Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Virtual Public Workshop
September 30th and October 1st
2021

Agenda

FDA's Office of Generic Drugs consistently utilizes mechanistic modeling and simulation to support regulatory decision making and has directly supported the development of modeling platforms through Generic Drug User Fee Amendments (GDUFA) regulatory research funding. These mechanistic modeling approaches include physiologically based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD) modeling. FDA staff use these tools in regulatory activities, including the assessment of abbreviated new drug applications (ANDA), pre-ANDA development meetings, citizen petition responses, controlled correspondences and product-specific guidances (PSGs), to address issues related to product bioequivalence (BE). This workshop is intended to provide the generic drug industry and other involved stakeholders with information about how mechanistic modeling and simulation can support product development and regulatory submissions.

FDA has driven advancements in modeling platforms for generic drugs that use complex routes of administration, such as topical/dermal, ophthalmic, and orally and nasally inhaled products. Mechanistic modeling is a tool that can be used to help increase access to complex generics because it provides an acceptable alternative method for establishing BE that does not include the need for lengthy comparative clinical endpoint BE studies in patients. Mechanistic modeling can play a critical role in supporting alternative BE approaches in non-complex oral generic drug products as well.

The purpose of this workshop is to engage the generic drug industry and other involved stakeholders regarding how mechanistic modeling and simulation can support their product development and regulatory submissions, share the current state of mechanistic modeling for BE assessment through case studies, establish a consensus on best practices for using PBPK and CFD modeling for BE assessment to help drive further investment by the generic drug industry into mechanistic modeling and simulation, and roll out the concept of a Model Master File to improve model-sharing between model developers, industry, and FDA.

FDA and the Center for Research on Complex Generics (CRCG)—which is a collaboration between the University of Maryland School of Pharmacy and the University of Michigan College of Pharmacy—are dedicated to advancing programs that stimulate scientific dialogue, disseminate current insights about complex generics, and generate new knowledge in support of FDA's mission to promote and protect the public health by increasing access to safe, high-quality, and effective generic medicines.

GENERAL TOPICS THAT WILL BE THE FOCUS OF THE WORKSHOP:

- Mechanistic modeling of orally inhaled generic drug products
- Mechanistic modeling of dermal generic drug products
- Mechanistic modeling of other locally-acting generic drug products
- Oral PBPK as alternative BE approach
- Oral PBPK for evaluating the impact of food on BE
- Challenges and successful cases for oral PBPK
- Model acceptance and model sharing for regulatory use

