Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development

In person (at The Universities at Shady Grove; Rockville, MD) and virtual workshop
Oct 12, 2023

The purpose of this one-day workshop is to discuss the challenges, experiences, and advances related to the development of oral physiologically based pharmacokinetic (PBPK) absorption modeling to support the establishment of biopredictive in vitro testing (e.g., dissolution) and to address risks associated with the extrapolation of bioequivalence (BE) in various contexts, such as from a fasting to a fed state, from subjects with normal to elevated gastric pH, for a biopharmaceutics classification system (BCS)-based biowaiver, for assessing BE in pediatrics, and for other risk-based BE assessments for oral products.

Agenda

8:30 AM – 8:40 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Anna Schwendeman, PhD	Co-Director, CRCG
8:40 AM – 8:50 AM	**Opening Remarks-Powers and Problems in PBPK Models**	
	William Jusko, PhD	SUNY Distinguished Professor, University of Buffalo
8:50 AM – 8:55 AM	**Overview of Workshop**	
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, FDA

Session 1: Advances of PBPK Modeling in Regulatory Contexts and to Support Harmonization

Session Moderators: Yu-Chung Tsang and Liang Zhao

This session will focus on the latest advances and challenges with utilizing oral PBPK absorption modeling and virtual simulation for drug development and regulatory submission purposes - to facilitate formulation design, risk assessment and support global harmonization. Speakers from FDA and industry will present specific cases of using oral PBPK absorption modeling and virtual simulation to assess BE, to evaluate alcohol dose dumping (ADD) risks, to support BE study design (e.g., using parent versus metabolite as analytes for BE assessment), and to evaluate the impact on BE of a problematic excipient contained in the formulation of a test product. The second part of this session will focus on PBPK approaches to predict systemic and local bioavailability (BA) of gastrointestinal (GI) locally acting oral products to support BE assessment and the limitations/knowledge gap relevant to using PBPK modeling for these products in healthy subjects vs. patient populations. The exploration of appropriate in vitro approaches/data to inform in vivo release will also be discussed.

8:55 AM – 9:00 AM	***Introduction to Session and Speakers***	
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, FDA
9:00 AM – 9:15 AM	***Advances on Using PBPK Modeling to Support BE Assessment for Oral Products***	
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
9:15 AM – 9:30 AM	***PBPK Absorption Modeling for Developing Patient-Centric Quality Standards***	
	Muhammad Ashraf, PhD	Laboratory Chief, DPQR, OTR, OPQ, FDA
9:30 AM – 9:45 AM	***Model Based Approaches to Establishing BE: Perspectives from the European Generic Sector***	
	Susana Almeida, PhD	Clinical Development and Safety Director, Medicines for Europe
9:45 AM – 10:00 AM	***PBPK/PBBM Applications in Drug Development***	
	Tycho Heimbach, PhD, FAAPS	Senior Principal Scientist, Merck & Co., Inc
10:00 AM – 10:10 AM	***Coffee Break***	
10:10 AM – 10:30 AM	***Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products***	
	Sherin Thomas, PhD	Pharmacologist, DQMM, ORS, OGD, FDA
	Nikoletta Fotaki, MSc, PhD, FAAPS	Professor of Biopharmaceutics, CTI, University of Bath
10:30 AM – 10:45 AM	***PBPK Models for the Evaluation of GI Locally Acting Products, from Industry Perspectives***	
	Harshil Shah, BPharm, MS	Senior Manager, Bioequivalence, Cosette Pharmaceuticals Inc

