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NEWS

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CERSI Conference Shows Quality is Key in Patient-Centric Drug Development

Researchers discuss how to leverage a variety of dissolution and translational modeling strategies to ensure patients continue to have access to safe, effective medications.

BALTIMORE, MD – The University of Maryland School of Pharmacy welcomed more than 150 researchers from across academia, government, and industry to Pharmacy Hall in May for "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development," a multi-day conference organized by the **University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)** in collaboration with the Food and Drug Administration (FDA). To help address regulatory agencies' need for a patient-centric assessment of drug product quality in today's global pharmaceutical environment, the conference featured numerous presentations and breakout sessions that aimed to help attendees better understand the use of dissolution and modeling/simulation approaches in drug product approvals and highlight novel approaches for developing new dissolution testing methods.

"Ensuring quality over the course of a drug product's life cycle can be challenging," said **James Polli, PhD**, the Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics in the **Department of Pharmaceutical Sciences (PSC)** at the School of Pharmacy and co-principal investigator for M-CERSI. "The organizers of this conference worked tirelessly to put together an event that I am confident will facilitate many fruitful discussions and help advance our collective understanding of the role of dissolution testing in promoting drug product development and assessment. My special thanks to Dr. Sandra Suarez Sharpe for her efforts to organize the FDA's participation in this workshop, as well as to the regulatory representatives from Europe, Canada, and Japan who attended our event."

Drug dissolution testing is an analytical test used to detect physical changes in a drug's active pharmaceutical ingredient as well as in the finished drug product. It is a requirement for all solid oral dosage forms and provides researchers in regulatory agencies and industry with important *in vitro* (outside of a living organism) drug release information for both quality control and drug development purposes.

Because it is a key enabler of drug product development and often required by regulatory agencies such as the FDA to justify certain process and formulation changes, effective strategies for developing *in vitro* dissolution testing methods and establishing corresponding acceptance criteria to ensure product quality are needed throughout a product's life cycle. However, recent advances in formulation and manufacturing technologies, evolving regulatory expectations, and

the development of new testing methods have resulted in inconsistencies in dissolution terminology, limitations for the current regulatory framework, and a lack of understanding on how to effectively implement *in vitro* and *in silico* (computer-simulated) approaches to advance product understanding.

“Over the past two decades, we have identified a number of issues related to dissolution testing that remain relevant today,” said Lawrence Yu, PhD, deputy office director for the Center for Drug Evaluation and Research (CDER) at the FDA, in his opening remarks. “My hope is that this conference becomes a starting point for discussions about how we can make progress in this field. Whether it is in how we collect our data or leverage new mathematical modeling approaches, there are many opportunities of which we can take advantage.”

The conference kicked-off with a day of presentations and breakout sessions dedicated to helping attendees better understand the role of dissolution testing in drug product development and as a quality control test. Presenters spoke about the challenges and opportunities that currently exist in the development of new *in vitro* testing methods to guide product development as well as the justification of quality control method conditions and acceptance criteria.

“Product quality is truly the foundation on which safety and efficacy rests,” said Sarah Pope Miksinski, PhD, office director for CDER at the FDA. “Think about the parent who is awake at 3 a.m. looking for a medication for his or her sick child. That parent is not thinking about the quality of that medication at that moment. He or she expects that the medication will work exactly as its intended. That is a really powerful concept, and it is inherent on us as regulators to remember individuals like that parent, and to make the right decisions using the best available evidence as we review and approve new medications for consumer use.”

During the second day, attendees learned more about the need to establish an *in vitro-in vivo* (inside of a living organism) link for dissolution testing, including novel approaches and *in silico* tools currently used in the development of dissolution and permeability testing. The conference concluded on the third day with a discussion of the regulatory applications for dissolution testing.

“This conference truly exceeded my expectations,” said Rob Ju, PhD, head of dissolution sciences for AbbVie. “I am thrilled to have been involved in the many meaningful, logical discussions held over the past three days and cannot wait to attend the next workshop. The knowledge that I gained here will certainly have a lasting impact on my work.”

“All of us attended this conference because we care about patients,” added Andreas Abend, PhD, director at Merck. “Patients rely on the quality of the medications that we develop, and it is our responsibility to ensure that those products work every time they are consumed. It is also symbolic that this event was held at the University of Maryland School of Pharmacy. When you enter a university, you are most likely there to teach or to learn. I think that approach can be applied to many of our attendees -- we are all here to learn, to teach, and to influence the direction in which science will lead us.”

Support for the conference was provided in part by AbbVie, Merck, and Novartis.

