Advancing the Use of Model-Integrated Evidence in Generic Drug Development and Assessment

Liang Zhao, PhD

Division Director

Division of Quantitative Methods & Modeling

Office of Research and Standards, Office of Generic Drugs, CDER/FDA

FY2024 Generic Drug Regulatory Science Initiatives Public Workshop

May 20th, 2024

Increasing Impact of Modeling & Simulation (M&S) in Generic Drug Development and Assessment

- **The GDUFA Regulatory Science Program** is transforming the landscape of generic drug development and evaluation by using cutting-edge modeling and simulation technologies into its framework
- **Model integrated evidence (MIE)*** refers to using model generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence
- **MIE Industry Meeting Pilot** launched on October 1st, 2023
- Please access the annual **GDFUA Science and Research Report** at: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

*: Clin Pharmacol Ther. 2019 Feb;105(2):338-349

Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year (FY) 2024

- Develop Methods for Generics to Address Impurities such as Nitrosamines
  - Evaluating practical strategies that may mitigate the potential risks of harmful impurities such as nitrosamine adducts (e.g., NDSRIs), and evaluating the effect of these strategies on the absorption and/or the bioavailability of active pharmaceutical ingredients (APIs), including **utilizing modeling and simulation approaches to assess the risk of altering the performance of a generic product in the event of a reformulation**
- Enhance the Efficiency of Equivalence Approaches for Complex Active Ingredients
- Enhance the Efficiency of BE Approaches for Complex Routes of Delivery
  - Implementing characterization-based (in vitro) methods, potentially together with **in vivo PK and modeling methods**, as alternatives to the use of comparative clinical endpoint BE studies for nasal and inhaled drug products
- Enhance the Efficiency of Equivalence Approaches for Complex Drug-Device Combination Products
  - Improving data analysis approaches for assessing comparative task analysis and comparative use human factors study results
- Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products
  - Utilizing oral physiologically based PK (PBPK) modeling to identify risk factors for food effects and formulation dependent drug interactions (e.g., proton pump inhibitors) to support global harmonization of the most efficient BE approaches for these products
- **Facilitate the Utility of MIE to Support Demonstrations of BE**
- **Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools**

QMM/MIE Impact Various Regulatory Activities (CY 2023)

	Type	No.	Examples
Regulatory	**ANDA Review Consults**	18	❖ BE risk assessment; Particle size distribution space determination; data truncation
	Pre-ANDA Meetings	40	❖ Topical dermatological/orally inhaled/long-acting injectable products/non-complex oral products
	Controlled Correspondences	6	❖ Evaluation of alternative BE approaches to the CE study for locally acting products
	BE Guidance	9	❖ PSGs: New/revised guidance on modified release products; use of pAUC as an additional BE metrics
Research	**Internal Regulatory Research Projects**	34	❖ Performance of BE assessment criteria (e.g., ones for NTI drugs) ❖ Artificial intelligence and machine learning for knowledge base management and review modernization
	New Contracts and Grants in GDUFA II since 10/2017	36	❖ Development of model-integrated BE for complex generic drugs ❖ Virtual platform development (e.g., long acting injectables, sparse sampling) ❖ Development of PBPK model for locally acting drug products ❖ Characterizing safety and efficacy of generic drugs, and expanding BCS class 3 waivers

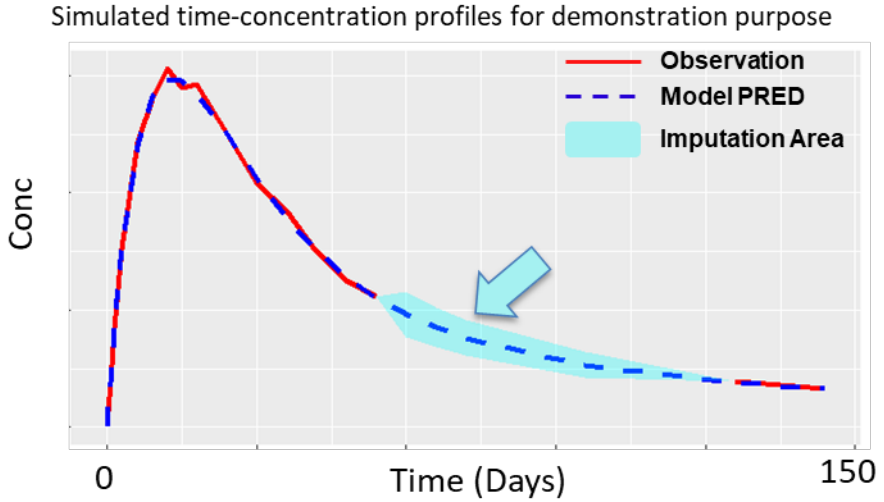
ANDA, abbreviated new drug application; BE, bioequivalence; CE, clinical endpoint; NTI, narrow therapeutic index; PK, pharmacokinetic; PD, pharmacodynamics; PBPK, physiologically based PK; PSG, product-specific guidance; BCS, Biopharmaceutics Classification System; pAUC, partial area under the curve.

