**WORKSHOP: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls**

*September 23-25, 2019*

A collaboration by FDA | CDER Office of Pharmaceutical Quality (OPQ), Small Business and Industry Assistance (SBIA), and University of Maryland CERSI

# Day 1: Monday, September 23
# In vitro Biopredictive Methods

*Moderators: Jennifer Dressman (Goethe University), Xavier Pepin (AstraZeneca) and Poonam Delvadia (FDA)*

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| *7:30 a.m.* | Registration opens | |
| *8:30* | Welcome and objectives of the workshop. | **Sandra Suarez**<br>Center for Drug Evaluation and Research (CDER) \| FDA |
| *8:40* | The impact and future of physiological based biopharmaceutics modeling (PBBM) in support of drug product quality. | **Paul Seo**<br>CDER \| FDA |
| *9:10* | Approaches to measure equilibrium (intrinsic) and kinetic solubility, surface pH and the impact on dissolution and membrane transport kenetics. | **Lynne Taylor**<br>Purdue University |
| *9:40* | The value of biorelevant media for measuring solubility and in the development of biopredictive dissolution methods. | **Jennifer Dressman**<br>Goethe University |
| *10:10* | Break | |
| *10:25* | Measurement and prediction of human permeability: current best practices, regional differences and future developments. | **Erik Sjögren**<br>Pharmatheus |
| *10:55* | Biopredictive dissolution methods with a view to integration in PBPK. Challenges for low solubility IR drug products. | **James Butler**<br>GlaxoSmithKlein |
| *11:25* | In vitro approaches to understanding supersaturation and precipitation of weak bases and enabling formulations. | **Ed Kostewicz**<br>Goethe University |
| *11:55* | Lunch | |
| *12:45 p.m.* | The importance of fluid volume kinetics in the development of biopredictive dissolution methods. | **Mirko Koziolek**<br>University of Greifswald |
| *1:15* | Introduction and expectations for breakout sessions | **Xavier Pepin**<br>AstraZeneca |

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| *1:30* | Break<br>*Transition to breakout sessions* | |
| *1:45*<br>**Breakout Session A**<br>*Salon C* | Best strategies for determining solubility, supersaturation and critical supersaturation. | Moderators<br>**Vidula Kolhatkar**<br>CDER \| FDA<br>**James Butler**<br>GSK<br><br>Scribes<br>**Jennifer Dressman**<br>Goethe University<br>**Lynne Taylor**<br>Purdue University |
| *1:45*<br>**Breakout Session B**<br>*Salon D* | Best strategies for the development of biopredictive (clinically relevant) dissolution methods, a key element for successful modeling and simulation. | Moderators<br>**Bertil Abrahamsson**<br>AstraZeneca<br>**Poonam Delvadia**<br>CDER \| FDA<br><br>Scribes<br>**Ed Kostewicz**<br>Goethe University<br>**Filippos Kesisoglou**<br>Merck & Co., Inc. |
| *1:45*<br>**Breakout Session C**<br>*Terrapin II* | Gastrointestinal systems parameters (mucus, volume, motility): Where are the pitfalls and how can we overcome them? | Moderators<br>**Mirko Koziolek**<br>University of Greifswald<br>**Xavier Pepin**<br>AstraZeneca<br><br>Scribes<br>**Andre Dallmann**<br>Bayer AG<br>**Yang Zhao**<br>CDER \| FDA |
| *1:45*<br>**Breakout Session D**<br>*Terrapin III* | Permeability along the gastrointestinal tract. Translation from biopharmaceutical measurement to a model parameter? | Moderators<br>**Xinyuan Zhang**<br>CDER \| FDA<br>**Neil Parrott**<br>Roche<br><br>Scribes<br>**Andrew Babiskin**<br>CDER \| FDA<br>**Erik Sjögren** |

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| | | Pharmatheus |
| *3:45* | Break<br>*Moderators and scribes to convene* | |
| *4:30* | Summary of breakout discussions | **Lead Moderators** |
| *5:15* | Discussion | |
| *6:00* | Adjourn | |