The University of Maryland Center for Excellence in Regulatory Science and Innovation and the Food and Drug Administration Present:

Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development

Financial Assistance Provided by AbbVie, Merck, and Novartis

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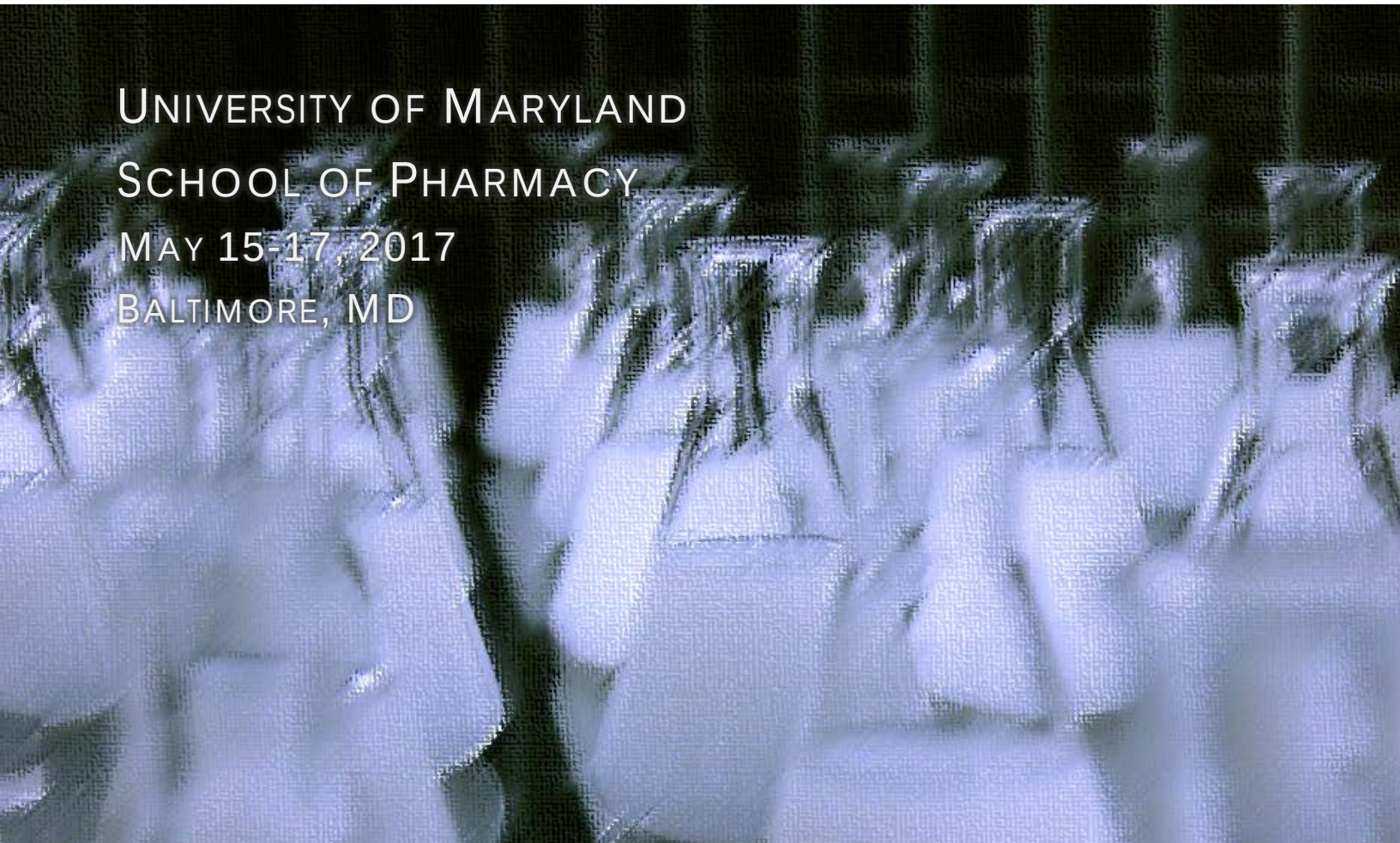