Population PK (PPK) Model Based Data Imputation To Serve As Pivotal Evidence For BE Evaluation

Medroxyprogesterone acetate injectable suspension 150 mg: a long-acting injectable indicated for the prevention of pregnancy. The recommended dose is every 3 months (13 weeks) administered by intramuscular injection.

Regulatory Issue: This pharmacokinetic BE study conducted by the applicant experienced a high volume of missing samples in the mid- to late phase in the majority of the subjects.

- Interrupted/truncated AUC profiles
- Issues in estimating terminal rate constant (λz)



MIE supports final ANDA approval in 2023:

A PPK model was developed, with sufficient validation, to perform data imputation at an individual level for the missing sampling points. Model-based data imputation served as pivotal evidence for ANDA approval.

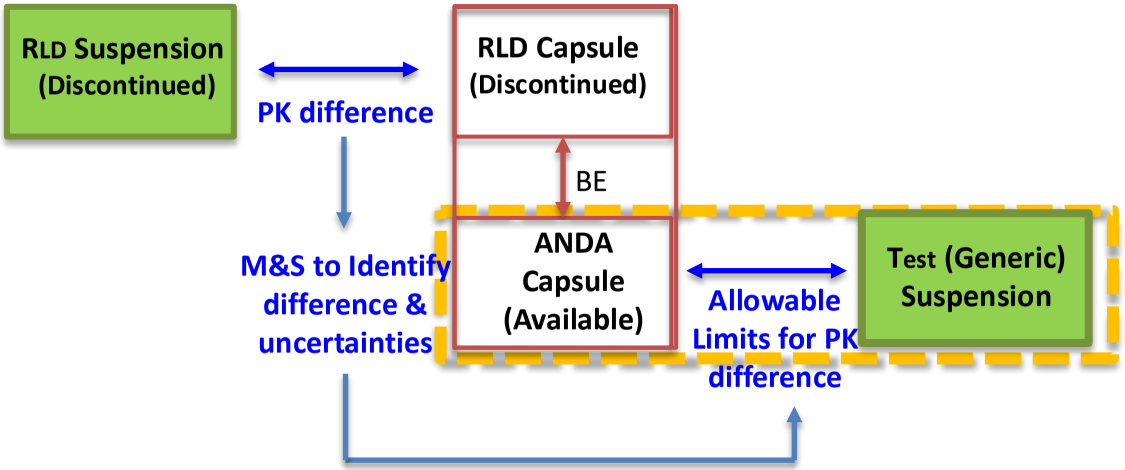
- Data imputation were conducted for 1000 times to account for uncertainty from the residual variability. The passing rate from 1000 imputations was 100%.

Supported by internal research project ORS-INT-2020-03 titled "Quantitative clinical pharmacology modeling and simulation-based supports for bioequivalence assessment during the COVID-19 public health emergency"

Model-Based Scientific Bridging for BE Demonstration With A Discontinued RLD

Question: Can we establish BE between a new test suspension product (T) and the original RLD suspension (R) without conducting a direct BE study between T and R?

MIE Approach: Conducting a comparative in vivo PK study using a currently available capsule product in place of the original RLD suspension to establish BE between T and R. Model-based scientific bridging allows to identify PK differences between formulations, therefore, can be used to define acceptable limits for PK difference between Suspension and Capsule for a typical cross-over BE study.



Regulatory Impact: Model-based bridging opens avenues for generic drug development in scenarios where the RLD and RS are unavailable.