## Day 2: Tuesday, September 24
## Best Practices for Model Development, Verification, and Validation

*Moderators: Neil Parrott (Roche) and Sandra Suarez (CDER | FDA)*

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| *8:30* | Welcome and logistics | **Sandra Suarez**<br>CDER \| FDA |
| *8:35* | Opportunities and challenges for modeling the clinical impact (i.e. systemic exposure) of formulation and manufacturing changes. | **David Good**<br>Bristol-Myers Squibb |
| *9:05* | Best practices in model development: input of solubility, supersaturation, precipitation and permeability. | **Christian Wagner**<br>Merck Healthcare KGaA |
| *9:35* | Best practices for model building: parameter optimization, sensitivity analysis and how to assess the match to clinical data. | **André Dallmann**<br>Bayer AG |
| *10:05* | Break | |
| *10:20* | Translating the effect of product manufacturing variants from in vitro to the clinic. Current possibilities and gaps for immediate release formulations. | **James Mullin**<br>Simulations Plus |
| *10:50* | Translating the effect of product manufacturing variants from in vitro to the clinic. Current possibilities and gaps for extended release formulations. | **Nikunjkumar Patel**<br>Certara |
| *11:20* | Approaches for entering dissolution into the absorption model, reasons for selection, model assumptions, and parameter estimation strategies. | **Filippos Kesisoglou**<br>Merck & Co., Inc. |

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| *11:50* | Lunch | |
| *12:35 p.m.* | Considerations for the verification and validation of models. | **Arian Emami Riedmaier**<br>AbbVie |
| *1:05* | Impact of population variability (intra and inter) and sample size for model validation and data needed to justify application of virtual bioequivalence. | **Amitava Mitra**<br>Sandoz |
| *1:35* | Introduction and expectations for breakout sessions | **Neil Parrott**<br>Roche |
| *1:50* | Break<br>*Transition to breakout sessions* | |
| 2:05<br>**Breakout Session A**<br>*Salon C* | Challenges to predict effects of formulation changes (e.g. particle size distribution changes) on dissolution and in vivo performance using in silico models. Are the tools ready? | Moderators<br>**Sandra Suarez**<br>CDER \| FDA<br>**Filippos Kesisoglou**<br>Merck & Co., Inc<br><br>Scribes<br>**Kimberly Raines**<br>CDER \| FDA<br>**James Butler**<br>GSK |
| 2:05<br>**Breakout Session B**<br>*Salon D* | Strategies to handle parameter uncertainty and variability within and between subjects. | Moderators<br>**Maziar Kakhi**<br>CDER \| FDA<br>**Neil Parrott**<br>Roche<br><br>Scribes<br>**David Good**<br>BMS<br>**Nikunjkumar Patel**<br>Certara |
| 2:05<br>**Breakout Session C**<br>*Terrapin II* | Best practices for model development, verification and validation, and criteria for defining prediction success. | Moderators<br>**Min Li**<br>CDER \| FDA<br>**Xavier Pepin**<br>AstraZeneca<br><br>Scribes<br>**Arian Emami Riedmaier**<br>AbbVie<br>**James Mullin** |

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| | | Simulations Plus |
| 2:05<br>***Breakout Session D***<br>*Terrapin III* | Approaches to establish sameness following manufacturing/formulation changes: Advantages and disadvantages of virtual bioequivalence. | Moderators<br>**Eleftheria Tsakalozou**<br>CDER \| FDA<br>**Amitava Mitra**<br>Sandoz<br><br>Scribes<br>**Yang Zhao**<br>CDER \| FDA<br>**Christian Wagner**<br>Merck Healthcare KGaA |
| *4:05* | Break<br>*Moderators and scribes to convene* | |
| *4:45* | Summary of breakout sessions | **Lead Moderators** |
| *5:30* | Discussion | |
| *6:15* | Adjourn | |

