PBBM Considerations for Base Models, Model Validation and Application Steps: Workshop Summary Report

AUTHORS

Tycho Heimbach[1*], Flora Musuamba Tshinanu[2], Kimberly Raines[3], Luiza Borges[4], Shinichi Kijima[5], Maria Malamatari[6], Rebecca Moody[3], Shereeni Veerasingham[7], Paul Seo[8], David Turner[9], Lanyan Fang[10], Cordula Stillhart[11], Philip Bransford[12], Xiaojun Ren[13], Nikunjkumar Patel[9], David Sperry[14] ,Hansong Chen[3], Amin Rostami-Hodjegan[9,15], Viera Lukacova[16], Duxin Sun[17], Jean-Flaubert Nguefack[18], Tessa Carducci[19], Manuela Grimstein[8], Xavier Pepin[16], Masoud Jamei[9], Konstantinos Stamatopoulos[20], Min Li[8], Maitri Sanghavi[9], Christer Tannergren[21], Haritha Mandula[3], Zhuojun Zhao[3], Tzuchi Rob Ju[22], Christian Wagner[23], Sumit Arora[24] , Michael Wang[1], Gregory Rullo[25], Amitava Mitra[26], Sivacharan Kollipara[27], Siri Kalyan Chirumamilla[9], James E. Polli[28], Claire Mackie[24*]

Affiliations

[1] Pharmaceutical Sciences and Clinical Supply, Merck & Co., Inc., Rahway, NJ, USA

[2] Belgian Federal Agency for Medicines and Health Products, Galileelaan 5/03, Brussel, Belgium

[3] Office of Pharmaceutical Quality (OPQ), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, Maryland, USA

[4]ANVISA, SIA Trecho 5 – Guará, Brasília – DF, Brazil

[5] Office of New Drug V, Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan.

[6] Medicines & Healthcare Products Regulatory Agency, 10 S Colonnade, London, UK.

[7] Pharmaceutical Drugs Directorate (PDD), Health Canada, 1600 Scott St, Ottawa, Canada.

[8] Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, Maryland, USA

[9] Certara Predictive Technologies, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

[10] Division of Quantitative Methods and Modeling (DQMM), Office of Research and Standards (ORS), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, Maryland, USA

[11] Pharmaceutical R&D, F. Hoffmann-La Roche Ltd., Basel, Switzerland.

[12] Data and Computational Sciences, Vertex Pharmaceuticals, Inc., Boston, MA, USA

[13] PK Sciences / Translational Medicine, BioMedical Research, Novartis, One Health Plaza, East Hanover, NJ, USA

[14] Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

[15] Centre for Applied Pharmacokinetic Research, University of Manchester, Stopford Building, Oxford Road, Manchester M139PT, UK

[16] Simulations Plus Inc., 42505 10th Street West, Lancaster, CA 93534 USA

[17] The University of Michigan North Campus Research Complex (NCRC),1600 Huron Parkway, Ann Arbor, MI 48109

[18] Head of Biopharmacy Team, Montpellier - Synthetics Platform – Global CMC – Sanofi, France

[19] Analytical Commercialization Technology, Merck & Co., Inc., 126 E. Lincoln Ave, Rahway, NJ 07065, USA

[20] Biopharmaceutics, DPD, MDS, GlaxoSmithKline, David Jack Centre, Park Road, Ware SG12 0DP, UK

[21] Biopharmaceutics Science, New Modalities & Parenteral Product Development, Pharmaceutical Technology & Development, Operations, AstraZeneca Gothenburg, Sweden.

[22] Analytical R&D, AbbVie Inc., 1 North Waukegan Road, North Chicago, Illinois 60064

[23] Global Drug Product Development, Global CMC Development, the Healthcare Business of Merck KGaA, Darmstadt, Germany

[24] Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse, Belgium.

[25] Regulatory CMC, AstraZeneca, 1 Medimmune Way, Gaithersburg, MD, US.

[26] Clinical Pharmacology, Kura Oncology Inc, Boston, MA, US

[27] Biopharmaceutics Group, Global Clinical Management, Dr. Reddy's Laboratories Ltd., Integrated Product Development Organization (IPDO), Bachupally, Medchal Malkajgiri District, Hyderabad-500 090, Telangana, India

[28] School of Pharmacy, University of Maryland, Baltimore, MD 21201 USA

*Email: Tycho.Heimbach@Merck.com
**Email : cmackie@its.jnj.com

SUPPORTING INFORMATION FOR PUBLICATION

PBBM INDUSTRY CASE EXAMPLE (DRUG C)

Drug C is weakly acidic drug with low solubility and high permeability (BCS class II compound). The drug product is immediate release (IR) tablet dosage form manufactured at a strength of 80 mg as a generic version to innovators. Pilot and pivotal studies have been conducted for generic submission and successful bioequivalence has been achieved during the pivotal study. However, the pivotal bioequivalence study was conducted only in male population and agency requested to provide justification for extrapolation of bioequivalence study results obtained in male subjects to both genders (male, female). In this context, PBBM was developed and utilized to justify the regulatory query.[1]

The PBBM was built using solubility, particle size, bio-predictive dissolution in fasting and fed conditions. Dissolution data was integrated into the model using Z-factor model, was adequate to account for dissolution in fasting and fed conditions. The distribution was captured well with the physiology of healthy American male and female subjects with age of 30 years and the tissue partition coefficients (Kp) were determined using Lukacova method. The API is a substrate for CYP3A4 and also the transporters BCRP, MRP3, OATP1B1, OATP1B3 and P-gp and thus, the disposition was accounted through appropriate V_{max} and K_m in Gastroplus.