Day 1: September 30, 2021

8:30 AM – 8:40 AM	**CRCG Welcome Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Anna Schwendeman, PhD	Co-Director, CRCG
8:40 AM – 8:50 AM	**Opening Remarks**	
	Jaqueline Corrigan-Curay, JD, MD	Principal Deputy Director, CDER, FDA
8:50 AM – 9:10 AM	**Keynote Address**	
	Use of PBPK in New Drug Development and Regulatory Review - Clinical Pharmacology Perspective	
	Shiew-Mei Huang, PhD	Deputy Director, OCP, OTS, CDER, FDA
9:10 AM – 9:15 AM	**Workshop Day 1 Overview**	
	Andrew Babiskin, PhD	Team Lead, DQMM, ORS, OGD, CDER, FDA
Symposium I:	***Mechanistic Modeling of Locally-Acting Generic Drug Products***	
Session 1:	**Mechanistic Modeling of Orally Inhaled Generic Drug Products**	
	Session Lead: Ross Walenga, PhD	
9:20 AM – 9:35 AM	***Overview of Complex Generic Orally Inhaled Drug Products***	
	Bryan Newman, PhD	Pharmacologist, DTP-I, ORS, OGD, CDER, FDA
9:35 AM – 9:50 AM	***ASME V&V 40 for Establishing Credibility of CFD Models***	
	Brent Craven, PhD	Research Scientist, DAM, OSEL, CDRH, FDA
9:50 AM – 10:05 AM	***Validation of Computational Predictions of Regional Lung Deposition***	
	Bo Olsson, PhD	Sr. Inhalation Consultant, Emmace Consulting AB
10:05 AM – 10:20 AM	***Case Study: Predicting Regional Lung Deposition of Pharmaceutical Aerosols with CFD***	
	Worth Longest, PhD	Prof., Mech. & Nuclear Eng., Pharmaceutics, Virginia Commonwealth Univ.
10:20 AM – 10:35 AM	***Modeling to Support Regulatory Needs of OIDPs***	
	Raja Mohamed, PhD	IVIVC Manager, Respiratory & Complex Products, Sandoz
10:35 AM – 10:50 AM	***ANDA and Pre-ANDA Experience with OIDP Modeling***	
	Ross Walenga, PhD	Chemical Engineer, DQMM, ORS, OGD, CDER, FDA
10:50 AM – 11:05 AM	***Use of Mechanistic Modelling to Determine the Sensitivity of in vitro CQAs to Regional Lung Deposition and Predict PK for OIDPs***	
	Clare Butler, PhD	Head of Global Inhalation IVIVC, Teva
11:05 AM – 11:20 PM	***Coffee Break***	
11:20 AM – 12:05 PM	***Live Panel Discussion***	
Moderators:	**Robert Lionberger, PhD**	Director, ORS, OGD, CDER, FDA
	Andrzej Przekwas, PhD	CTO, CFD Research Corporation
Panelists:	**Bryan Newman, PhD**	Pharmacologist, DTP-I, ORS, OGD, CDER, FDA
	Brent Craven, PhD	Research Scientist, DAM, OSEL, CDRH, FDA
	Bo Olsson, PhD	Sr. Inhalation Consultant, Emmace Consulting AB
	Worth Longest, PhD	Prof., Mech. & Nuclear Eng., Pharmaceutics, Virginia Commonwealth Univ.
	Ross Walenga, PhD	Chemical Engineer, DQMM, ORS, OGD, CDER, FDA
	Clare Butler, PhD	Head of Global Inhalation IVIVC, Teva
	Raja Mohamed, PhD	IVIVC Manager, Respiratory & Complex Products, Sandoz
	Günther Hochhaus, PhD	Prof., Department of Pharmaceutics, Univ. of Florida
	Bing Li, PhD	Associate Director for Scientific Innovation, OB, OGD, CDER, FDA
	Markham Luke, MD, PhD	Director, DTP-I, ORS, OGD, CDER, FDA
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, CDER, FDA
12:05 PM – 12:55 PM	***Lunch Break***	
Session 2:	**Mechanistic Modeling of Dermal Generic Drug Products**	
	Session Lead: Eleftheria Tsakalozou, PhD	
1:00 PM – 1:15 PM	***Research Overview and Regulatory Experience on Mechanistic Modeling for Generic Dermatological Drug Products***	
	Khondoker Alam, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
1:15 PM – 1:30 PM	***Towards Building a Dermal PBPK model for BE Assessment: The Role of Drug Product Characterization and Drug Product Performance Data***	
	Priyanka Ghosh, PhD	Sr. Staff Fellow, DTP-I, ORS, OGD, CDER, FDA
1:30 PM – 1:45 PM	***PBPK Modeling of Dermal Penetration from Topical Formulations***	
	Jessica Spires, PhD	Sr. Scientist II, Simulations Plus, Inc.

