FY2018 GDUFA Science and Research Report: Oral Absorption Models and Bioequivalence

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 Reports:
  Advances in Predictive Dissolution and Physiological Models of Drug Absorption
  (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503047.htm)
  Modified Release Drug Products: Therapeutic Equivalence between Brand-Name Drugs and Generics
  (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm512495.htm)
- FY2016 GDUFA Science and Research Reports:
  Advances in Predictive Dissolution and Physiological Models of Drug Absorption
  (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549178.htm)
  Modified Release Drug Products: Therapeutic Equivalence between Brand-Name Drugs and Generics
  (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549172.htm)
- FYs 2013-2017 GDUFA Science and Research Reports:
  Predictive Dissolution and Physiological Models of Oral Absorption
  Modified Release Drug Products
  (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm)

Introduction

A better understanding of oral absorption process will help accelerate generic drug development and enable more efficient ANDA review. The key research goals are to continue to expand the use of Biopharmaceutics Classification System (BCS) for immediate-release (IR) products, provide bioequivalence (BE; defined as "the absence of a significant difference in the rate and extent to which an active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study") approaches for locally acting gastrointestinal (GI) drugs, and establish development and review tools for low-solubility IR drugs and modified-release (MR) formulations.

Research

Research highlights during FY2018 for advances in predictive dissolution and physiological models of oral drug absorption are:

- Grant# 1U01FD005259 awarded to Dr. Lynne Taylor aims to identify critical process parameters and critical quality attributes for amorphous solid dispersion (ASD) drug products and develop dissolution methods that can measure them and make predictions about in vivo performance. Tacrolimus, a poorly water-soluble compound, was identified as the model drug. The team has conducted dissolution testing under sink and non-sink conditions to evaluate the in vivo supersaturation/precipitation process of ASD of tacrolimus. A four-way crossover in vivo BE study has recently been completed comparing: (1) fresh reference ASD drug, (2) fresh generic ASD drug, (3) aged generic ASD drug (low crystallinity), and (4)

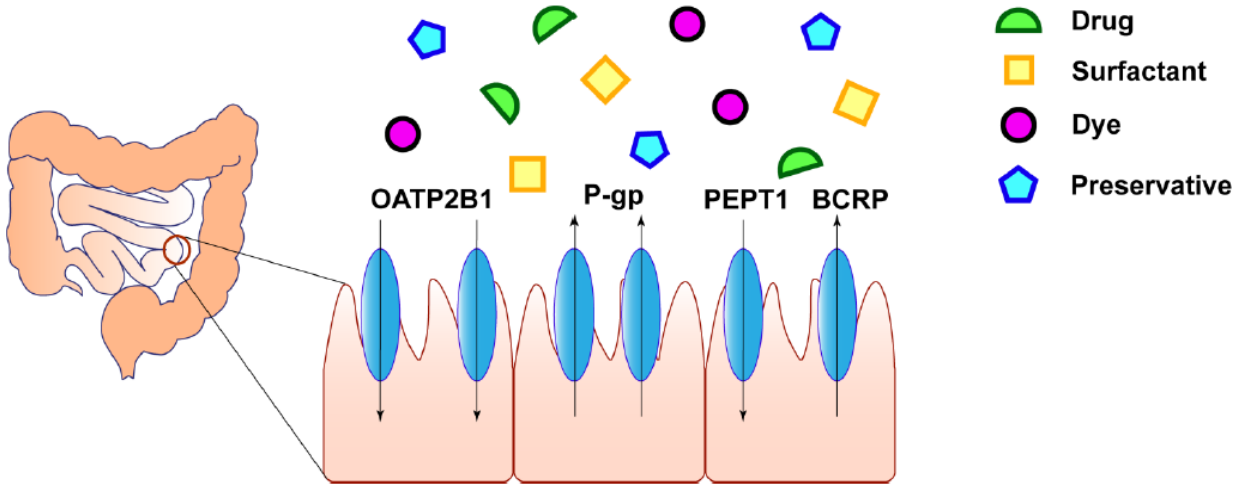
aged generic ASD drug (high crystallinity), to better understand the correlation between in vitro dissolution (sink vs. nonsink) and in vivo pharmacokinetics (PK) and bioanalytical analysis of the samples is ongoing.

