

FY2018 GDUFA Science and Research Report: Quantitative Clinical Pharmacology

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2015 GDUFA Science and Research Report: Pharmacokinetic/Pharmacodynamic Models and Pharmacometrics
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503046.htm>)
- FY2016 GDUFA Science and Research Report: Pharmacokinetic/Pharmacodynamic Models and Pharmacometrics
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549177.htm>)
- FYs 2013-2017 GDUFA Science and Research Report: Pharmacokinetic/Pharmacodynamic Models and Pharmacometrics
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm>)

Introduction

Quantitative Clinical Pharmacology (QCP) is a quantitative platform that describes drug disposition, drug action, and associated variability in humans. In generic drugs, QCP approaches integrate physiological, biological, and drug properties to set up clinically relevant bioequivalence (BE) criteria, evaluate post-market signals on generic switches, and explore alternate BE study designs. QCP-based approaches are essential to evaluate the study design and sensitivity and reduce cost and time of complex product development. For instance, we have developed modeling and simulation toolsets to direct the design and evaluation of pharmacokinetics (PK) or comparative clinical endpoint BE studies, enabling the assessment of alternative BE approaches for complex products. Our approaches have been applied in various regulatory activities, including consultation responses, citizen petition responses, development of product-specific guidances (PSGs), pre-abbreviated new drug application (ANDA) meetings and ANDA reviews related to complex products.

Research

QCP was highlighted in the FDA public workshop titled “Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review” (October 2-3, 2017). Dr. Scott Gottlieb, FDA commissioner, delivered the keynote speech. He considered the use of sophisticated quantitative methods and computational modeling in drug development, evaluation, and review a central aspect of fully implementing the Drug Competition Action Plan, spurring innovation, and improving regulatory decision-making. He elaborated that modeling and simulation play an important role in many aspects of the development and review processes of generic drugs. Dr. Gottlieb shared FDA’s intentions to increase investment in advancing the development of the state-of-the-art modeling and simulation technologies and applying them to generic drug development and review. Dr. Kathleen Uhl, director of the Office of Generic Drugs (OGD), delivered the opening remarks. Dr. Uhl highlighted the opportunities for using quantitative methods and modeling for the development and review of generic drugs and the potential to improve first-cycle generic drug approval rates, reduce cost and time of product development, and expedite approval of safe and effective generic products. Some specific examples from the QCP research program are highlighted below.

Evaluation of Model-based Bioequivalence (MBBE) Statistical Approaches for PK Studies with Sparse Sampling Scheme

In traditional BE analysis, two one-sided tests (TOST) are conducted on the area under the concentration-time curve (AUC) and the maximal concentration (C_{max}), generally derived from PK studies with rich sampling, which is not always feasible. Bioequivalence studies where rich sampling may be challenging include ophthalmic PK studies in cataract surgery patients, PK studies for long-acting injectables and oncology drugs that are unsafe to give to healthy subjects.

We collaborated with Dr. France Mentre's group (University Paris Diderot and INSERM, France) to implement a model-based (MB) TOST using 1) an empirical standard error (SE) or confidence interval (CI) from a parametric bootstrap method, and 2) a CI from the posteriori distribution of the treatment effect sampled by Hamiltonian Monte Carlo (HMC) using Stan. These approaches were evaluated on scenarios with rich/sparse sampling designs and moderate between subject variability ($BSV \leq 30\%$). For a scenario with a sparse sampling protocol, the work confirmed that the MB TOST with asymptotic SE obtains inflated type I error estimates. MB TOST with bootstrap SE or HMC CI showed more accurate type I error estimates (i.e., included in the 95% prediction interval around 0.05 for 500 simulations = [0.0326;0.0729]). All approaches of MB TOST showed sufficient power (between 0.76 and 1) under the rich and sparse sampling scenarios. The research project explored and assessed approaches which are less sensitive to the type I error inflation on PK studies with sparse sampling as compared to that of the MB TOST with an asymptotic SE. Implementation of these approaches may provide alternative BE assessment methodologies in situations where conventional BE approaches are not feasible.