The PBBM was validated extensively with pilot and pivotal bioequivalence data using bio-predictive dissolution inputs in fasting and fed conditions. The model was able to differentiate between bioequivalent and non-bioequivalent batches in both fasting and fed conditions.

The validated model was used to demonstrate gender impact on bioequivalence. For this purpose, simulations in female population was performed by changing female physiology with same weight, age as that of male and PK parameters were predicted in female subjects. Subsequently, simulated female/male ratios were calculated and compared against measured ratios in order to demonstrate PBBM ability to predict gender impact accurately.

The results indicated that there is an increase of 10-24% for C_{max} with no change in AUC in females as compared to male population (Table S1). The simulated gender impact is closer to that of literature reported gender impact (~20% increase in C_{max} with no effect on AUC) and thus gender impact is accurately predicted by the model (Table S1 and Figure S1). This model based

justification along with literature data was utilized to justify the regulatory query wherein bioequivalence results in male population were successfully extrapolated to both genders.

Model questions (COU): The pivotal bioequivalence study was conducted only in male population and agency requested to provide justification for extrapolation of bioequivalence study results obtained in male subjects to both genders (male, female). PBBM was developed, validated and used to demonstrate that the bioequivalence results in male population can be extrapolated to both genders.

Model influence: ***Medium,*** as model has provided supportive evidence and information about reference product is already available in literature.

Model decision consequence: ***Medium,*** because the reference product was already indicated for both genders.

Table S1: Simulated Vs Reported PK data for Gender effect

Gender effect	Male Geo Mean PK^	Females Geo mean PK^	Simulated Female/Male ratios^	Reported Female/Male ratios
C_{max} (ng/mL)	166, 82	183, 101	**110.0, 124.0**	**~120 %**
AUC_{0-t} (ng.h/mL)	383, 322	415, 333	**108.0, 103.3**	**~90%**
AUC_{0-inf} (ng.h/mL)	383, 322	415, 333	**108.0, 103.3**	**~90%**

^Fasted , Fed state values, respectively

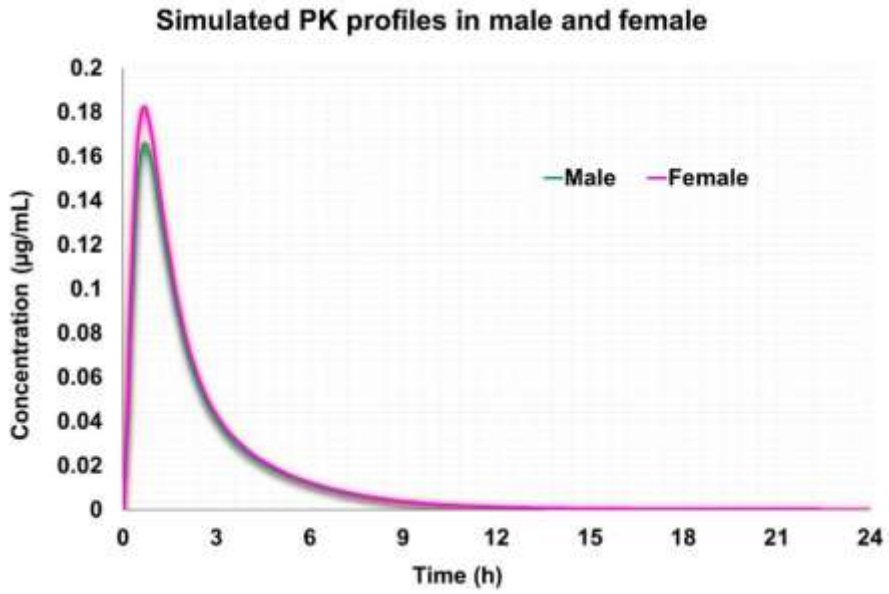

Figure S1: Simulated male vs female plasma conc time profiles. Modified from. [1]

Reference:

(1) Boddu, R.; Kollipara, S.; Vijaywargi, G.; Ahmed, T. Power of integrating PBPK with PBBM (PBPK-BM): a single model predicting food effect, gender impact, drug-drug interactions and bioequivalence in fasting & fed conditions. Xenobiotica 2023, 53 (4), 260-278. DOI: 10.1080/00498254.2023.2238048.