10:45 AM – 11:25 AM	***Panel Discussion***	
Moderators:	**Yu-Chung Tsang, PhD**	CSO, Biopharmaceutics, Biostatistics, Global Regulatory Affairs, Apotex Inc
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, FDA
Panelists:	**Susana Almeida, PhD**	Clinical Development and Safety Director, Medicines for Europe
	Muhammad Ashraf, PhD	Laboratory Chief, DPQR, OTR, OPQ, FDA
	Nikoletta Fotaki, MSc, PhD, FAAPS	Professor of Biopharmaceutics, CTI, University of Bath
	Tycho Heimbach, PhD, FAAPS	Senior Principal Scientist, Merck & Co., Inc
	Xiaojian Jiang, PhD	Deputy Director, DB II, OB, OGD, FDA
	Rebecca Moody, PhD	Biopharmaceutics Reviewer, DB, ONDP, OPQ, FDA
	Amin Rostami-Hodjegan, PhD, FCP	Professor of Systems Pharmacology, University of Manchester
	Harshil Shah, BPharm, MS	Senior Manager, Bioequivalence, Cosette Pharmaceuticals Inc
	Romi Singh, PhD	Senior VP, Sun Pharmaceuticals, India
	Sherin Thomas, PhD	Pharmacologist, DQMM, ORS, OGD, FDA
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA

Session 2: PBPK Modeling to Evaluate Food Impact on Bioequivalence Supporting ICH M13A

Session Moderators: Tycho Heimbach and Ethan Stier

This session will focus on discussing the latest advancements and challenges related to evaluating the impact of food on oral drug absorption/BA and BE, as well as the importance of in vitro biopredictive dissolution for PBPK modeling. The session will also discuss the use of PBPK modeling to support waivers of fed BE studies and ICH M13A guideline.

11:25 AM – 11:30 AM	***Introduction to Session and Speakers***	
	Ethan Stier, PhD	Associate Director for Lifecycle Management, OCP, OTS, FDA
11:30 AM – 11:45 AM	***Integrating Forward and Reverse Translation in PBPK Modeling for Waiving Fed BE Study: Itraconazole Case Study***	
	Rodrigo Cristofoletti, PhD	Assistant Professor, University of Florida
11:45 AM – 12:00 PM	***Role of Biopredictive Dissolution and Oral PBPK to Evaluate the Impact of Food on Drug Absorption***	
	Jozef Al-Gousous, PhD	Lecturer, Johannes Gutenberg University Mainz
	Peter Langguth, RPh, PhD	Professor, Johannes Gutenberg University Mainz
12:00 PM – 12:15 PM	***Using PBPK Modeling to Support a Waiver of Fed BE Study, from Industry Perspectives***	
	Rebeka Jereb, PhD	Senior Scientist Clinical Innovations, Lek, a Sandoz company
12:15 PM – 12:45 PM	***Panel Discussion***	
Moderators:	**Tycho Heimbach, PhD, FAAPS**	Senior Principal Scientist, Merck & Co., Inc
	Ethan Stier, PhD	Associate Director for Lifecycle Management, OCP, OTS, FDA
Panelists:	**Tausif Ahmed, PhD**	VP & Head, Biopharmaceutics & Bioequivalence, Dr. Reddy's Laboratories Ltd
	Jozef Al-Gousous, PhD	Lecturer, Johannes Gutenberg University Mainz
	Susana Almeida, PhD	Clinical Development and Safety Officer, Medicines for Europe
	Rodrigo Cristofoletti, PhD	Assistant Professor, University of Florida
	Jianghong Fan, PhD	Senior Staff Fellow, DPM, OCP, OTS, FDA
	Rebeka Jereb, PhD	Senior Scientist Clinical Innovations, Lek, a Sandoz company
	Vidula Kolhatkar, PhD	Pharmacologist, DB II, OB, OGD, FDA
	Peter Langguth, RPh, PhD	Professor, Johannes Gutenberg University Mainz
	Paulo Paixão, PhD	Member of the MWP, EMA; Assistant Professor, University of Lisbon
	Mohan Krishna Rayeni, MPharm	Scientist-Biopharmaceutics and IVIVC, Sandoz Development Center
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Lei Zhang, PhD	Deputy Director, ORS, OGD, FDA
12:45 PM – 1:30 PM	***Lunch Break***	

Session 3: PBPK Modeling to Support Bioavailability and Bioequivalence Assessment in Pediatric Populations

Session Moderators: Gilbert Burckart and Rebeka Jereb

This session will focus on the application of PBPK absorption modeling in pediatric regulatory submissions, the latest advancements and challenges for assessing relative BA and BE, and to support the development of pediatric drug products. This session will also discuss the development of biopredictive in vitro dissolution for pediatric products and to support assessments of BA and BE in pediatric populations.