We also collaborated with Dr. Andrew Hooker (Uppsala University, Sweden) to develop novel nonlinear mixed effect (NLME)-based approaches for BE evaluation and optimal trial design of PK studies with sparse sampling. This project was to explore model-based BE (MBBE) approaches for products where conventional BE studies are challenging to conduct such as long-acting injectables (LAIs) and ophthalmic products with sparse design PK studies (Table 1). Successful completion of this project may result in recommendation of novel NLME-based BE evaluation method for products such as anti-cancer, pediatric, and ophthalmic products where NLME-based BE methods will be developed for extremely sparse PK data.

Table 1. Proposed algorithm for non-linear mixed effect MBBE approach

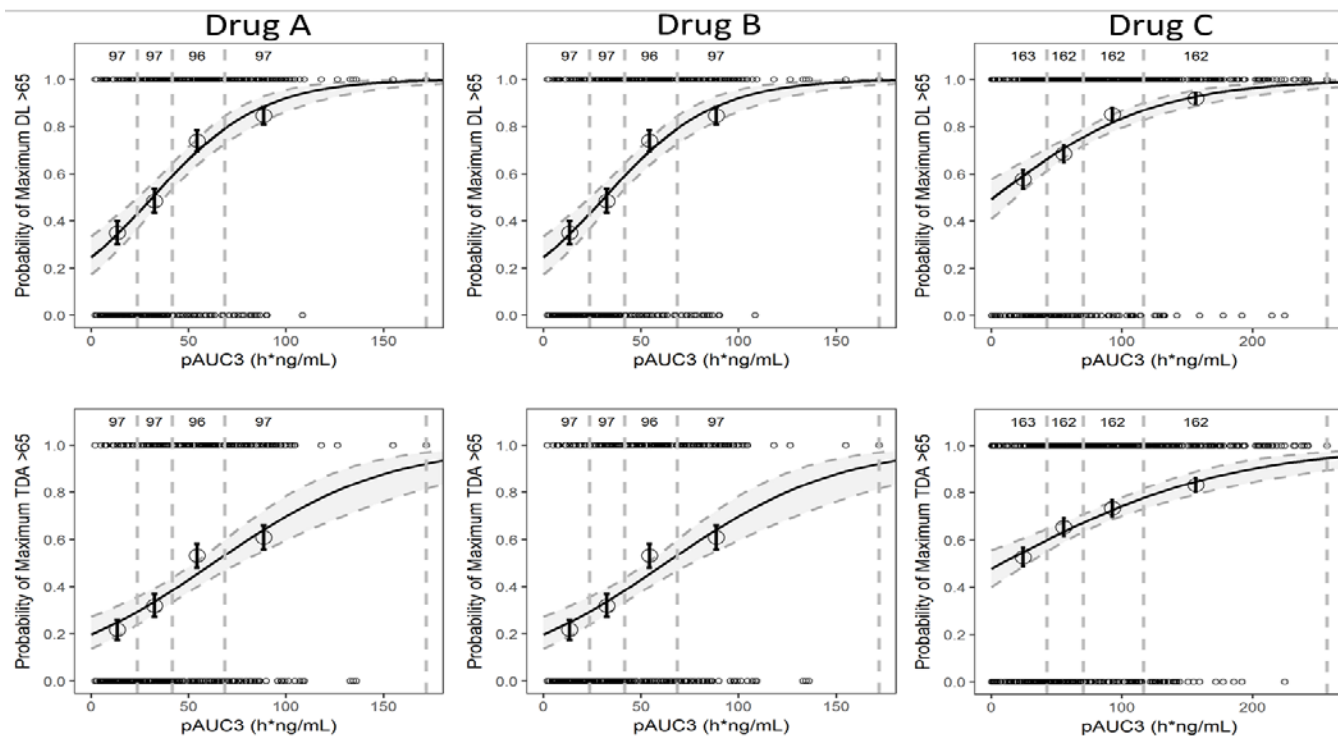
repeat
Step 1 Sample a model parameter vector $\Theta \in (\theta, \Omega, \Sigma)$ from the uncertainty distribution of the maximum-likelihood estimates Θ_{ML} .
Step 2 Simulate a population of individuals (assuming no period effects, sequence effects or inter-occasion variability if present in the model).
Step 3 Compute the NCA metrics for each individual and treatment.
Step 4 Compute population summary metrics of individual NCA metrics for each treatment.
until Enough samples are taken to quantify the uncertainty;
Step 5 Compare distributions of population summary metrics, accept or reject bioequivalence based on pre-specified boundaries.

