation**
Ayman El-Kattan, Ph.D., *Senior Director & DMPK Head, IFM Therapeutics*
- 11:30 a.m. – 12:10 p.m.** **Use of In Silico Mechanistic Models to Support Interspecies Extrapolation of Oral Bioavailability and Formulation Optimization: Model Example Using GastroPlus**
Viera Lukacova, Ph.D., *Director, Simulation Sciences, Simulations Plus, Inc.*
- 12:10 – 12:30 p.m.** **Q&A/Morning Panel Discussion**

END OF WEBEX PROGRAMMING

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Moderator: Albert E. Jergens, DVM, Ph.D., DACVIM, *Professor & Associate Chair for Research and Graduate Studies, College of Veterinary Medicine, Iowa State University*

12:30 – 1:30 p.m.

Lunch

1:30 – 2:00 p.m.

Comparison of Permeability with Data Generated in Ussing Chamber (human, dog, rat), Intestinal Perfusion, MDCK and Caco-2 Cells
Sid Bhoopathy, Ph.D., *Chief Operating Officer, Absorption Systems*

2:00 – 2:30 p.m.

Canine Organoids for Drug Permeability Testing: Moving Beyond Caco-2 Cell Systems
Jonathan Mochel, DVM, MSc, Ph.D., *Associate Professor, College of Veterinary Medicine, Iowa State University*

2:30 – 3:00 p.m.

Use of the Dog to Predict Supersaturation and Its Impact on Drug Absorption
Sara Carlert, Ph.D., *Associate Principal Scientist, AstraZeneca*

3:00 – 3:30 p.m.

Afternoon Break

3:30 – 4:00 p.m.

Use of Flux Measurements in Lieu of In Vitro Dissolution to Assess the Complex Interplay Between Solubility, Permeability and Formulation Effects
Konstantin Tsinman, Ph.D., *Chief Scientific Officer, Pion, Inc.*

4:00 – 4:30 p.m.

Use of Dogs to Support Formulation Development for Large Molecule Oral Drug Delivery
Patrick Sinko, Ph.D., RPh, *Distinguished Professor of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey*

4:30 – 4:50 p.m.

Q&A/Moderated Discussion

4:50 – 5:30 p.m.

Networking Reception

5:30 p.m.

Day One Concludes

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DAY TWO: Tuesday, October 16, 2018

In Vitro and In Silico BE Assessments: Opportunities, Strengths and Challenges

Moderator: Ajaz Hussain, Ph.D., *President, National Institute for Pharmaceutical Technology and Education (NIPTE)*

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|--------------------------------|---|
| 8:00 – 8:30 a.m. | Registration & Coffee |
| 8:30 – 9:00 a.m. | Aiming for the Future: Exploring Possibilities
Marilyn Martinez, Ph.D., <i>Senior Scientist, U.S. Food & Drug Administration, Center for Veterinary Medicine</i> |
| 9:00 – 9:30 a.m. | Drug Product Characterization as a Mechanism for Supporting Biowaivers
Mansoor Khan, Ph.D., <i>Professor & Vice Dean, Texas A&M University-College Station, Rangel College of Pharmacy</i> |
| 9:30 – 10:00 a.m. | Assessing the Impact of Excipients on BE
Talia Flanagan, Ph.D., <i>Associate Principal Scientist, AstraZeneca</i> |
| 10:00 – 10:30 a.m. | Morning Break |
| 10:30 – 11:00 a.m. | Assessing Product Performance of Non-Systemically Acting Drugs
David C. Sperry, Ph.D., <i>Senior Research Advisor, Small Molecule Design & Development, Eli Lilly and Company</i> |
| 11:00 a.m. – 12:10 p.m. | In Silico BE: Strengths, Weaknesses, Potential Applications
11:00 – 11:30 a.m.
Masoud Jamei, Ph.D., <i>Vice President of R&D, Certara UK Limited (Simcyp Division)</i>

Absorption Modelling for Virtual Trials: Current Applications and a Vision for the Future
11:30 a.m. – 12:00 p.m.
Xavier Pepin, Ph.D., <i>Principal Scientist Biopharmacy, AstraZeneca</i>

12:00 – 12:10 p.m.
Presentation Discussion |
| 12:10 – 12:30 p.m. | Q&A/Morning Panel Discussion |

END OF WEBEX PROGRAMMING

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Moderator: Ajaz Hussain, Ph.D., *President, National Institute for Pharmaceutical Technology and Education (NIPTE)*

12:30 – 1:20 p.m.	Lunch
1:20 – 1:30 p.m.	Workshop Evaluation
1:30 – 2:00 p.m.	Product Understanding as a Mechanism for Developing Dissolution Method Raafat Fahmy, Ph.D., <i>Science Advisor for Chemistry and Manufacturing Issues, U.S. Food & Drug Administration, Center for Veterinary Medicine</i>
2:00 – 2:30 p.m.	Using In Vitro Tools to Predict Pulmonary Drug Delivery Ben Forbes, Ph.D., <i>Professor, Institute of Pharmaceutical Sciences, Kings College London</i>
2:30 – 3:00 p.m.	Translational Applications of Tissue Chip Technologies Murat Cirit, Ph.D., <i>Director of Translational Center of Tissue Chip Technologies, Massachusetts Institute of Technology (MIT)</i>
3:00 – 3:30 p.m.	Afternoon Break
3:30 – 4:10 p.m.	Case Studies From Eye, Skin and GI Tract Mansoor Khan, Ph.D., <i>Professor & Vice Dean, Texas A&M University-College Station, Rangel College of Pharmacy</i>
4:10 – 4:40 p.m.	Q&A/Moderated Discussion
4:40 – 4:45 p.m.	Closing Comments
4:45 p.m.	Workshop Concludes