- Grant# 3U01FD004979 was awarded to Drs. Kathy Giacomini and Brian Shoichet to enhance our understanding of pharmaceutical excipients (**Figure 1**). Dr. Giacomini's group screened a total of 121 oral molecular excipients for interactions with transporters to help provide a scientific foundation for expansion of BCS Class 3 waivers to non-Q1/Q2 formulations. Dr. Shoichet's group has been focusing on development of an open access online excipients database (http://excipients.ucsf.bkslab.org/) with over 3,100 excipients, 639 of which have specific molecular structure (curated) and using chemoinformatic in silico methods to screen excipients against over 20,000 possible molecular targets.
- Contract# HHSF223201510157C awarded to Dr. Gordon L. Amidon incorporates the most recent advances in gastroenterology, imaging technology, computational mass transport analysis, and development of in vivo predictive dissolution (IPD) methodologies into a GI motility dependent (i.e., under fasted or fed conditions) predictive absorption approach (i.e., oral absorption physiologically-based pharmacokinetic (PBPK) modeling for oral drug products (**Figure 2**). The major findings in FY2018 include: (1) The upper GI human fluids have extremely low buffer capacity; (2) Gastric emptying is non-first-order; (3) Dosing that is random relative to contractual (motility) phase is the single most important contributor to C_{max} variation; and, (4) GI fluid volumes are very low. These data add to our current understanding of GI physiology and will help improve the physiological relevance of in vitro testing methods and in silico transport analysis for prediction of bioperformance of oral solid dosage forms.
- Contract# HHSF223201610004I was awarded to Dr. David Moreton to investigate the dependence of in vivo PK on the formulation design of generic oral extended-release products (matrix) in comparison with that of their Reference Listed Drug (RLD) (osmotic pump) when co-administered with proton pump inhibitors (PPIs)/antacids. The research team has completed a crossover, single-dose, four-treatment, fasting study to evaluate BE between the reference and generic nifedipine extended-release tablets, with or without co-administration of multiple-dose omeprazole/sodium bicarbonate in healthy subjects. The gastric pH and gastric motility of the subjects in different treatments was also measured by a GI pH monitoring system throughout the PK studies.
- Grant# 1U01FD005865 was awarded to Dr. David Barnes Turner with the aim to develop and establish a comprehensive mechanism-based absorption model to predict in vivo PK profiles of supersaturating formulations, and to further establish an in vitro-in vivo correlation (IVIVC) for each of these drug products. The Classical Nucleation Theory (CNT) model that can handle separate particle size distributions (PSDs) for two different solid states of drug with associated different solubility's have been implemented, are available for testing, and will be available in Simcyp V18. A tool had been developed to model ASD with the dual solid state, excipient and food effects had been incorporated into the PBPK model, and the model will be ready for testing and available in Simcyp V18. For the development of mechanistic IVIVC tools for supersaturating drug products, the addition of tools to input non-monotonic (including a precipitation as well as dissolution) in vitro dissolution profiles into the Simcyp Simulator both for bottom-up modelling (standard PBPK modelling) and for the physiologically-based (PB) IVIVC module (single stage method) have been completed and ready for testing.
- The goal of grant# 1U01FD005838 awarded to Dr. Brad Reisfeld is to incorporate population PK modeling aspects in PBPK models to allow for parameter estimation at the individual data level. Several tasks in simulated tempering Markov chain Monte Carlo (MCMC) sampling have been completed including memory management improvement. Analysis algorithm to reduce PBPK model parameter dimensionality has been focused on making the Global Sensitivity Analysis (GSA) analysis more robust and convenient. In particular, the initial version of an R package, pksensi, has been developed. A user-

friendly, open source computational platform for implementing an integrated approach for population PBPK modeling is being developed and tested.