RLD: reference listed drug

K Feng, Model-based Bridging to Establish Bioequivalence With a Discontinued Reference Listed Product, 2022 ACCP Annual Meeting Transforming Global Health through Clinical Pharmacology, Bethesda September 24-27, 2022.

PBPK Model to Evaluate the Impact of Alcohol Dose Dumping

Background: For topiramate extended release (ER) capsules, increased release of 200 mg Test product was observed under alcohol dose dumping (ADD) study with 20% ethanol, but not for ADD study with 5% or 40% ethanol.

Question: Can PBPK model be used to evaluate whether increased release of the Test product at pH 1.1 with 20% ethanol would significantly impact the systemic exposure compared to the RLD which has lower release?

Review and Impact:

- Reviewer developed PBPK model. The Test and RLD products are predicted to be bioequivalent using developed bi-phasic dissolution profiles, i.e., increased release in Test product at pH 1.1 with 20% ethanol will not result in significant differences in systemic exposure, compared to RLD.
- Based on review with PBPK modeling, we concluded that there is no significant safety concern arising from the ADD study with higher release from the Test product and support tentative approval of this ANDA.

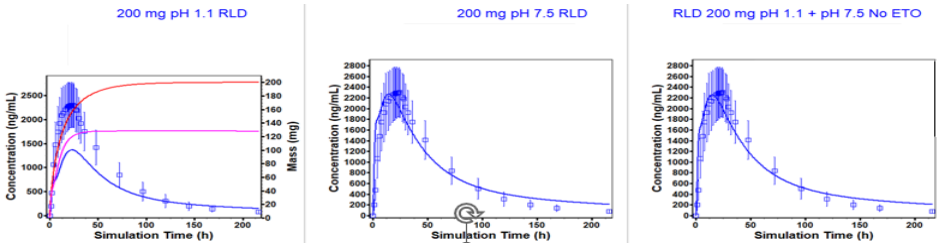


Figure 1. Model prediction of PK profile following administration with RLD of 200 mg topiramate ER capsules incorporated with dissolution testing results without ethanol at (A) pH 1.1, (B) pH 7.5, and (C) bi-phasic (dissolution at pH 1.1 within 1 hour and dissolution at pH 7.5 after 1 hour). Dissolution at pH 1.1 is not bio-predictive whereas bi-phasic dissolution is bio-predictive to the PK profiles of RLD.

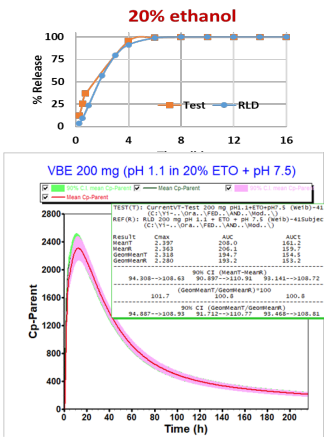


Figure 2. Bi-phasic dissolution profiles can mimic drug release in different GI segments of stomach (dissolution at pH 1.1 with or without 20% ethanol within 1 hour) and intestine (dissolution at pH 7.5 after 1 hour). VBE simulation results suggest that bi-phasic dissolution profiles are considered biorelevant/bio-predictive to the PK profiles following 200 mg ~~T~~topiramate ER ~~C~~capsules administration.

Ongoing GDUFA Funded Research
PBPK for Extended-Release Product

- Evaluation of Oral Extended-Release Tablets to Support a Demonstration of Bioequivalence for Additional Strengths (U01FD007959)
  - Grant with Dr. Jie Shen at Northeastern University
- Purpose of the grant
  - Understand how formulation variables (e.g., drug and excipient attributes) across multiple strengths of an extended release (ER) oral drug product influence drug release.
  - Develop mechanistic models parameterized with dissolution data to compare oral ER generic drug products and their corresponding RS (Reference Standard) products across multiple strengths to establish dissolution safe spaces.

Link: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

PBPK Modeling to Support Evaluation of Bioequivalence of Mesalamine DR Tablets, a GI Locally Acting Product

Background: Mesalamine DR tablets is indicated for mildly to moderately active ulcerative colitis. f2 values for dissolution profile comparison between test and RLD products were found to be <50 at pH 6.8 and 6.9 buffer, even though the two products were found to be bioequivalent for systemic PK.