Workshop Participating Organizations:



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**Speaker Biographies & Abstracts
(listed alphabetically)**

**Sid Bhoopathy, Ph.D.**

Chief Operating Officer
Absorption Systems
Philadelphia, PA

Dr. Bhoopathy received his Bachelors in Pharmacy from Kakatiya University in 1996 and a Ph.D. in pharmaceutical sciences from Virginia Commonwealth University in 2001. He is the Chief Operating Officer of Absorption Systems and in this capacity, directs the convergence of the commercial, technical, and scientific aspects of the company to execute its strategic and tactical growth plans.

Absorption Systems is a world leader in BCS based biowaivers for oral products and in developing bio-exemption strategies for locally applied and locally acting complex drug products. The focus of this company is to maximize the translational synergies of various non-clinical models. Using this multi-platform approach, Dr. Bhoopathy has led efforts to successfully classify and bio-waive over 50 drug substances for both the branded and generic drug companies. This accrued experience with a variety of drug substances has resulted in him being an expert in several discussion groups and regulatory forums regarding the conduct and predictability of these non-clinical tools. He is currently applying this knowledge to accelerate and extend equivalence assurance to other classes of complex drug products.

Dr. Bhoopathy has held leadership positions at the AAPS and is the Chair of the Generic Pharmaceuticals Focus Group. He has been honored as an Emerging Leader by Pennsylvania Bio; in 2013, recognized as a 40 under Forty, Most Talented Young Leader by the Philadelphia Business Journal for leadership, vision and commitment to the life sciences industry; and in 2017, Dr. Bhoopathy was selected as a winner of the 2017 Executive Management Award for his creative management vision and innovative strategies.

Presentation

*Comparison of Permeability with Data Generated in Ussing Chamber (human, dog, rat),
Intestinal Perfusion, MDCK and Caco-2 Cells*
Monday, October 15, 2018, 1:30 – 2:00 p.m.

Permeability is an important property of a drug substance as it helps guide various aspects of drug development. Multiple non-clinical techniques are available for its determination and in this presentation we will review these approaches. Cell monolayers, as surrogates for intestinal absorption are one of the more popular and prevalent techniques and data will be presented for a series of compounds from different permeability classes in Caco-2 and MDCK cells. The same subset of compounds evaluated using cell monolayers were also assessed in the intestinal perfusion model and in Ussing chamber studies with excised rat, dog and human excised tissue. Outcomes from these studies will be shared including model limitations, variability of these test systems and correlation to human fraction absorbed. Considerations and solutions for obtaining reliable measured permeability values will also be discussed.

**Sara Carlert, Ph.D.**

Associate Principal Scientist

Early Product Development, Pharmaceutical Sciences, IMED Biotech Unit

AstraZeneca

Gothenburg, Sweden

Sara Carlert, Ph.D., is an Associate Principal Scientist within Biopharmaceutics at AstraZeneca, Gothenburg, Sweden. She has worked extensively with evaluation and development of pre-clinical and clinical formulations, with a special interest in poorly soluble drugs and absorption predictions, and is currently working in the Pharmaceutical Sciences department. The department has accountability of chemistry and formulation development spanning from early pre-clinic up to Phase II. Sara also co-leads a focus group for supersaturation and precipitation in the IMI OrBiTo Consortium, coordinating in vitro, in vivo and in silico work in the field. She received her M.Sc. in Chemical Engineering and her Ph.D. in Biopharmaceutics at Uppsala University and her research has been focused on crystallization and the in vitro-in vivo-in silico correlation of intestinal precipitation from oral administration. She is also involved in evaluating and developing preclinical and clinical in silico absorption prediction models.

Presentation*Use of the Dog to Predict Supersaturation and Its Impact on Drug Absorption*

Monday, October 15, 2018, 2:30 – 3:00 p.m.

The ability to create and maintain higher concentration in the GI tract than permitted by equilibrium solubility has been a focus for many formulation strategies as the proportion of poorly soluble drugs on the market has increased. Many articles have been published regarding finding human in vivo predictive in vitro methods for investigating this kinetic phenomenon. Very few direct measurements of intestinal concentrations have been reported in literature, and the in vitro methods are often struggling with overpredicting the in vivo relevance of precipitation.

This presentation examines alternatives to using in vitro measurements of supersaturation and precipitation in the form of dog studies. As the gastric and intestinal physiology of large dogs is very similar to human physiology, dogs have been used when no viable in vitro method has been available. However, there are important differences in human and canine physiology and functionality that can be of importance for interpreting results that will be discussed. Examples of both direct measurements of dog intestinal supersaturation and indirect formulation studies comparing dog and human plasma concentrations will be discussed. Finally, a gap analysis has been performed for guidance of future work directed at building a detailed human correlation from dog supersaturation and precipitation data.

**Murat Cirit, Ph.D.**

Director of Translational Center of Tissue Chip Technologies
Massachusetts Institute of Technology (MIT)
Cambridge, MA

Murat Cirit, Ph.D., is the director of the Translational Center of Tissue Chips Technology at MIT. His research focuses on the organ on a chip technology and pharmacology applications. Murat completed his PhD at NCSU focusing on systems biology. After completion of his PhD, he worked in Merrimack Pharmaceutical in oncology field. He brings an interdisciplinary and systematic approach combining systems biology, systems pharmacology and organ on a chip technologies.