1:30 PM – 1:35 PM	***Introduction to Session and Speakers***	
	Gilbert Burckart, PharmD	Associate Director for Pediatrics, OCP, OTS, FDA
1:35 PM – 1:50 PM	***Regulatory Applications and Research of Absorption Modeling for Pediatric Products***	
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, FDA
1:50 PM – 2:05 PM	***Is Pediatric Absorption Modeling Ready for BE Assessment?***	
	Gaohua Lu, PhD	Senior Director, Head of PBPK, Bristol Myers Squibb
2:05 PM – 2:20 PM	***PBPK Absorption Modeling and Virtual Bioequivalence Assessment to Support a Pediatric Formulation Regulatory Submission***	
	Kazuko Sagawa, PhD	Research Fellow, Pfizer Global Research and Development
2:20 PM – 2:50 PM	***Panel Discussion***	
Moderators:	**Gilbert Burckart, PharmD**	Associate Director for Pediatrics, OCP, OTS, FDA
	Rebeka Jereb, PhD	Senior Scientist Clinical Innovations, Lek, a Sandoz company
Panelists:	**Siva Vaithiyalingam, PhD**	Senior Vice President Regulatory Affairs, Cipla Ltd
	Jianghong Fan, PhD	Senior Staff Fellow, DPM, OCP, OTS, FDA
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, FDA
	Nikoletta Fotaki, MSc, PhD, FAAPS	Professor of Biopharmaceutics, CTI, University of Bath
	Gaohua Lu, PhD	Senior Director, Head of PBPK, Bristol Myers Squibb
	Viera Lukacova, PhD	Chief Scientist, Simulations Plus, Inc.
	Nikunjkumar Patel, PhD	Senior Director of PBPK Consultancy, Certera Inc
	Kazuko Sagawa, PhD	Research Fellow, Pfizer Global Research and Development
2:50 PM – 3:00 PM	**Closing Remarks for Virtual Attendees**	
	Robert Lionberger, PhD	Director, ORS, OGD, FDA
3:00 PM – 3:10 PM	***Coffee Break***	
3:10 PM – 3:15 PM	***Introduction of In-Person Round Table Discussion***	
	Liang Zhao, PhD	Director, DQMM, ORS, OGD, FDA
3:15 PM – 4:15 PM	***In-Person Round Table Discussion for Session 1***	
	Advances of PBPK Modeling in Regulatory Contexts and to Support Harmonization	
Moderators:	**Myong-Jin (MJ) Kim, PhD**	Director, DTPII, ORS, OGD, FDA
	Nikunjkumar Patel, PhD	Senior Director of PBPK Consultancy, Certera Inc
	Yu-Chung Tsang, PhD	CSO, Biopharmaceutics, Biostatistics, Global Regulatory Affairs, Apotex Inc
Scribes:	**Yi-Hsien Cheng, PhD**	Pharmaceutical Scientist, DQMM, ORS, OGD, FDA
	Sherin Thomas, PhD	Pharmacologist, DQMM, ORS, OGD, FDA
3:15 PM – 4:15 PM	***In-Person Round Table Discussion for Session 2***	
	PBPK Modeling to Evaluate Food Impact on Bioequivalence Supporting ICH M13A	
Moderators:	**Tycho Heimbach, PhD, FAAPS**	Senior Principal Scientist, Merck & Co., Inc
	Ethan Stier, PhD	Associate Director for Lifecycle Management, OCP, OTS, FDA
Scribes:	**Khondoker Alam, PhD**	Senior Staff Fellow, DQMM, ORS, OGD, FDA
	Arindom Pal, PhD	ORISE Fellow, DQMM, ORS, OGD, FDA
3:15 PM – 4:15 PM	***In-Person Round Table Discussion for Session 3***	
	PBPK Modeling to Support BA and BE Assessments in Pediatric Populations	
Moderators:	**Lanyan (Lucy) Fang, PhD**	Deputy Director, DQMM, ORS, OGD, FDA
	Viera Lukacova, PhD	Chief Scientist, Simulations Plus, Inc
Scribes:	**Gaohua Lu, PhD**	Senior Director, Head of PBPK, Bristol Myers Squibb
	Eleftheria Tsakalozou, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
4:15 PM – 4:40 PM	***Break Time for Participants and Prepare for Discussion Summary***	
4:40 PM – 5:15 PM	***Round Table Discussion Summary for Sessions 1, 2, and 3***	
Moderator:	**Liang Zhao, PhD**	Director, DQMM, ORS, OGD, FDA
5:15 PM – 5:30 PM	**Closing Remarks for Entire Workshop**	
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, FDA