Adapted from Dr. Andrew Hooker’s presentation at FDA public workshop titled “Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review”, October 2-3, 2017.

Quantitative analysis of PK/Pharmacodynamic (PK/PD) Relationship of Abuse-Deterrent Opioid Products

The goal of this internal project was to use PK/PD analysis to inform FDA evaluation of abuse-deterrent properties and help develop the general guidance on “[General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Product](#)”¹ and PSG for abuse-deterrent opioid drug products. To achieve this goal, the project team evaluated the relationships between different PK metrics and abuse potential responses using the clinical results from the new drug applications (NDAs) of opioid drug products. The results suggest that early partial AUCs (pAUCs) (e.g., pAUC_{0-3 hr}) may be associated with maximum Drug Liking Visual Analogue Scale (VAS) (Figure 1). Therefore, the PSGs of abuse-deterrent opioid drug products recommend early pAUCs, in addition to conventional PK metrics (e.g., C_{max}, AUC_t and AUC_{inf}), to establish that a generic abuse-deterrent opioid product is no less abuse-deterrent than its reference product.

Figure 1. The Correlation of Probability of Maximum Drug Liking or Maximum Taking it Again VAS Score Greater Than 65 (MAXDL/MAXTDA>65) with Early Partial AUC Over 0-3 hours (pAUC3) for Three Drugs with Abuse-Deterrent Properties.



¹ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf>

Research Projects and Collaborations

New Grants and Contracts

- New Grant (1U01FD006549) *Development of a Virtual Bioequivalence Trial Simulation Platform That Integrates Population Pharmacokinetic Modeling Algorithms into Physiologically-Based Pharmacokinetic Models* with Michael N. Neely at Children's Hospital of Los Angeles
- New Contract (HHSF223201810112C) *Research Proposal to Better Understand Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products* with Hannah Batchelor at University of Birmingham

Continuing Grants and Contracts

- Active Grant (1U01FD005235) *Pharmacokinetic and Pharmacodynamic (PK-PD) Studies of Cardiovascular Drugs* with Larisa Humma Cavallari at University of Florida
- Active Grant (1U01FD005240) *Pharmacokinetic Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder* with Thomas J Spencer at Massachusetts General Hospital
- Active Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Robert Ward at University of Utah
- Active Grant (1U01FD005192) *Pharmacometric Modeling and Simulation for Generic Drug Substitutability Evaluation and Post Marketing Risk Assessment* with Jogarao V Gobburu at University of Maryland
- Active Grant (3U01FD005210-03S1) *A Model and System Based Approach to Efficacy and Safety Questions Related to Generic Substitution* with Lawrence Lesko at University of Florida
- Active Grant (1U01FD005188) *Population Pharmacokinetic and Pharmacodynamic, Dose-Toxicity Modeling and Simulation for Narrow Therapeutic Index (NTI) Drugs* with Jogarao V Gobburu at University of Maryland
- Active Contract (HHSF223201510102C) *Computational Drug Delivery: Leveraging Predictive Models to Develop Bioequivalent Generic Long-Acting Injections* with Sam Rothstein at Qrono, Inc.
- Active Grant (1U01FD005442) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Catherine Sherwin at University of Utah
- Active Grant (1U01FD005444) *Data-Fusion Based Platform Development of Population PKPD Modeling and Statistical Analysis for Bioequivalence Assessment of Long-Acting Injectable Products* with Seongkyu Yoon at University of Massachusetts
- Active Grant (1U01FD005463) *Development of PBPK Simulation for Long-Acting Injectable Microspheres* with Viera Lukacova at Simulations Plus
- Active Grant (1U01FD005875) *Generic Drug Substitution in Special Populations* with Jingjing Qian at Auburn University
- Active Contract (HHSF223201610110C) *Evaluation of Model-Based Bioequivalence Statistical Approaches for Sparse Design PK Studies* with France Mentre at University of Paris
- Active Contract (HHSF223201710015C) *Evaluation and Development of Model-Based Bioequivalence Analysis Strategies* with Andrew Hooker at Uppsala University

Active FDA Research

- *Quantitative Analysis of PKPD Relationship of Abuse Deterrent Opioid Products*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Batch to Batch Variability of Inhalation Products*

- *Clinical Trial Simulation for Clinical Endpoint Bioequivalence Studies*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*

Outcomes

General Guidance

- *Final Guidance on “General principles for evaluating the abuse deterrence of generic solid oral opioid drug products”* FDA Guidance Posting. November 2017. [Link to Posting](#).