University of Maryland
School of Pharmacy
May 15-17, 2017
Baltimore, MD

Conference Agenda

Monday, May 15

Time	Activity
8:00-8:30 a.m.	Registration
8:30-8:35 a.m.	Welcome and Logistics James Polli, PhD Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics Department of Pharmaceutical Sciences University of Maryland School of Pharmacy Sandra Suarez Sharp, PhD Master Biopharmaceutics Reviewer CDER/FDA
8:35-8:45 a.m.	Opening Remarks Lawrence Yu, PhD Deputy Office Director CDER/FDA
8:45-9:00 a.m.	Introduction and Objectives of the Workshop Andreas Abend, PhD Director Merck Rob Ju, PhD Head, Dissolution Sciences AbbVie The Role of Dissolution Testing in Drug Product Development Challenges and Opportunities in Developing in vitro Methods to Successfully Guide Product Development and Justification of QC Method Conditions and Acceptance Criteria
9:00-9:30 a.m.	The Future of Dissolution Testing: Key Element for the Need of Patient-Centric Assessment of Quality – Regulatory Perspective Sarah Pope Miksinski, PhD Office Director CDER/FDA
9:30-10:00 a.m.	Industry Perspective on the Current Status and Future of Dissolution Testing for Product Development and Quality Control

	Rob Ju, PhD Head, Dissolution Sciences AbbVie Haiyan Grady, PhD Associate Scientific Director Takeda Pharmaceuticals
10:00-10:15 a.m.	BREAK
10:15-11:00 a.m.	USE OF BIO-PREDICTIVE METHODS DURING EARLY FORMULATION SCREENING WITH CASE STUDIES Jesse Kuiper, PhD Principal Scientist Merck
11:00-12:00 p.m.	DISSOLUTION METHODOLOGIES FROM BIORELEVANT TO QUALITY CONTROL: CHALLENGES AND GAPS Xujin Lu, PhD Senior Principal Scientist Bristol-Myers Squibb Jian-Hwa Han, PhD Section Manager AbbVie Danna Mattocks, PhD Senior CMC Project Manager TherapeuticsMD
12:00-12:50 p.m.	LUNCH
12:50-1:35 p.m.	THE USE OF SURROGATES FOR DISSOLUTION TESTING FOR IR FORMULATIONS: WHEN IS IT FEASIBLE? -- CASE STUDIES Limin Zhang Senior Research Scientist Bristol-Myers Squibb Andre Hermans, PhD Principal Scientist Merck
1:35-2:15 p.m.	STATUS AND CHALLENGES OF DISSOLUTION MODELS FOR REAL TIME RELEASE TESTING Hanlin Li, PhD Associate Director Vertex German Drazer, PhD Associate Professor Rutgers University

2:30-4:30 p.m.	BREAKOUT SESSIONS (CHOOSE ONE) 10-Minute Presentation Followed by Discussion on Pre-Selected Questions DEFINITION/DISCUSSION OF TERMINOLOGIES (E.G., QC VS. PHYSIOLOGICALLY RELEVANT VS. CLINICALLY RELEVANT VS. BIO-PREDICTIVE VS. DISCRIMINATING DISSOLUTION TESTING) **Speakers:** Dorys Argelia Diaz, MBA, Associate Director, Pfizer, and Pramod Kotwal, PhD, Director, Merck **Facilitators:** Cindy Buhse, PhD, Director, FDA; Angelica Dorantes, PhD, Acting Branch Chief, FDA; Johannes Kraemer, PhD, CEO, Phast GmbH; Dorys Argelia Diaz, MBA, Associate Director, Pfizer; Pramod Kotwal, PhD, Director, Merck; and Haiyan Grady, PhD, Associate Director, Takeda **Questions for Discussion:** (TBD) BRIDGING BIOPREDICTIVE → QC METHODS: FRAMEWORK, APPROACHES, AND INFORMATION SUGGESTED TO REACH FOLLOWING SCENARIOS: 1. SCENARIO WHERE QC METHODS CAN BE BIOPREDICTIVE 2. SCENARIO WHERE IT IS CHALLENGING FOR QC METHODS TO BE BIOPREDICTIVE (PARALLEL R&D BIOPREDICTIVE AND QC METHODS) **Speakers:** David Curran, Scientist, GlaxoSmithKline, and Yiqing Lin, PhD, Senior Scientist, Biogen **Facilitators:** Erika Stippler, PhD, Director, USP; Kimberly Raines, PhD, Acting Branch Chief, FDA; Danna Mattocks, PhD, Senior Manager, TherapeuticsMD; Yiqing Lin, PhD, Senior Scientist, Biogen; David Curran, PhD, Scientist, GSK; and Banu Zolnik, PhD, Biopharmaceutics Reviewer, FDA **Questions for Discussion:** (TBD)
4:30-5:00 p.m.	SUMMARY OF BREAKOUT DISCUSSIONS
5:15-6:15 p.m.	SPEAKER/FACILITATORS/NOTE TAKERS DAY 1 CLOSE-OUT