Presentation

Translational Applications of Tissue Chip Technologies

Tuesday, October 16, 2018, 2:30 – 3:00 p.m.

In vitro models have been developed and utilized in various stages for the preclinical development. Compared to animal models, *in vitro* models have advantages such as high-throughput capability, low cost, well-controlled experimental parameters and fewer ethical concerns etc. However, the simplicity of the conventional *in vitro* models makes them incapable of achieving adequate physiological relevance for mimicking the human body, which is a dynamic system that has complex three-dimensional microenvironment, intracellular communications and organ interactions. Hence, there is an urgent need to develop more physiologically relevant *in vitro* systems for better simulating the human body in response of drugs and providing more reliable *in-vitro in-vivo* translation (IVIVT) from preclinical results to clinical outcomes.

Tissue chip technologies are to provide an improved approach for more predictive preclinical drug discovery via a highly integrated experimental/computational paradigm. Success will require quantitative characterization of MPSs and mechanistic analysis of experimental findings sufficient to translate resulting insights from *in vitro* to *in vivo*. We describe a systems pharmacology perspective on this problem, incorporating more mechanistic detail for tissue chip studies than traditional pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) models yet within broadly comprehensive scope. These systems pharmacology approaches offer new insight into design of experiments, data interpretation and organ-specific responses, which can be translated to *in vivo* responses, such as patient-to-patient variability, drug efficacy and toxicity.

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Ayman El-Kattan, Ph.D.
Senior Director and DMPK Head
IFM Therapeutics
Boston, MA

Presentation

ECCS as a Tool for Facilitating Interspecies Extrapolation

Monday, October 15, 2018, 11:10 – 11:30 a.m.



Raafat Fahmy, Ph.D.

Science Advisor for Chemistry and Manufacturing Issues
U.S. Food & Drug Administration, Center for Veterinary Medicine
Rockville, MD

Raafat Fahmy, Ph.D., has over twenty-five years of experience in the pharmaceutical industry. For the past decade, Dr. Fahmy served as a science advisor at the Food and Drug Administration and collaborated with the academia in several research programs.

His critical path research supports innovation, and efficiency in pharmaceutical development, manufacturing, and quality control. He has also authored several textbook chapters, articles, and scientific papers.

He Provides guidance and addresses important issues to the agency and the industry pertaining to drug quality, formulations and manufacturing issues.

Presentation

Product Understanding as a Mechanism for Developing Dissolution Method
Tuesday, October 16, 2018, 1:30 – 2:00 p.m.

Whether designing in vitro dissolution studies or analyzing the resulting data, it is necessary to appreciate the interrelationship between in vitro product performance, drug physicochemical properties, product formulation, product in vivo dissolution behavior, and the biological variables influencing oral drug absorption.

In vitro dissolution testing can serve as an effective and efficient tool for evaluating the influence of formulation and manufacturing variables on drug release characteristics. The targeted purpose will determine the method used and the implications of the test results. Regardless of its intended purpose, it is necessary to understand the factors influencing the in vitro dissolution outcomes to avoid the introduction of error into the data interpretation. This will influence the selection of the in vitro test procedure, ensuring that the method can identify changes in the critical formulation and manufacturing variables. There is also a need to understand the factors influencing in vivo product bioavailability both from a dissolution and an absorption perspective. Finally, to achieve in vivo relevance, it is necessary to understand how the selected in vitro dissolution test method reflects the variables impacting in vivo product dissolution behavior. This presentation summarizes and integrates these many diverse variables, fostering an appreciation of the strengths and potential landmines that may be encountered during the generation and analysis of the in vitro dissolution profiles associated with oral dosage forms.

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**Talia Flanagan, Ph.D.**

Associate Principal Scientist, Biopharmaceutics
AstraZeneca Macclesfield
Cheshire, UK

Talia is Associate Principal Scientist in the Biopharmaceutics group in Pharmaceutical Technology and Development, AstraZeneca Macclesfield. She has extensive and diverse experience of developing and overseeing biopharmaceutics and clinically relevant dissolution strategies on drug projects, with particular focus on oral products Phase 2 to post-launch. Talia has significant experience of global regulatory submissions and regulatory authority interactions in the development and post-approval settings as a biopharmaceutics and dissolution expert, and is chair of AstraZenecas Bioequivalence Expert Panel. Her research interests include biopharmaceutics in Quality by Design, IVIVC/IVIVR, clinically relevant dissolution tests and specifications, and biopharmaceutics in special populations. Talia is EFPIA Deputy Topic Lead on the ICH M9 Expert Working Group. She has been an invited speaker at several national and international conferences/workshops in the field of biopharmaceutics and clinically relevant specifications, and has authored/co-authored 18 manuscripts and one book chapter in these fields. Talia received a Master of Pharmacy with honours (2002) and Doctor of Philosophy (2007) degrees from the Welsh School of Pharmacy, Cardiff University.

Presentation*Assessing the Impact of Excipients on BE*

Tuesday, October 16, 2018, 9:30 – 10:00 a.m.

Excipients are selected for inclusion in drug products to perform a variety of functions. However, some excipients can also have an unintended impact on drug product performance *in vivo*. Some of these effects would not be detected by standard *in vitro* dissolution tests, so this can be an area of concern when assessing formulation equivalence. This presentation will review the mechanisms by which excipients can impact drug absorption, including effects on release rate/amount of drug in solution, transit and luminal volumes, altered effective permeability and altered metabolism. Approaches for assessing the impact of excipient changes on drug absorption will be also discussed, and an example of mechanistic assessment using PBPK absorption modelling will be presented.