1:45 PM – 2:00 PM	***Modeling and Simulation Approaches of Topically Applied Drugs to Support Formulation Optimization, Clinical Development and Regulatory Assessment – Case Studies Discussion***	
	Sebastian Polak, PhD	Sr. Scientific Advisor, Simcyp Division, Certara UK
2:00 PM – 2:15 PM	***Scientific and Regulatory Considerations on Dermal PBPK Modeling for Virtual BE Assessments and Decision-making***	
	Eleftheria Tsakalozou, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
2:15 PM – 2:55 PM	***Live Panel Discussion***	
Moderators:	**Sam Raney, PhD**	Associate Director for Science, ORS, OGD, CDER, FDA
	Sumit Arora, PhD	Sr. Scientist, Biopharmaceutics, Janssen R&D
Panelists:	**Khondoker Alam, PhD**	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
	Priyanka Ghosh, PhD	Sr. Staff Fellow, DTP-I, ORS, OGD, CDER, FDA
	Eleftheria Tsakalozou, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
	Jessica Spires, PhD	Sr. Scientist II, Simulations Plus, Inc.
	Sebastian Polak, PhD	Sr. Scientific Advisor, Simcyp Division, Certara UK
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Srinivasa Sammeta, PhD	Associate Director, Product Development, Teva
	Ping Zhao, PhD	Sr. Program Officer, Quantitative Sciences, Bill & Melinda Gates Foundation
2:55 PM – 3:10 PM	***Coffee Break***	
Session 3:	**Mechanistic Modeling of Other Locally-Acting Generic Drug Products**	
	Session Lead: Ming-Liang Tan, PhD	
3:15 PM – 3:30 PM	***GDUFA Research Update on Mechanistic Modeling Approaches for Generic Ophthalmic, Nasal, Implant and Injectable Drug Products***	
	Ming-Liang Tan, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
3:30 PM – 3:45 PM	***Current Scientific Considerations in Modeling for In Vitro BE of Topically Administered Ophthalmics***	
	Sajeev Chandran, PhD	Director, Advanced Drug Delivery & IVIVC, Biopharmaceutics, Lupin
3:45 PM – 4:00 PM	***PBPK Modeling for Different Locally-Administered Drug Products***	
	Rebeka Jereb, MSc	Scientist, Clinical Development, Sandoz
4:00 PM – 4:45 PM	***Live Panel Discussion***	
Moderators:	**Andrew Babiskin, PhD**	Team Lead, DQMM, ORS, OGD, CDER, FDA
	Maxime Le Merdy, PharmD	Sr. Scientist, Simulations Plus, Inc.
Panelists:	**Ming-Liang Tan, PhD**	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
	Sajeev Chandran, PhD	Director, Advanced Drug Delivery & IVIVC, Biopharmaceutics, Lupin
	Rebeka Jereb, MSc	Scientist, Clinical Development, Sandoz
	Khondoker Alam, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
	Robert Bies, PharmD, PhD	Prof., Department of Pharmaceutical Sciences, SUNY
	Darby Kozak, PhD	Deputy Director, DTP-I, ORS, OGD, CDER, FDA
	Ross Walenga, PhD	Chemical Engineer, DQMM, ORS, OGD, CDER, FDA
4:45 PM – 4:55 PM	**Closing Remarks – Day 1**	
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA

Day 2: October 1, 2021

8:30 AM – 8:40 AM	**Welcome and Opening Remarks**	
	Sally Choe, PhD	Director, OGD, CDER, FDA
8:40 AM – 9:00 AM	**Keynote Address**	
	PBPK Models: Opportunities for Enhancements	
	William Jusko, PhD	Prof., Department of Pharmaceutical Sciences, SUNY
9:00 AM – 9:05 AM	**Workshop Day 2 Overview**	
	Lei Zhang, PhD	Deputy Director, ORS, OGD, CDER, FDA
Symposium II:	***Mechanistic Modeling of Oral Generic Drug Products***	
Session 1:	**Oral PBPK as an Alternative BE Approach and a Tool for Supporting Risk Assessment and Biowaiver**	
	Session Lead: Fang Wu, PhD	
9:10 AM – 9:25 AM	***PBPK Absorption Modeling to Support Risk Assessment and Biowaiver for Generic Oral Products***	
	Fang Wu, PhD	Sr. Pharmacologist and Scientific Lead, DQMM, ORS, OGD, FDA
9:25 AM – 9:40 AM	***PBPK Biopharmaceutics Guidance and Progress on Risk Assessment***	
	Kimberly Raines, PhD	Branch III Chief, DB, ONDP, OPQ, CDER, FDA
9:40 AM – 9:55 AM	***Impact of Excipients on Drug Permeation to Support Biowaivers for Non-Q1/Q2 Products***	
	Chris Bode, PhD	Vice President Scientific & Corporate Communications, Absorption Systems