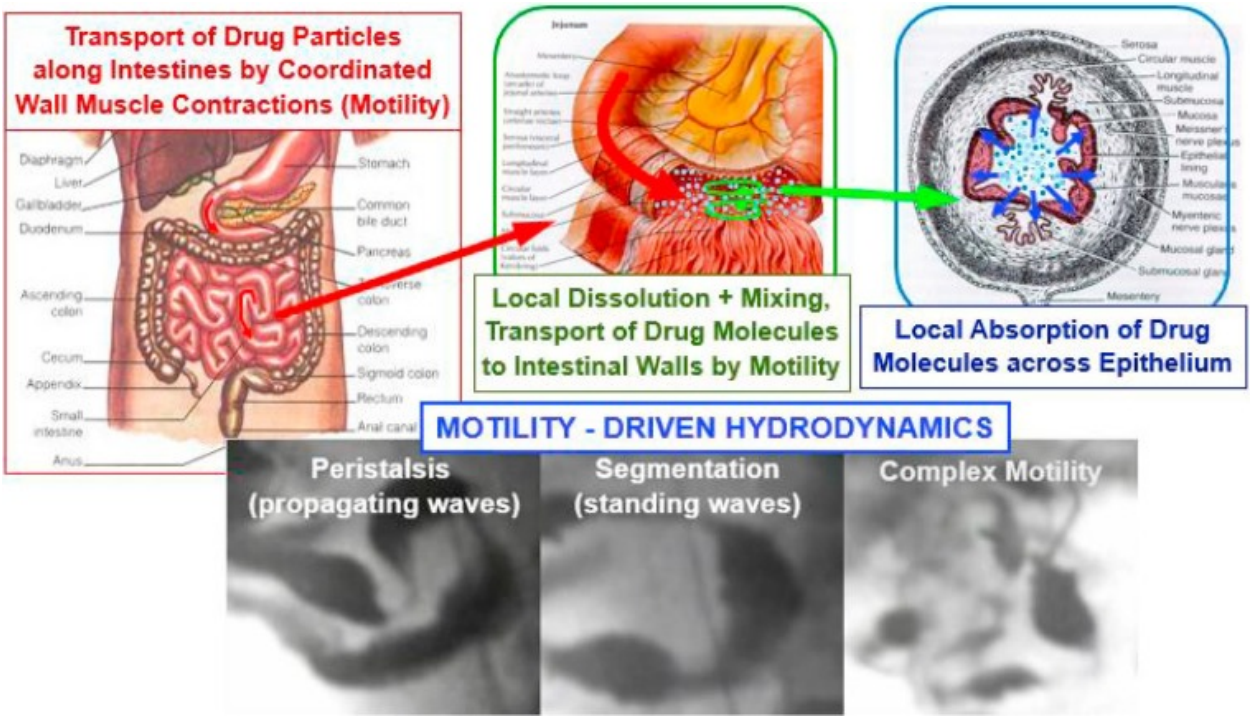
- Internal collaboration with the Office of Testing and Research (OTR) and the Office of Pharmaceutical Quality (OPQ) evaluated the BE of generic sucralfate tablet using in vitro characterization techniques and supported the draft guidance for industry on the BE of sucralfate oral tablets. The internal collaboration focused on monitoring of tablet disintegration, aggregation (**Figure 3**), protein binding, in vitro bioassay and bovine serum albumin (BSA) binding assay to compare the generic and RLD sucralfate tablets. The release of aluminum ions from different formulations were also determined using a validated inductively coupled plasma-mass spectrometry (ICP-MS) procedure.

Figure 1. Graphical Representation of the Interactions between Intestinal Transporters (OATP2B1, P-gp, PEPT1 and BCRP) with the Active Pharmaceutical Ingredient (Drug Substance) and Excipients (Surfactant, Dye, Preservative) Following the Administration of an Oral Dosage Form.