Product-Specific Guidances

- *New Draft Guidance for Everolimus Oral Tablet, for Suspension*. FDA Guidance Posting. Oct. 19, 2017. [Link to Posting](#).
- *New Draft Guidance for Ivermectin Topical Cream*. FDA Guidance Posting. Oct. 19, 2017. [Link to Posting](#).
- *Revised Draft Guidance for Hydrocodone Bitartrate Oral Tablet, Extended Release*. FDA Guidance Posting. July 20, 2018. [Link to Posting](#).
- *Revised Draft Guidance for Morphine Sulfate; Naltrexone Hydrochloride Oral Capsule, Extended Release*. FDA Guidance Posting. July 20, 2018. [Link to Posting](#).
- *Revised Draft Guidance for Oxycodone Hydrochloride Oral Tablet, Extended Release*. FDA Guidance Posting. July 20, 2018. [Link to Posting](#).
- *New Draft Guidance for Betrixaban Oral Capsule*. FDA Guidance Posting. July 20, 2018. [Link to Posting](#).
- *Revised Draft Guidance for Morphine Sulfate Oral Tablet, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. [Link to Posting](#).
- *Revised Draft Guidance for Oxycodone Oral Capsule, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. [Link to Posting](#).
- *New Draft Guidance for Morphine Sulfate Oral Tablet, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. [Link to Posting](#).
- *New Draft Guidance for Oxycodone Hydrochloride Oral Tablet*. FDA Guidance Posting. Sept. 13, 2018. [Link to Posting](#).

Publications

- Brown, J. D. and Pham, P. N. *The Need for Deliberate and Thorough Design and Critique of Observational Comparative Effectiveness Research*. Research in Social and Administrative Pharmacy. (2018) **14**:1085–1087. doi: [10.1016/j.sapharm.2018.07.012](#). PMID:[30041916](#).
- Fang, L., Kim, M. J., Li, Z., Wang, Y., DiLiberti, C. E., Au, J., Hooker, A., Ducharme, M. P., Lionberger, R., and Zhao, L. *Model-Informed Drug Development and Review for Generic Products: Summary of FDA Public Workshop*. Clin Pharmacol Ther. (2018) **104**(1):27–30. doi: [10.1002/cpt.1065](#). PMID: [29603191](#).
- Gandhi, A., Beekman, C., Parker, R., Fang, L., Babiskin, A., and Matta, M. K. *Novel and Rapid LC-MS/MS Method for Quantitative Analysis of Methylphenidate in Dried Blood Spots*. Bioanalysis. (2018) **10**(11):839–850. doi: [10.4155/bio-2018-0024](#). PMID: [29863895](#).
- Hohmann, N., Hansen, R., Garza, K. B., Harris, I., Kiptanui, Z., and Qian, J. *Association Between Higher Generic Drug Use and Medicare Part D Star Ratings: An Observational Analysis*. Value in Health. (2018) **21**:11861191. doi: [10.1016/j.jval.2018.03.005](#). PMID:[30314619](#).
- Rower, J. E., Stockmann, C., Linakis, M. W., Kumar, S. S., Liu, X., Korgenski, E. K., Sherwin, C. M. T., and Molina, K. M. *Predicting Tacrolimus Concentrations in Children Receiving a Heart Transplant Using a*

Population Pharmacokinetic Model. *BMJ Paediatr Open*. (2017) 1:e000147. doi: [10.1177/1060028017705393](https://doi.org/10.1177/1060028017705393). PMID: 29177199.