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Ben Forbes, Ph.D.

Professor, Institute of Pharmaceutical Sciences
Kings College London
London, UK

Presentation

Using In Vitro Tools to Predict Pulmonary Drug Delivery

Tuesday, October 16, 2018, 2:00 – 2:30 p.m.

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Ajaz Hussain, Ph.D.

President

National Institute for Pharmaceutical Technology and Education (NIPTE)

Washington, DC

Moderator

Tuesday, October 16, 2018

Day Two--In Vitro and In Silico BE Assessments: Opportunities, Strengths and Challenges

**Masoud Jamei, Ph.D.**

Vice President of Research & Development
Certara UK Limited (Simcyp Division)
Sheffield, UK

Masoud Jamei is the Vice President of Research and Development at Simcyp Division of Certara UK Limited where he leads a team of around 40 scientists and 15 software developers focusing on the design, development and implementation of various aspects of systems pharmacology models including *in vitro-in vivo* extrapolation techniques, Physiologically-Based Pharmacokinetics / Pharmacodynamics (PBPK/PD) models of small and large molecules and applying top-down Population PK (PopPK) data analysis to PBPK models in healthy volunteer and patient populations. He has been the author or co-author of over 70 manuscripts and book chapters and over 150 abstracts in the field of modelling and biosimulation. He has also been an invited speaker and a session organiser/moderator at national and international meetings and also leads well-known Simcyp hands-on workshops on model-informed drugs development.

He currently serves as a Vice-Chair of the Special Interest Group (SIG) on PK/PD and Systems Pharmacology of the Board of Pharmaceutical Sciences (BPS) of International Pharmaceutical Federation's (FIP) and is the past Chair of the AAPS Systems Pharmacology Focus Group.

In 2002 he earned a Ph.D. in Control Systems Engineering at the University of Sheffield, UK, and carried out one year of post-doctoral research there. He was an Honorary Lecturer at the University of Sheffield (2008-2011) and a visiting Senior Lecturer at the University of Manchester (2011-2014). In 2003 he joined Simcyp Limited.

Presentation

In Silico BE: Strengths, Weaknesses, Potential Applications

Tuesday, October 16, 2018, 11:00 – 11:30 a.m.

Commonly, Bioequivalence (BE) studies are conducted to assess whether two formulations containing the same dose of same chemical entity, generally in the same dosage form, are substitutable. This is assessed using the extent and rate of absorption. Usually these studies are carried out in healthy volunteers at various stages of drug (product) development, for example, linking early and late phase clinical formulations, comparing clinical versus to be marketed formulations, evaluating change of formulation (tablet vs. capsule), manufacturing sites, excipients, etc and finally comparing generic versus branded drug products. The number of conducted BE studies is very high and modelling and simulation (*In Silico* or virtual BE) can significantly help in reducing, refining and replacing these studies. In this presentation, strengths, weaknesses and some applications of *in silico* BE studies are presented.

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**IOWA STATE
UNIVERSITY**

**College of
Veterinary Medicine**

Albert Jergens, DVM, Ph.D., DACVIM

Professor & Associate Chair for Research and Graduate Studies

College of Veterinary Medicine, Iowa State University

Ames, IA

Moderator

Monday, October 15, 2018

Day One--Translational Strategies: Human-Canine Oral Bioavailability Predictions

**Mansoor Khan, Ph.D.**

Professor & Vice Dean

Texas A&M University-College Station, Rangel College of Pharmacy

College Station, TX

Dr. Mansoor A. Khan has served US FDA for over 11 years as the Director of Product Quality Research and a Senior Biomedical Research Scientist (SBRS) at CDER, He led research teams on biotech products and small molecules, chemistry and stability, drug delivery systems and bioavailability/bioequivalence, and chemistry reviews of new and generic drugs for several complicated products. In Sept of 2015, he joined Texas A&M University as Professor and Vice Dean at Texas A&M Health Science Center College of Pharmacy in their College Station Campus. He also serves as the Interim Head of the Department of Pharmaceutical Sciences. Prior to joining FDA in 2004, Dr. Khan was a Professor of Pharmaceutics and Director of Graduate Program in the School of Pharmacy at Texas Tech University Health Science. He is a registered pharmacist, and earned his Ph.D. degree in Industrial Pharmacy from the St. John's University School of Pharmacy in 1992. He has published over 300 peer-reviewed manuscripts, five texts including "Pharmaceutical and Clinical Calculations" and "Quality by Design for Biopharmaceutical Drug Product Development, 25 book chapters, 250 poster presentations, and more than 250 invited presentations world-wide. Dr. Khan's research focus is primarily in the area of formulations design and development, and biopharmaceutics. He led the FDA new drug review team that approved the first 3D product on Aug 3, 2015.

Dr. Khan has held several leadership positions at the AAPS including elected chair of pharmaceutics and drug delivery (PDD) and the founding chair of formulations design and development (FDD). He served on the USP Dosage Form Expert Committee and Injections and Implanted Expert Panel for the period 2010-2015. He currently serves on the editorial board of Pharmaceutical Technology, International Journal of Pharmaceutics, AAPSPHarmSciTech, and the Drug Delivery and Translational Research. He has received FDA/CDER 2015 outstanding ANDA reviews award, over ten FDA/CDER Team Excellence Awards, FDA/CDER Scientific Achievement Award, and FDA/CDER Exemplary Performance Awards, outstanding alumni award from St. Johns University, College of Pharmacy, Excellence Award from Texas A&M University Health Science Center,. He received the 2012 AAPS Research Achievement Award in Formulations Design and Development. He is also an AAPS and AAiPS Fellow.