TUESDAY, MAY 16

TIME	ACTIVITY
8:00-8:30 a.m.	REGISTRATION
8:30-8:35 a.m.	WELCOME AND LOGISTICS Tycho Heimbach, PhD Director

	Novartis Rob Ju, PhD Head, Dissolution Science AbbVie THE NEED FOR ESTABLISHING *IN VITRO-IN VIVO* LINK Novel Approaches and *in silico* Tools in the Development of Bio-Predictive Dissolution and Permeability Testing (BCS 2/4)
8:35-9:05 a.m.	CHALLENGES AND STRATEGIES IN ESTABLISHING AN *IN VITRO-IN VIVO* LINK Paul Seo, PhD Division Director CDER/FDA
9:05-9:35 a.m.	NOVEL APPROACHES IN HUMAN PK STUDY DESIGN (E.G., STABLE ISOTOPES TECHNIQUE) TO OVERCOME THE CHALLENGES IN THE CONDUCT OF DEDICATED BA/BE STUDIES (CASE STUDIES) Timothy H. Montague, PhD Clinical Statistics ADD TA Head GSK
9:35-10:10 a.m.	DEVELOPMENT OF CANAGLIFIOZIN: MECHANISTIC ABSORPTION MODELING DURING LATE-STAGE FORMULATION AND PROCESS OPTIMIZATION Nico Holmstock, PhD Scientist, Preformulation and Biopharmaceutics Janssen R&D, Johnson and Johnson
10:10-10:25 a.m.	BREAK
10:25-11:00 a.m.	APPLICATION OF STOCHASTIC DECONVOLUTION IN IVIVC DEVELOPMENT Maziar Kakhi, PhD Staff Fellow CDER/FDA
11:00-11:35 a.m.	PBPK ABSORPTION MODELING CHALLENGES IN PREDICTING CLINICAL OUTCOMES ACROSS BCS/BDDCS CLASSES (PPI EFFECTS, FORMULATION ASSESSMENTS, FOOD EFFECTS): CASE STUDIES FROM INDUSTRY PERSPECTIVE Tycho Heimbach, PhD Director Novartis
11:35-12:10 p.m.	CASE STUDIES OF MECHANISTIC ABSORPTION MODELING AND IVIVC USED IN DEVELOPMENT PROJECTS Andres Olivares-Morales, PhD Project Leader, M&S Scientist Roche
12:10-1:00 p.m.	LUNCH

1:00-2:10 p.m.	THE UTILITY OF *IN SILICO* PBPK ABSORPTION MODELING AND SIMULATION AS A TOOL TO INCREASE THE SUCCESS OF DEVELOPING BIO-PREDICTIVE DISSOLUTION METHODS: SUCCESS AND LIMITATIONS (CASE STUDIES FROM REGULATORY PERSPECTIVE) HoPi Lin, PhD Biopharmaceutics Reviewer CDER/FDA Liang Zhao, PhD Division Director CDER/FDA
2:10-2:45 p.m.	APPLICATIONS OF PBPK MODELING FOR THE DEVELOPMENT OF BIORELEVANT DISSOLUTION METHODS WITH CASE STUDIES – INDUSTRY PERSPECTIVE Xavier Pepin, PhD Principal Scientist, Biopharmacy AstraZeneca
	BREAKOUT SESSIONS (CHOOSE ONE) 10-20 Minute Presentation Followed by Discussion on Pre-Selected Questions
3:00-5:00 p.m.	GAPS IN KNOWLEDGE TO INCREASE THE CONFIDENCE IN THE USE OF *IN SILICO* PBPK ABSORPTION MODELS FOR REGULATORY DECISION MAKING: SPACE OF API AND FORMULATION ATTRIBUTES WHERE IN SILICO PBPK MAY HAVE LIMITED UTILITY **Speakers**: Xavier Pepin, PhD, Principal Scientist, Biopharmacy, AstraZeneca, and Carrie Coutant, PhD, Principal Research Scientist, Eli Lilly **Facilitators**: Marilyn Martinez, PhD, Senior Biomedical Research Scientist, FDA; Xavier Pepin, AstraZeneca; Carrie Coutant, PhD, Principal Research Scientist, Eli Lilly; and HoPi Lin, PhD, FDA **Questions for Discussion**: (TBD) WHICH DATA SHOULD BE SUBMITTED TO SUPPORT THE VALIDATION/VERIFICATION OF *IN SILICO* PBPK ABSORPTION MODELS FOR REGULATORY DECISION MAKING? WHAT ARE THE RECOMMENDED VALIDATION ACCEPTANCE CRITERIA FOR PBPK M&S **Speakers**: Nikunjkumar Patel, PhD, Senior Research Scientist (M&S), Certara, and Denise Morris, PhD, Assistant Director, SimulationsPlus **Facilitators**: Ping Zhao, PhD, Lead, PBPK Program, FDA; Tycho Heimbach, Novartis; Filippos Kesisoglou, Merck; Min Li, FDA; Amitava Mitra, PhD, Associate Director, Sandoz **Questions for Discussion**: (TBD)
5:00-5:30 p.m.	SUMMARY OF BREAKOUT DISCUSSIONS
5:45-6:30 p.m.	SPEAKER/FACILITATORS/NOTE TAKERS DAY 2 CLOSE-OUT