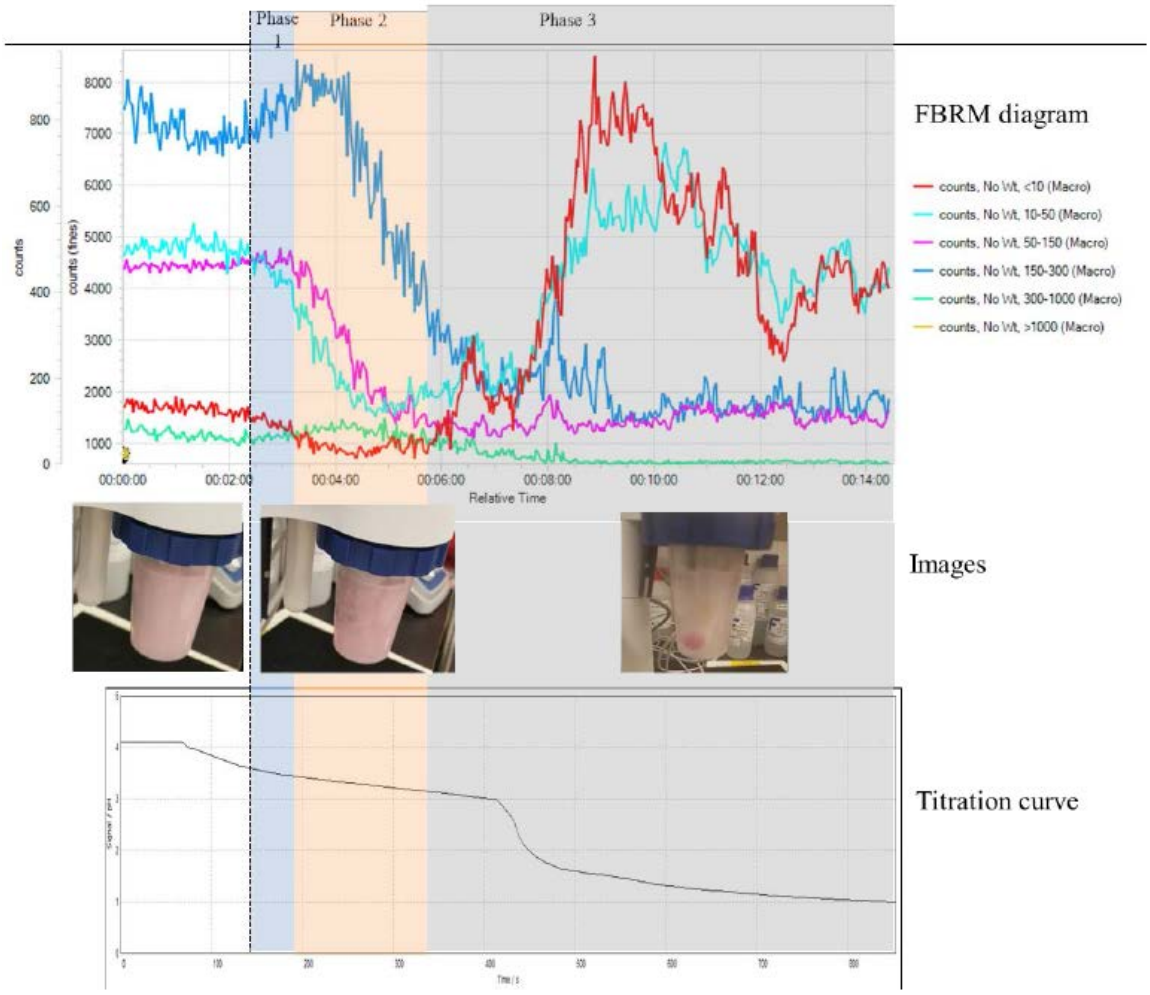
Adapted from Ling Zou, Peter Spanogiannopoulos, Zhanglin Ni, Eleftheria Tsakalozou, Lei Zhang, Peter J. Turnbaugh, Kathleen M. Giacomini. *Interactions of Azo Dyes Commonly Used in Oral Drug Products with the Organic Anion Transporting Peptide 2B1 (OATP2B1) and Human Gut Bacteria*, ASCPT, 2018.