Presentation*Drug Product Characterization as a Mechanism for Supporting Biowaivers*

Tuesday, October 16, 2018, 9:00 – 9:30 a.m.

**→ Exploring the science
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Understanding oral drug absorption and formulation
behavior via *in silico*, *in vitro* and translational strategies.**Viera Lukacova, Ph.D.**

Director, Simulation Sciences
Simulations Plus, Inc.
Lancaster, CA

Dr. Lukacova is Director of Simulation Sciences at Simulations Plus, Inc. Over the last decade she has been contributing to the research in the area of mechanistic absorption and PBPK modeling and the development of GastroPlus™, DDDPlus™, and MembranePlus™ software packages widely used throughout the pharmaceutical industry in early drug development, formulation, pre-clinical, and clinical research.

She also contributes to modeling studies helping companies with their drug development programs ranging from early discovery stage, through formulation development, and up to clinical pharmacology and interactions with regulatory agencies. She authored a number of papers in computational chemistry, basic research of transport of small molecules through artificial membranes, and pharmacokinetic and pharmacodynamic modeling in peer-reviewed journals and served as a reviewer of publications in the same areas.

Presentation

Use of In Silico Mechanistic Models to Support Interspecies Extrapolation of Oral Bioavailability and Formulation Optimization: Model Example Using GastroPlus
Monday, October 15, 2018, 11:30 a.m. – 12:10 p.m.

A variety of *in vitro*, *in silico*, and animal assays and models are applied within the pharmaceutical drug development process to improve its efficiency from bench to bedside. Mechanistic *in silico* models provide a unique platform by combining all of this information into a single framework for accurate predictions of the complex drug behavior *in vivo* in animals, healthy subjects and specific patient populations. This presentation will focus on the differences in intestinal physiology between human and animals that may affect formulation behavior in different species and the use of mechanistic models within GastroPlus™ in extrapolation of drug and formulation behavior between animals and human by accounting for these physiological differences.

**Marilyn Martinez, Ph.D.**

Senior Biomedical Research Scientist
U.S. Food & Drug Administration, Center for Veterinary Medicine
Rockville, MD

USP Affiliation:

Government Liaison, USP Expert Panel, Solubility Criteria for Veterinary Drugs

Marilyn is a Senior Biomedical Research Scientist for the US Food and Drug Administration, Center for Veterinary Medicine (CVM). In addition to her responsibilities at the CVM, her activities and include her role as a voting member of the Veterinary Antimicrobial Susceptibility Testing Subcommittee of the Clinical Laboratory Standards Institute, chair of the Veterinary International Conference on Harmonization bioequivalence expert working group, Adjunct Professor in the College of Veterinary Medicine, North Carolina State University, Federal Liaison to OrBITO, member of the Editorial Board of the Journal of Veterinary Pharmacology and Therapeutics, government liaison to the USP Expert Panel on Solubility Criteria for Veterinary Drugs, and Associate Editor of the AAPS Journal. She is the recipient of the 2015 Lloyd Davis Lifetime Achievement Award, and was elected as Fellow of the American Association of Pharmaceutical Scientists and the Controlled Release Society. She received her Ph.D. from the Department of Physiology and Biophysics, Georgetown University School of Medicine.

Presentations
Introduction to the Two One-Day Workshops: Why These Topics?

Monday, October 15, 2018, 8:45 – 9:00 a.m.

Aiming for the Future: Exploring Possibilities

Tuesday, October 16, 2018, 8:30 – 9:00 a.m.

Current technologies provide diverse opportunities to appreciate the *in vivo* challenges influencing drug product development and patient-specific dosing recommendations. This includes the increasing level of understanding strengthened by the sophisticated *in vitro* and *in silico* tools that have been invaluable in guiding decision-making processes impacting formulation development, product dosing regimen determinations, and for appreciating patient-specific influences that can alter dose-exposure-response relationships. In addition to their value in supporting drug products capable of achieving some therapeutic target, these methods are highly efficient, leading to significant time and financial savings.

By combining *in vitro* data generated using such exploratory methods as organoids (2D and 3D) or organ on a chip technologies with *in silico* models that integrate drug and patient population-specific information (physiologically-based pharmacokinetic models), these tools can promote the development of medications and dosage regimens that improve our ability to address patient needs. Lastly, modern innovative tools, when used properly, enable us to achieve the humane goal of Replace, Reduce, and Refine, thereby minimizing animal pain and distress associated with traditional methods of animal experimentation. However, as with any model system (*in vitro* or *in silico*), their effective and efficient application is contingent on recognizing factors and method-specific variables that can influence the degree of bias in resulting conclusions and the corresponding accuracy of the *in vivo* predictions.

The Day 2 presentations are intended to showcase the strengths and weakness of these *in vitro* and *in silico* approaches as we aim for the future and explore how we each can utilize the emerging technologies to expand our therapeutic options in an effort to address an ever-evolving landscape of (human or veterinary) patient needs.