Question: Can we use PBPK modeling to evaluate the risk of bioinequivalence for the test product at site of action?

Review and Impact:

- Reviewers developed PBPK modeling and incorporated three-stage dissolution data, showing that the applicant's dissolution data at pH 7.0 and 7.2 as stage 3 is biopredictive for both RLD and test product for systemic exposure.
- The colon amount was predicted to be similar between RLD and test product when incorporating biopredictive dissolution data at pH (7.0 and 7.2 as stage 3) and the test product is predicted to be bioequivalent to the RLD in terms of the percentage of drug absorbed in the colon, which is in line with Applicant's PBPK model prediction results.
- **Impact**: PBPK model predictions in combination with other scientific review evidence support the approval of this ANDA.

Application of Reviewer PBPK model:

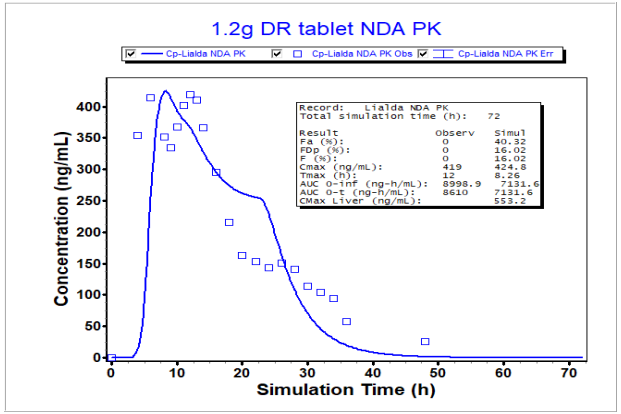


Figure 1. Model prediction versus observed PK data for RLD incorporating three stage dissolution data with stage 3 at pH 7.2 (DQMM reviewer simulation).

pH at Stage 3 Dissolution	PK Parameter	Predicted for Colon for RLD	Predicted for Colon for Test
7.2	Cmax (mg)	157.7	152.4
	AUCt (mg*h)	2592	2609
7	Cmax (mg)	156.6	153.6
	AUCt (mg*h)	2580	2567
6.9	Cmax (mg)	157	153.2
	AUCt (mg*h)	2521	2422

Table 1. Summary of PK parameters Cmax (mg) and AUCt (mg*h) for amount of drug in colon from the simulation results generated by incorporating dissolution profiles at pH 7.2, 7.0 and 6.9.

Ongoing GDUFA Funded Research
PBPK for Gastrointestinal Locally Acting Products

Research focused on improving in vitro bioequivalence (BE) methods and developing predictive in silico models. The following ongoing projects intend to develop in vitro biopharmaceutic data including solubility and dissolution data will be generated for locally acting GI drug products. Using the generated in vitro biopharmaceutics data, model-based virtual BE evaluation will be simulated in healthy and patient population.

- Title: Development of Physiologically Based Biopharmaceutics Modeling (PBBM) Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients. *(Grant #1U01FD007660-01; University of Bath)*

- Title: Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract. *(Grant # 1U01FD007662; University of Florida)*

Dermal PBPK Modeling Supporting Product-Specific Guidance (PSG) Revision for Dapsone Gel

Background: Dapsone topical gels, 5% and 7.5% are single-phase gel products with partially suspended dapsone. PSG Option 1 recommends a characterization-based bioequivalence (BE) approach involving IVRT BE study, an IVPT BE study, a BE study with pharmacokinetic (PK) endpoints, and other product characterization tests for Q1/Q2/Q3 products; Option 2 recommends a comparative clinical endpoint BE study

Question: Could a mechanistic modeling and simulation approach that accounts for the impactful Q3 attributes support development of PSGs for single phase gels with suspended API?