Wednesday, May 17

Time	Activity
8:00-8:30 a.m.	Registration
8:30-8:35 a.m.	Welcome and Logistics Sandra Suarez Sharp, PhD Master Biopharmaceutics Reviewer CDER/FDA Evangelos Kotzagiorgis, MSc Scientific Administrator European Medicines Agency
8:35-9:35 a.m.	Regulatory Applications of Bio-Predictive Dissolution Testing Framework of Setting Clinically Relevant Specifications: Approach, Information Needed, and Criteria Sandra Suarez Sharp, PhD Master Biopharmaceutics Reviewer CDER/FDA Evangelos Kotzagiorgis, MSc Scientific Administrator European Medicines Agency Andreas Abend, PhD Director Merck
9:35-10:05 a.m.	The Role of Bio-Predictive Dissolution Method in the Selection of CMA, CPPs, and Verification of Design Space(s): Case Studies Mike Cohen, PhD Research Fellow Pfizer
10:05-10:20 a.m.	Break
10:20-11:00 a.m.	The Role of Bio-Predictive Dissolution Testing in Increasing the Success Rate of IVIVR/IVIVC: Key Approach in Support of Major Post-approval Changes (Biowaivers) in Reference to Regulatory Guidelines Min Li, PhD Acting Biopharmaceutics Lead CDER/FDA

Anna Nordmark, PhD
Pharmacokinetic Assessor at MPA
European Medicines Agency

11:00-11:25 a.m.

The Utility of On Level C IVIVC for Setting Clinically Relevant Specifications: Case Studies and Implications

Filippos Kesisoglou, PhD
Senior Principal Scientist
Merck

11:25-12:10 p.m.

Establishing Clinical Relevant Specifications During Product Life Cycle: Case Studies

Barbara Davit, PhD, JD
Distinguished Scientist
Merck

Patrick Marroum, PhD
Senior Research Fellow
AbbVie

12:10-1:00 p.m.

Lunch

BREAKOUT SESSIONS (Choose One)

10-Minute Presentation Followed by Discussion on Pre-Selected Questions

1:00-3:00 p.m.

Similarities, Differences, and Shared Challenges in the EMA and U.S. FDA: Recommended Approaches to Setting Clinically Relevant Drug Product Specifications

Speakers: Nagesh Bandi, PhD, Executive Director, Merck, and Michael Cohen, Pfizer
Facilitators: Evangelos Kotzagiorgis, EMA; Sandra Suarez, FDA; Andreas Abend, Merck; Poonam Delvadia, PhD, Acting Biopharmaceutics Lead, FDA; and Nagesh Bandi, Merck
Questions for Discussion: (TBD)

Similarities, Differences, and Shared Challenges in the EMA and U.S. FDA: Recommended Use of *in silico* PBPK Absorption M&S in Regulatory Decision Making in Relation to Biowaivers

Speakers: Erik Sjogren, PhD, Associate Professor in Biopharmaceutics, Uppsala University, and Barbara Davit, Merck
Facilitators: Paul Seo, Director, FDA; Shereeni Veerasingham, PhD, Assessment Officer, Health Canada; Erik Sjogren, Uppsala University; Xinyuan (Susie) Zhang, PhD, Clinical Pharmacology Reviewer, FDA; and Shinichi Kijima, MSc, Clinical Pharmacology Reviewer, PMDA
Questions for Discussion: (TBD)

3:00-3:30 p.m.

Summary of Breakout Discussions

3:30-4:00 p.m.	Meeting Wrap-Up and Follow-Up Actions
4:15-5:15 p.m.	Speaker/Facilitators/Note Takers Day 3 Close-out