**Jonathan Mochel, DVM, MSc, Ph.D.**

Associate Professor

College of Veterinary Medicine, Iowa State University

Ames, IA

Dr. Jon Mochel obtained his Veterinary Medical Degree from the National Veterinary School of Alfort. He completed his Doctorate studying Neurosciences in collaboration with the College de France, and received the Silver Medal from Paris XII for his work. Dr. Mochel holds a MS in Pharmacology and Pharmacokinetics and is a Diplomate of the European College of Veterinary Pharmacology and Toxicology (ECVPT). He completed his Ph.D at Leiden University, with a focus on the mathematical modeling of the renin-angiotensin system for cardiovascular diseases. He is a founder of the Animal Health Modeling & Simulation Society which aims at promoting the dissemination of mathematical modeling in Veterinary Sciences. Dr. Mochel is an Associate Professor in the Department of Biomedical Sciences at Iowa State University and the Chair of the Education and Residency Committee of the ECVPT. He is a Fellow of the American Academy of Veterinary Pharmacology and Therapeutics and a NIH Study Section Reviewer for the ECR Program. He is currently the Vice-President of the European Association of Veterinary Pharmacology and Toxicology. His research pertains to the analysis of clinical data obtained from spontaneous animal models of human diseases to bridge the knowledge gap between experimental models and patients.

Presentation*Canine Organoids for Drug Permeability Testing: Moving Beyond Caco-2 Cell Systems*

Monday, October 15, 2018, 2:00 – 2:30 p.m.

Recent advance in biomedical research has allowed the development of intestinal stem cells (ISCs) in 3-dimensional (3D) culture systems supporting *in vitro* epithelial growth into organoids^(3,4). Stem cell-derived organoids have multiple advantages over traditional 2D epithelial systems utilizing cancer-derived cell lines (e.g. Caco-2, T84, and HT29)⁽⁵⁾, or spontaneously immortalized epithelial cells (e.g. Rat Intestinal Epithelial (RIE) cultures) which barely reproduce the structure and function of the intestinal epithelium. The benefit of the 3D organoid culture lies in the method's ability to better harness innate endogenous cellular programming within higher order cellular tissue organization⁽⁶⁾. Furthermore, organoids can be collected from hosts having different genotypes, environmental risk factors (e.g. diet, microbiota) or drug sensitivity profiles, thereby more faithfully reflecting the diversity of the host background when cultured *in vitro*.

While methods are available for evaluating drug-intestinal cross-talks for human therapeutics, there is currently very little corresponding information in canines. There is, therefore, a *critical need* to develop new methods for studying drug-gut interactions using scalable and physiological platforms in dogs. 3D organoids provide an opportunity to address these issues in a system that is relatively inexpensive and does not require the use of invasive experimental approaches. In addition, organoids are easy to grow under standard laboratory conditions, allowing for this to be a readily transferable technology. The development of a microphysiological gut system that morphologically, biologically and structurally replicates the endogenous epithelium shows tremendous potential to evaluate the transport and intestinal metabolism of drugs administered through the oral route.

Exploring the science of drug absorption

October 15-16, 2018

Understanding oral drug absorption and formulation behavior via in silico, in vitro and translational strategies.

**Devendra Pade, Ph.D.**

Senior Research Scientist

Certara UK Limited (Simcyp Division), Blades Enterprise Center
Sheffield, UK

Devendra Pade, Ph.D. is a Senior Research Scientist at Certara-UK (Simcyp Division). He received his Ph.D. 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/Teva) on the development of orally inhaled respiratory drug products.

Presentation

In Silico Modeling of Oral Drug Absorption in Dogs vs Humans: Differences in GI Tract Physiology of Humans and Dogs (intestinal transporters, gut metabolism, absorptive surface area)

Monday, October 15, 2018, 10:30 – 11:10 a.m.

The beagle dog is widely used as an ideal pre-clinical biopharmaceutical model for studying drug-formulation behaviour of orally administered drugs for humans. Though some physiological and anatomical parameters in the beagle GI tract are similar to that of humans, there are significant differences between the two species that can affect drug behaviour and absorption. Physiologically based pharmacokinetic (PBPK) models in conjunction with mechanistic oral drug absorption models have the ability to highlight the effect of these differences on the drug products' behaviour in the respective species. Investigating the impact of these differences on drug products in the GI tract and mechanistically evaluating the interaction between the drug, the formulation and the GI environment can provide insights into predicting oral drug absorption across species.



Xavier Pepin, Ph.D.

Principal Scientist, Pharmaceutical Technology and Development
AstraZeneca UK
Cheshire, UK

Xavier is a pharmacist (University Paris XI). He has a Ph.D. in granulation technology where he studied powder surface energy and liquid bridges during wet high-shear granulation. He has more than 20 years' experience in the pharmaceutical industry and has occupied several positions from preformulation, clinical and commercial formulation development, industrial transfer, regulatory CMC and biopharmaceutics. He's worked in biopharmaceutical tools for 10 years in transversal collaboration with scientists from CMC, Clin Pharm & MPK departments, using in vitro, in silico, and in vivo tools to support biopharmaceutical evaluation of drugs along the development value chain and post marketing. He was the co-leader of WP4 in silico tools for the OrBiTo IMI project 2012-2018.

He has 20 publications in the field of powder surface energy, granulation technology and biopharmaceutics.

His hobbies are building homes and furniture, cycling and travelling.

Presentation

Absorption Modelling for Virtual Trials: Current Applications and a Vision for the Future
Tuesday, October 16, 2018, 11:30 a.m. – 12:00 p.m.