## Day 3: Wednesday, September 25
## Applications to PBBM to support Drug Product Quality

*Moderators: Amitava Mitra (Sandoz) and Andrew Babiskin (CDER \|FDA)*

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| *8:30 a.m.* | Welcome and Logistics | **Andrew Babiskin**<br>CDER \| FDA |
| *8:35* | FDA expectations in building a safe space to gain regulatory flexibility based on PBBM. | **Yang Zhao**<br>CDER \| FDA<br>**Sandra Suarez**<br>CDER \| FDA |
| *9:05* | European Medicines Agency expectations in building a safe space to gain regulatory flexibility based on PBBM. | **Evangelos Kotzagiorgis**<br>European Medicines Agency (EMA) |
| *9:35* | Case Study: Application of PBBM in risk assessment of effect of acid reducing agents (ARA) on pharmacokinetics and formulation development. | **Neil Parrott**<br>Roche |

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| *10:05* | Break | |
| *10:20* | Prediction of human pharmacokinetics utilizing in vitro chewing method and physiologically based pharmacokinetic (PBPK) analyses for abuse-deterrent hydrocodone bitartrate extended release tablets. | **Satish Sharan**<br>CDER \| FDA |
| *10:50* | Case Study: Bridging physiology-based dissolution testing to quality control testing using PBBM. | **Christophe Tistaert**<br>Janssen |
| *11:20* | The use of PBBM and biomarkers to provide detailed understanding of in vivo dissolution and absorption for acalabrutinib. | **Xavier Pepin**<br>AstraZeneca |
| *11:50* | Lunch | |
| *12:40 p.m.* | Case Study: A physiologically based biopharmaceutics modeling for food effects – possibilities and opportunities. | **Tycho Heimbach**<br>Novartis |
| *1:10* | Introduction and expectation for breakout sessions | **Amitava Mitra**<br>Sandoz |
| *1:25* | Break<br>*Transition to breakout sessions* | |
| *1:40*<br>**Breakout Session A**<br>*Salon C* | Discussion of several terminologies related to physiologically based pharmacokinetics modeling in support of drug product quality (e.g., physiologically based biopharmaceutics modeling). | Moderators<br>**Banu Zolnik**<br>CDER \| FDA<br>**Erik Sjögren**<br>Pharmatheus<br><br>Scribes<br>**Fang Wu**<br>CDER \| FDA<br>**Tycho Heimbach**<br>Novartis |
| *1:40*<br>**Breakout Session B**<br>*Salon D* | Risk-based approach in the development and implementation of PBBM modeling to support drug product quality and clinically relevant specifications setting. | Moderators<br>**Om Anand**<br>CDER \| FDA<br>**Shefali Kakar**<br>Novartis<br><br>Scribes |

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| | | **Min Li**<br>CDER \| FDA<br>**Xavier Pepin**<br>AstraZeneca |
| *1:40*<br>**Breakout Session C**<br>*Terrapin II* | The road towards harmonization among regulatory agencies on evidentiary standards for PBBM. | Moderators<br>**Shereeni Veerasingham**<br>Health Canada<br>**Shinichi Kijima**<br>Pharmaceuticals and Medical Devices Agency (PMDA)<br>**Baoming Ning**<br>National Institutes for Food and Drug Control (NIFDC)<br>**Gustavo Mendes Lima Santos**<br>Anvisa<br>**Kimberly Raines**<br>CDER \| FDA<br><br>Scribes<br>**Greg Rullo**<br>AstraZeneca<br>**Haritha Mandula**<br>CDER \| FDA |
| *1:40*<br>***Breakout Session D***<br>*Terrapin III* | Strategies for bridging biorelevant and quality control dissolution via PBBM. | Moderators<br>**Sandra Suarez**<br>CDER \| FDA<br>**Christophe Tistaert**<br>Janssen<br>Scribes<br>**Poonam Delvadia** CDER \| FDA<br>**Jennifer Dressman**<br>Goethe University<br>**Paul Dickinson**<br>SEDA |
| *3:40* | *Break*<br>*Moderators and scribes to convene* | |
| *4:30* | Summary of breakout sessions | **Lead Moderators** |
| *5:15* | Conclusions and next steps | |
| *5:30* | Discussion | |
| *6:00* | Adjourn | |