Appendix of Abbreviations

AAPS	American Association of Pharmaceutical Scientists
ACT	Access to COVID-19 Tools
ADD	Alcohol Dose Dumping
ADME	Absorption, Distribution, Metabolism, and Excretion
ANDA	Abbreviated New Drug Application
Anvisa	Brazilian Health Regulatory Agency
APS	Academy of Pharmaceutical Sciences
ARA	Acid-Reducing Agents
ASCPT	American Society for Clinical Pharmacology and Therapeutics
BA	Bioavailability
BBB	Blood-Brain Barrier
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BLA	Biologics License Application
BPharm	Bachelor of Pharmacy
BS or BSc	Bachelor of Science
CDER	Center for Drug Evaluation and Research
CMO	Contract Manufacturing Organization
CPP	Clinical Pharmacology and Pharmacometrics
CRCG	Center for Research on Complex Generics
CRO	Contract Research Organization
CRL	Complete Response Letter
CSO	Chief Scientific Officer
CTI	Centre of Therapeutic Innovation
DB	Division of Biopharmaceutics
DB II	Division of Bioequivalence II
DDI	Drug-Drug Interaction
DIV	Division
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry Powdered Inhaler
DPM	Division of Pharmacometrics
DPQR	Division of Product Quality Research
DTPI	Division of Therapeutic Performance I
DTPII	Division of Therapeutic Performance II
DQMM	Division of Quantitative Methods and Modeling
EU	European Union
FAAPS	Fellow of the American Association of Pharmaceutical Scientists
FBPS	Fellow of the British Psychological Society
FCP	Fellow of the American College of Clinical Pharmacology
FDA	United States Food and Drug Administration
FE	Food Effects
FJSSX	Fellow of the Japanese Society for the Study of Xenobiotics

FTIH	First Time in Human
GDUFA	Generic Drug User Fee Amendments
GLP	Good Laboratory Practice
HDL	High-Density Lipoprotein
ICCM	Institute of Computational Comparative Medicine
ICH	International Council for Harmonization
IGBA	International Generic and Biosimilar Medicines Association
IND	Investigational New Drug
IQ	Innovation & Quality
ITC	International Transporter Consortium
IVIVC	In Vitro In Vivo Correlation
IVIVR	In Vitro In Vivo Relationship
IVRDT	In Vitro Release and Dissolution
JPKPD	Journal of Pharmacokinetics & Pharmacodynamics
Ltd.	Limited
MPharm	Master of Pharmacy
MS or MSc	Master of Science
NDA	New Drug Application
NG	Nasogastric
NTI	Narrow Therapeutic Index
OB	Office of Biostatistics
OBAM	Oral Biopharmaceutics and Absorption Modeling
OCP	Office of Clinical Pharmacology
OGD	Office of Generic Drugs
ONDP	Office of New Drug Product
OPQ	Office of Pharmaceutical Quality
ORS	Office of Research and Standards
ORISE	Oak Ridge Institute for Science and Education
OTS	Office of Translational Sciences
OTR	Office of Testing and Research
PBBM	Physiologically Based Biopharmaceutics Modeling
PBPK	Physiologically Based Pharmacokinetic Modeling
PD	Pharmacodynamics
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetics
PKPD	Pharmacokinetics Pharmacodynamics
pMDI	Pressurized Metered Dose Inhaler
PSG	Product Specific Guidance
QSP	Quality Selection Process
R&D	Research and Development
RLD	Reference Listed Drug
SUPAC	Scale-Up and Post-Approval Changes
SVP	Senior Vice President
TDDS	Transdermal Drug Delivery Systems

USP	United States Pharmacopeia
SUNY	the State University of New York
VP	Vice President
WHO	World Health Organization