Virtual BE can be used to define acceptable product specifications in terms of critical material attributes or process parameters by positioning the clinical reference and operating range in a "safe space", the size of which can be supported by in silico modelling. Pilot clinical studies are recommended where high-quality data are generated on a small number of subjects, which allows expansion to virtual trials. Variability can be assessed in silico and evidenced in vivo through the use of selected biomarkers. Once the critical product attribute and system parameters are identified, models can be validated on clinical data and expanded to test virtual scenarios. Two examples are provided illustrating the need for biomarkers, and the approach of moving from individual based models to population models.

**Christos Reppas, Ph.D.**

Department of Pharmacy
National and Kapodistrian University of Athens
Athens, Greece

Christos Reppas is Professor in Pharmaceutics, Department of Pharmacy, National and Kapodistrian University of Athens (UoA), Greece. He received his Pharmacy Degree from UoA in 1982 and his Ph.D in 1986 from the same University. From 1988 to 1989 he completed a postdoctoral fellowship in Pharmaceutics at the University of Michigan (USA) and then he joined UoA in 1989 as a Lecturer. He has held research positions with the University of London (UK), the University of Michigan (USA), Glaxo R&D (UK) and the University of Frankfurt/Main (Germany). Research interests focus to the effects of gastrointestinal physiology on intraluminal performance of xenobiotics and the development of *in vitro* tests that are predictive of the intraluminal dosage form and drug performance. He has supervised 10 completed PhD Theses and is currently supervising 3. He is coauthor of more than 120 peer reviewed papers and chapters in international journals and books, two books and one patent. He is member of the editorial board of AAPS Journal, Journal of Pharmacy and Pharmacology, Biopharmaceutics and Drug Disposition and Journal of Drug Delivery Science and Technology.

Presentation

*Characterization of GI Fluids Content, Viscosity, Volume in Dogs and Humans:
Comparison Under Fasted and Fed Conditions*

Monday, October 15, 2018, 9:00 – 9:30 a.m.

This presentation consists of three parts.

Firstly, existing information on luminal pH, buffer capacity, osmolality, surface tension, bile salt and phospholipid content, effective permeability of high and low permeability drugs, enzyme activity, viscosity and volume in humans vs. dogs in the fasted state will be summarized.

In the second part, existing information on luminal pH, buffer capacity, osmolality, surface tension, bile salt and phospholipid content, viscosity and volume in humans vs. dogs in the fed state will be summarized. A distinction between the fed state conditions in dogs simulating the human fed state vs. the canine fed state will be made for each parameter.

The presentation will close with few slides with high level comments on the current status of the dog model in the development of oral drug products for humans.

**Patrick Sinko, Ph.D., RPh, FAAPS, FAAS, FCRS**

Distinguished Professor of Pharmaceutics, Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey
New Brunswick, NJ

Dr. Patrick J. Sinko is a Pharmacist and a Pharmaceutical Scientist at Rutgers, The State University of New Jersey. He holds the rank of Distinguished Professor (II) and is the Parke-Davis Endowed Chair in Pharmaceutics and Drug Delivery in the Ernest Mario School of Pharmacy. Dr. Sinko received his Bachelors in Pharmacy from the Rutgers University College of Pharmacy in 1982 and his PhD in Pharmaceutics from the University of Michigan College of Pharmacy in 1988. He was elected Fellow in the American Association for the Advancement of Science (2011), American Association of Pharmaceutical Scientists (2003) and the Controlled Release Society (2017). Dr. Sinko was the Founding Chair of the AAPS Nanotechnology Focus Group and he served on the Council of the AAAS (elected) and the Board of Scientific Advisors of the Controlled Release Society (elected). Dr. Sinko was appointed Distinguished Professor Visiting Professor in Fuzhou University, College of Chemistry and as a High-End Foreign Expert in Pharmaceutical Science by the China State Administration of Foreign Experts Affairs. He also serves on the Research Advisory Committee for the Dr. Susan Love Research Foundation. Dr. Sinko has served on numerous scientific advisory and review panels in the United States and Europe. He is the Editor of Martin's Physical Pharmacy and Pharmaceutical Sciences (Fifth, Sixth and Seventh Editions) and is on the Editorial Advisory Board for several journals. Dr. Sinko has authored or coauthored over 475 publications including research papers, abstracts, and book chapters (h-index = 55). He is the Principal Investigator of an active research laboratory that focuses on biopharmaceutics, pharmaceutical formulations and molecular-, nano- and micro-scale drug delivery with specific applications to the treatment or prevention of HIV/AIDS, breast and lung cancer, glioblastoma multiforme, chemical terrorism countermeasures and TB. During his career, Dr. Sinko has received several awards for his teaching and research, including the Rutgers University Board of Trustees Award for Excellence in Research and highly selective National Institutes of Health FIRST and MERIT Awards. His lab has been continuously funded by the NIH for over 25 years.

Presentation**Use of Dogs to Support Formulation Development for Large Molecule Oral Drug Delivery**

Monday, October 15, 2018, 4:00 – 4:30 p.m.