9:55 AM – 10:10 AM	***Are We Ready to Apply Oral PBPK Modeling for BE Determination?***	
	Yu Chung Tsang, PhD	CSO, Biopharmaceutics & Biostatistics, Apotex
10:10 AM – 10:45 AM	***Live Panel Discussion***	
Moderators:	**Hongling Zhang, PhD**	Acting Division Director, DB-II, OB, OGD, CDER, FDA
	Tycho Heimbach, PhD	Sr. Principal Scientist/Director, Pharmaceutical Sciences, Merck
Panelists:	**Fang Wu, PhD**	Sr. Pharmacologist and Scientific Lead, DQMM, ORS, OGD, FDA
	Kimberly Raines, PhD	Branch III Chief, DB, ONDP, OPQ, CDER, FDA
	Chris Bode, PhD	Vice President Scientific & Corporate Communications, Absorption Systems
	Yu Chung Tsang, PhD	CSO, Biopharmaceutics & Biostatistics, Apotex
	Amitava Mitra, PhD	Director, Clinical Pharmacology & Pharmacometrics, Janssen R&D
	James Polli, PhD	Prof. in Industrial Pharmacy and Pharmaceutics, Univ. of Maryland
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, CDER, FDA
	CDR Yi Zhang, PhD	Sr. Advisor, DTP-II, ORS, OGD, CDER, FDA
10:45 AM – 11:00 AM	***Coffee Break***	
Session 2:	**Oral PBPK for Evaluating the Impact of Food on BE**	
	Session Leads: Fang Wu, PhD and Miyoung Yoon, PhD	
11:05 PM – 11:20 AM	***Development of PBPK Model for Predicting Food Impact on BE Assessment***	
	Abdullah Al Shoyaib, PhD	ORISE Fellow, DQMM, ORS, OGD, CDER, FDA
11:20 AM – 11:35 AM	***Predicting the Power of Food: Assessing Confidence in PBPK Modeling of Food Effect***	
	Arian Emami Riedmaier, PhD	Sr. Principal Scientist and PBPK Lead, Bristol Myers Squibb
11:35 AM – 11:50 AM	***Impact of Food and Formulation on Bioequivalence: A Generic Industry Perspective***	
	Anita Kumar, MPharm, MSc	Vice President, R&D, Amneal
11:50 AM – 12:25 PM	***Live Panel Discussion***	
Moderators:	**Partha Roy, PhD**	Director, OB, OGD, CDER, FDA
	Neil Parrot, MSc	Distinguished Scientist, Research Innovation Center Basel, Roche
Panelists:	**Arian Emami Riedmaier, PhD**	Sr. Principal Scientist and PBPK Lead, Bristol Myers Squibb
	Anita Kumar, PhD	Vice President R&D, Amneal
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Rebeka Jereb, MSc	Scientist, Clinical Development, Sandoz
	Nilufer Tampal, PhD	Acting Associate Director for Scientific Quality, OB, OGD, CDER, FDA
	Fang Wu, PhD	Sr. Pharmacologist and Scientific Lead, DQMM, ORS, OGD, FDA
	Yuching Yang, PhD	PBPK Co-Lead, DPM, OCP, OTS, CDER, FDA
12:25 PM – 1:15 PM	***Lunch Break***	
Session 3:	**Challenges and Successful Cases for Oral PBPK**	
	Session Leads: Youssef Mousa, PhD and Fang Wu, Ph.D.	
1:20 PM – 1:35 PM	***Integrating Biopharmaceutic Data and Gastrointestinal Physiology Using Mechanistic Modeling***	
	Rodrigo Cristofoletti, PhD	Assistant Prof., Department of Pharmaceutics, Univ. of Florida
1:35 PM – 1:50 PM	***Modeling for Success: A Case Example for Oseltamivir Phosphate***	
	Youssef Mousa, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
1:50 PM – 2:25 PM	***Live Panel Discussion***	
Moderators:	**Lanyan (Lucy) Fang, PhD**	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Filippos Kesisoglou, PhD	Distinguished Scientist, Merck
Panelists:	**Rodrigo Cristofoletti, PhD**	Assistant Prof., Department of Pharmaceutics, Univ. of Florida
	Youssef Mousa, PhD	Staff Fellow, DQMM, ORS, OGD, CDER, FDA
	Jianghong Fan, PhD	Sr. Staff Fellow, DPM, OCP, OTS, CDER, FDA
	Tycho Heimbach, PhD	Sr. Principal Scientist/Director, Pharmaceutical Sciences, Merck
	Myong-Jin Kim, PhD	Director, DTP-II, ORS, OGD, CDER, FDA
	Duxin Sun, PhD	Prof., Director of PK Core, College of Pharmacy, Univ. of Michigan
	Yu Chung Tsang, PhD	CSO, Biopharmaceutics & Biostatistics, Apotex
	Banu Zolnik, PhD	Acting Biopharmaceutics Team Lead, DB, ONDP, OPQ, CDER, FDA
2:25 PM – 2:40 PM	***Coffee Break***	
Symposium III/Session 4:	***Model Acceptance and Model Sharing for Regulatory Use***	
	Session Lead: Andrew Babiskin, PhD	
2:45 PM – 3:00 PM	***Regulatory Perspective: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use***	
	Andrew Babiskin, PhD	Team Lead, DQMM, ORS, OGD, CDER, FDA
3:00 PM – 3:15 PM	***Nonregulatory Perspective: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use***	