Presentations

- Dahmane, E., Gobburu, J., and Ivaturi, V. *Pharmacometric Approach to Define Narrow Therapeutic Index (NTI) Drugs & Evaluate Bioequivalence (BE) Criteria for NTI Drugs*. Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug. White Oak, MD, Oct. 2, 2017.
- Fang, L. *Leveraging Quantitative Methods in Reviewing Complex/Locally Acting Products*. Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review. White Oak, MD, Oct. 2, 2017.
- Fang, L. *Marriage Between Quantitative Approaches and Regulatory Science: A Reality Check on Where We Are*. Presentation at American Conference on Pharmacometrics. Fort Lauderdale, FL, Oct. 17, 2017.
- Fang, L. *Is Bioequivalence Established in Adults Relevant for Pediatrics?* Presentation at American Association of Pharmaceutical Scientists Annual Meeting Workshop: Dermatological Drug Products: Developmental & Regulatory Considerations. San Diego, CA, Nov. 12, 2017.
- Hooker, A. *Model-Based Approaches as Guidance to Bioequivalence Decision Making: Design and Analysis Considerations*. Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review. White Oak, MD, Oct. 2, 2017.
- Hooker, A. C. *Improved Model-Based Bioequivalence Strategies*. Presentation at American Conference on Pharmacometrics. Fort Lauderdale, FL, Oct. 17, 2017.
- Li, M. *Batch-to-Batch Pharmacokinetic Variability of Orally Inhaled Drug Products*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.
- Schmidt, S. Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review. Oct. 2, 2017.
- Schmidt, S. Presentation at GDUFA Regulatory Science Public Workshop. May 24, 2018.
- Sharan, S. *Evaluation of Residual Levonorgestrel As Potential Bioequivalence Metric for A Long Acting Intrauterine System Using Quantitative Modeling and Simulation Approach*. Presentation at American Association of Pharmaceutical Scientists Webinar. Webinar, MD, Oct. 12, 2017.
- Sharan, S. *Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits for Complex Formulations*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Zhao, L. *Leveraging Quantitative Methods and Modeling to Modernize*. Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review. White Oak, MD, Oct. 2, 2017.
- Zhao, L. *Application of Quantitative Methods and Modeling to Generic Drug Development*. Presentation at International Symposium of Quantitative Pharmacology. Beijing, China, Dec. 1, 2017.

Posters

- Gonzalez Sales, M., Fan, J., Fang, L., Hu, M., Lionberger, R., and Zhao, L. *Age Is a Statistically Significant Predictor of the Within Subject Variability in Dabigatran Pharmacokinetics*. Poster Presentation at American Conference of Pharmacometrics. Ft. Lauderdale, FL, Oct. 15, 2017.
- Kim, H., Fang, L., and Zhao, L. *Quantitative Assessment of Additional Metrics in the Bioequivalence Evaluation of Oxcarbazepine Extended Release Tablet*. Poster Presentation at ASCPT Annual Meeting. Orlando, FL, Mar. 22, 2018.

- Kiptanui et al. *Consistency of Publicly-Accessible Generic Drug Labels with Reference Listed Drug Labels in Dailymed: A Case Analysis for the Special Populations*. Poster Presentation at International Society for Pharmacoepidemiology and outcomes research. Baltimore, MD, May 19, 2018.
- Kiptanui et al. *Consistency of Publicly-Accessible Generic Drug Labels with Reference Listed Drug Labels in Dailymed: A Case Analysis for the Special Populations*. Poster Presentation at 33th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Prague, Cech, Aug. 22, 2018.
- Pan, L., Lionberger, R., and Zhao, L. *The Development of a Novel Measure for Subject by Formulation Interaction*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Shahraz et al., *Development of In Vitro-in-Vivo Correlation for Long Acting Injectable Microsphere Formulations*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Qian, J., Li, C., Huo, N., Mishuk, A., Chen, L., Hansen, R., Harris, I., and Kiptanui, Z. *Generic Substitution Patterns of Levothyroxine and Escitalopram in Subgroups of U.S. Medicare Beneficiaries*. Poster Presentation at 33th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Prague, Cech, Aug. 22, 2018.
- Sales, M., Fang, L., and Zhao, L. *Population Pharmacokinetic Analysis of Dabigatran in Bioequivalence Studies*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Prokash et al, *Data-Fusion Based Platform for Comparing Pharmacokinetics of Long-Acting Injectable Products*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.