The oral bioavailability of high molecular weight compounds (macromolecules) such as oligonucleotides, peptides, proteins and nanocarriers is poor (<~5%) and highly variable due to many factors including low intestinal permeability, charge effects, interactions with mucin, and chemical and/or enzymatic instability. Common study formats such as in vitro assays (e.g., Caco-2 or other cell models) or rodent models that are used to assess the potential for oral absorption fail to recapitulate the biological barriers encountered by macromolecules after oral administration. While the use of higher species can be controversial, the ability to assess the effects of gastric emptying, the local intestinal environment and other factors in rabbits, dogs and pigs offers numerous advantages that increase the potential for successful translation to humans. In this presentation the use of the dog model for assessing macromolecular delivery will be discussed using three case studies: (1) effect of excipient screening (oligonucleotides), (2) bioavailability enhancement of large peptides using an Intestinal-Vascular Access Port dog model, and (3) the oral delivery of nanoparticles.

**David C. Sperry, Ph.D.**

Senior Research Advisor, Small Molecule Design & Development
Eli Lilly and Company
Indianapolis, IN

Dr. Sperry is a Sr. 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.

Presentation

Assessing Product Performance of Non-Systemically Acting Drugs
Tuesday, October 16, 2018, 10:30 – 11:00 a.m.

Non-systemically acting drugs offer unique therapeutic delivery potential. In some cases, these drugs can access targets that are not as readily achieved through a conventional oral systemic absorption route. However, these agents offer unique challenges for assessing and controlling product performance. Understanding the mechanistic steps necessary to arrive at the desired therapeutic action is critical to controlling product performance. This presentation will review the classes of non-systemically acting drugs, using examples to illustrate the varied mechanisms present for different types of agents. We will then cover a specific example of a non-systemically acting drug (liprotamase) in some detail. By starting with the mechanism of action and working backwards, we will develop product performance measures and a control strategy suitable for the product. This work illustrates both the challenges and path forward to assess product performance for non-systemically acting drugs.

**Konstantin Tsinman, Ph.D.**

Chief Scientific Officer
Pion, Inc., USA
Billerica, MA

Dr. Konstantin Tsinman joined Pion Inc. in 1998 as a principal developer of the high throughput permeability and solubility instruments and gradually grew up to become Chief Scientific Officer of Pion.

Current research interests include:

- using *in vitro* flux measurements to predict *in vivo* absorption characteristics of drug products;
- investigating physicochemical factors influencing absorption of the pharma compounds;
- expanding the scope of applications for *in situ* UV fiber-optic technique;
- implementation of UV-Vis spectroscopy for real time concentration monitoring of multi-component systems.

Dr. Tsinman has been involved in multiple collaborative research projects with scientists from industry and academic institutions. He has co-authored more than 30 articles published in primary scientific journals and holds several patents. He received his PhD in Physics in 1994 from the Institute for Metal Physics, Kiev, Ukraine.

Presentation

Use of Flux Measurements in Lieu of In Vitro Dissolution to Assess the Complex Interplay Between Solubility, Permeability and Formulation Effects

Monday, October 15, 2018, 3:30 – 4:00 p.m.

Amount and the rate of absorption for the active pharmaceutical ingredient (API) to the blood circulation from the orally administered drug products is determined by the flux of API through epithelial lining of the small intestine. The flux values would depend on the amount of the dissolved API available at the site of permeation as well as on the rate with which drug penetrates the membranes separating GIT from blood capillaries. The former quantity is governed by dissolution and solubility of API in the corresponding medium at biorelevant load while the latter is determined by effective permeability of the compound through the biological membranes.

Establishing meaningful correlations between *in vivo* absorption and *in vitro* measurements have been presenting a significant challenge for pharmaceutical researchers especially when dealing with poorly soluble compounds and their formulations. One of the reason is that in many cases the effect of solubilizing formulations was studied through USP-type dissolution measurements without taking into account biorelevant dissolution medium/volume parameters and interconnection between formulation additives and dissolution/solubility/permeability values.

This presentation introduces principles and devices that can be utilized for flux measurements in a systematic and reproducible manner. Measuring flux and its dependence on formulations allows assessment of complex interplay between solubility, permeability and dissolution rate in formulation development. The case will be made that flux measurements can be used for early prediction of fraction absorbed, formulation ranking, bioequivalence study risks, drug-drug interactions from pH modifying agents and other biorelevant *in vitro* studies.

**Maria Vertizoni, Ph.D.**

Department of Pharmacy
National and Kapodistrian University of Athens
Athens, Greece

Dr. Maria Vertizoni is 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. 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 70 peer reviewed papers.

Presentation

*Examples of Dissolution Differences When Using Canine vs Human Biorelevant Media:
Working to Optimize In Vitro Methods That Support the Translation of In Vivo Oral Drug
Product Dissolution in Dogs vs Humans*

Monday, October 15, 2018, 9:30 – 10:00 a.m.

Biorelevant media for evaluation of dosage form performance in the gastrointestinal lumen of Caucasian adults were first introduced in the late 1990s. Since then, our knowledge of the gastrointestinal environment in humans under conditions simulating the Bioavailability/Bioequivalence studies has improved and a variety of additional media have been proposed, making it now possible to simulate most regions of the human gastrointestinal tract in both prandial states in humans. Relevant biorelevant media have been shown to be a useful tool in oral drug product development.

For the purpose of developing canine therapeutics, the physiological diversity resulting from selective breeding and the largely uncontrolled dosing conditions can lead to wide variability in oral drug product performance and makes the development of biorelevant media more difficult. To date, only media for the simulation of the canine upper gastrointestinal environment in the fasted state have been proposed.

In this presentation, the usefulness of human and canine biorelevant media proposed to date will be evaluated. Specifically, the ability of human and canine biorelevant media to estimate solubility in the gastrointestinal tract and to predict oral absorption in humans and in dogs, respectively, will be illustrated with case examples.