	Carl Peck, MD	Adjunct Prof., Bioengineering, School of Pharmacy, UCSF
3:15 PM – 3:30 PM	***Regulatory Perspective: What Can Be a Model Master File and How to Share It?***	
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, CDER, FDA
3:30 PM – 3:45 PM	***Nonregulatory Perspective: What Can Be a Model Master File and How to Share It?***	
	Amin Rostami-Hodjegan, PhD	Prof. of Systems Pharmacology, Univ. of Manchester / CSO, Certara
3:45 PM – 4:35 PM	***Live Panel Discussion***	
Moderators:	**Liang Zhao, PhD**	Director, DQMM, ORS, OGD, CDER, FDA
	Donald Mager, PhD	Prof. and Vice Chair, Department of Pharmaceutical Sciences, SUNY
Panelists:	**Andrew Babiskin, PhD**	Team Lead, DQMM, ORS, OGD, CDER, FDA
	Carl Peck, MD	Adjunct Prof., Bioengineering, School of Pharmacy, UCSF
	Amin Rostami, PhD	Prof. of Systems Pharmacology, Univ. of Manchester / CSO, Certara
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Stella Grosser, PhD	Director, DB-VIII, Office of Biostatistics, OTS, CDER, FDA
	Viera Lukacova, PhD	Chief Scientist, Lancaster Division, Simulations Plus, Inc.
	Erik Sjögren, PhD	Assoc. Prof., Biopharmaceutics, Uppsala Univ. / Sr. Consultant, Pharmetheus
	Hao Zhu, PhD	Deputy Director, DPM, OCP, OTS, CDER, FDA
4:35 PM – 4:45 AM	**Workshop Summation**	
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, CDER, FDA
4:45 PM – 4:55 PM	**Closing Remarks**	
	Robert Lionberger, PhD	Director, ORS, OGD, CDER, FDA

Appendix of Abbreviations

ANDA	Abbreviated New Drug Application
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFD	Computational Fluid Dynamics
CRCG	Center for Research on Complex Generics
CQA	Critical Quality Attribute
CSO	Chief Scientific Officer
CTO	Chief Technology Officer
BE	Bioequivalence
DAM	Division of Applied Mechanics
DB	Division of Biopharmaceutics
DB-II	Division of Bioequivalence II
DB-VIII	Division of Biostatistics VIII
DPM	Division of Pharmacometrics
DQMM	Division of Quantitative Methods and Modeling
DTP-I	Division of Therapeutic Performance I
DTP-II	Division of Therapeutic Performance II
FDA	United States Food and Drug Administration
GDUFA	Generic Drug User Fee Amendments
JD	Juris Doctor
MD	Doctor of Medicine
MPharm	Master of Sciences of Pharmacy
MSc	Master of Science
OB	Office of Bioequivalence
OCP	Office of Clinical Pharmacology

OGD	Office of Generic Drugs
OIDP	Orally Inhaled Drug Product
ONDP	Office of New Drug Products
OPQ	Office of Pharmaceutical Quality
ORISE	Oak Ridge Institute for Science and Education
ORS	Office of Research and Standards
OSEL	Office of Science and Engineering Laboratories
OTS	Office of Translational Sciences
PBPK	Physiologically Based Pharmacokinetic
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetics
Prof.	Professor
R&D	Research and Development
Sr.	Senior
SUNY	State University of New York
UCSF	University of California, San Francisco
Univ.	University