Solution: A dermal PBPK model was developed leveraging drug product specific Q3 data and validated for its cutaneous and systemic PK predictions utilizing data from ANDAs. The model was sensitive to particle size distribution and apparent viscosity inputs. The model showed that when the test product and the RS meet the “no difference” criterion and are Q3 the same, especially with respect to apparent viscosity and particle size distribution, they are bioequivalent in the plasma within the scope of a VBE assessment, in accordance with the outcome of the in vivo BE study with PK endpoints

Regulatory impact: The modeling results supported the revision of the PSG/Option 1 for dapsone topical gels which now does not include an IVPT BE or an in vivo BE study with PK endpoints. The PSG revision facilitated the approval of several ANDAs for dapsone topical gels

GDUFA-funded Research Supporting the Dermal PBPK Modeling Program

Grant	Grant Duration	Institute	Grant No.
Progressing integration of in vitro topical formulation characterisation, release and permeation data to the next level - PBPK based extrapolation to bioequivalence assessment in virtual populations	2021-2023	Certara UK,Ltd	U01FD007323
Dermal Drug Product Quality and Bioequivalence Assessment through Advanced MAM and PBPK Simulation	2021-2023	SimulationsPlus, Inc	U01FD007320
Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics	2021-2023	University of Manchester	U01FD007348
Formulation toolbox for topically applied drugs to account for physical parameters, dynamic metamorphosis and influence of excipients	2024-2027	Certara UK,Ltd	U01FD007954
Development and Validation of a Multi-functional, Multi-purpose Quantitative Tool for Dermal Physiologically-Based Pharmacokinetic Modeling	2024-2027	University of Bath	U01FD007957

CFD and PBPK Modeling Research Supporting PSG Revision

Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol

Background: Formoterol fumarate; glycopyrrolate inhalation metered aerosol, 0.0048 mg/inh; 0.0090 mg/inh, is a suspension-based metered dose inhaler with phospholipid porous particles. PSG Option 1 recommends Q1/Q2 sameness, device similarity, six in vitro BE studies, one comparative characterization study, and two in vivo PK BE studies; Option 2 recommends device similarity, five in vitro BE studies, one comparative characterization study, one in vivo PK BE study, and one in vivo comparative clinical endpoint BE study

Question: What are biorelevant BE limits for recommended in vitro and in vivo studies?

Solution: Regulatory research employing computational fluid dynamics (CFD) and PBPK modeling was conducted via eight external grants and contracts as well internal research has helped clarify regulatory expectations on establishment of model credibility, statistical methods for comparison of results, and regional lung geometry sub-division

Regulatory impact: The regulatory research helped support the first ever inclusion of mechanistic modeling language in a PSG for an orally inhaled drug product, that is intended to facilitate the use of modeling to determine biorelevant BE limits for recommended in vitro and in vivo studies

GDUFA-funded Research Supporting the CFD and PBPK Modeling Research

Grant/Contract	Institute	Grant or Contract No.	End Date
A Predictive Multiscale Computational Tool for Simulation of Drug Absorption and Pharmacokinetics, and Optimization of Pulmonary Drug Delivery	CFD Research Corporation	1U01FD005214	3/28/2018
Development of Computational Models to Predict Delivery of Inhalation Drug Powders: From Deagglomeration in Devices to Deposition in Airways	University of Sydney	1U01FD006525	8/31/2021
A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways	University of Iowa	1U01FD005837	6/30/2022
Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery	Princeton University	1U01FD006514	6/30/2022
A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs	CFD Research Corporation	HHSF223201810182C	8/9/2022
A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia	University of North Carolina at Chapel Hill	1U01FD007338	7/31/2024
Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers	Virginia Commonwealth University	1U01FD007353	1/31/2025
Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs	University of Florida	75F40122C00182	9/29/2025

Seeking Your Comments on Addressing Generic Drug Development Needs via Quantitative Methods and Modeling in FY 2025!

Potential thoughts on

- Facilitating the utility of MIE to support demonstrations of BE
  - Supporting science driven abbreviated BE pathways
  - BE space for in vitro evaluations
  - Novel study designs and in vivo programs (e.g., oncology products and long acting injectables)
  - Best practices for virtual BE studies
- Supporting nitrosamine mitigation strategies
- Assessment of complex active ingredients
- Enhancing the efficiency of BE approaches for complex routes of delivery
- Enhancing the efficiency of equivalence approaches for complex drug-device combination products (e.g., more efficient human factor analysis)
- Abbreviated BE approaches for oral and non-oral products
  - Biowaivers
- Use of AI and ML Tools for generic drug development
  - PSG and assessment tools
  - Neural networks for pharmacometrics models

U.S. FOOD & DRUG ADMINISTRATION

Seeking Your Input on Future Research under the GDUFA Regulatory Science Program!