Figure 2. The Role of Intestinal Transport and Contractile Patterns (Motility) on Motility in Drug Release (Dissolution), Drug Particle and Molecular Transport, and Drug Absorption.



The upper images illustrate global transport of intestinal content (upper left image) by peristaltic contractile patterns (left lower image). Peristalsis both transports and mixes drug particles (middle upper image) as drug molecules are released and mixed and absorbed (upper right image) within localized "pockets" of fluid that change in time by the axially moving local contractile patterns (lower left image). In addition, standing wave "segmentation" motility patterning (lower middle image) predominantly mix drug particles and molecule locally within pockets, and increases lateral transport of drug molecules to the mucosal surface (upper right image), where they can be absorbed. Whereas peristalsis and segmentation are the more common canonical motility patterns, more complex patterns, with mixes of peristalsis and segmentation, can occur (bottom right image), as are periods with little or no motility. Each different motility pattern impacts hydrodynamic contributions to dissolution and transport differently. Adapted from Hens B *et al.*, *Formulation predictive dissolution (fPD) testing to advance oral drug product development: An introduction to the US FDA funded '21st Century BA/BE' project*, International Journal of Pharmaceutics, Volume 548, Issue 1, 2018, Pages 120-127, ISSN 0378-5173, https://doi.org/10.1016/j.ijpharm.2018.06.050.

Figure 3. A Representative Focused Beam Reflectance Measurement (FBRM) Image.



The representative Focused Beam Reflectance Measurement (FBRM) image shows three phases of major changes in particle count and images of CARAFATE® tablet during acid titration (1N HCl) at 37˚C.

Projects and Collaborations

Continuing Grants and Contracts

- Active Contract (HHSF223201310144C) *Prediction of In Vivo Performance for Oral Solid Dosage Forms* with Gordon Amidon at University of Michigan
- Active Contract (HHSF223201510157C) *In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence (BE) Regulation* with Gordon Amidon at University of Michigan
- Active Grant (3U01FD004979-02S3-P2) *Effect of Excipient Transporter Interactions on BCS Class Drugs* with Kathleen M Giacomini at University of California San Francisco

- Active Grant (1U01FD005978-P2) *Effect of Excipient Transporter Interactions on BCS Class Drugs* with Kathleen M Giacomini at University of California San Francisco
- Active Grant (1U01FD005259) *Formulation, Processing and Performance Interrelationship for Amorphous Solid Dispersions* with Lynne S Taylor at Purdue University
- Active Contract (HHSF223201510146C) *Wireless Sampling Pill to Measure In Vivo Drug Dissolution in GI Tract and Computational Model to Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients* with Duxin Sun at University of Michigan
- Active Grant (1U01FD005865) *Design, Development, Implementation and Validation of a Mechanistic Physiologically-Based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behaviour of Supersaturating Drug Products* with David Barnes Turner at Simcyp, Ltd.
- Active Contract (HHSF223201710137C) *Phase Behavior and Transformation Kinetics of a Poorly Water Soluble Weakly Basic Drug Upon Transit from Low to High pH Conditions* with Lynne Taylor at Purdue University
- Active Contract (HHSF223201610004I-HHSF22301001T) *Evaluation of Formulation Dependence of Drug-Drug Interaction with Proton Pump Inhibitors (PPIs) for Oral Extended-Release Drug Products* with David Moreton at Biopharma Services USA

Active FDA Research

- *Dissolution Measurements of ER Product to Support the Development of Predictive Models of BE*
- *Physicochemical Characterization of Sucralfate Tablets to Support In Vitro BE Methods Identification of Critical Factors for Oral Solution Bioequivalence New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Comparison of Steady State and Single Dose BE Studies for MR Products*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Evaluation of the Need for Sprinkle BE Studies*
- *Identification of the Critical BE Issues for Gastro-Retentive Delivery Systems*
- *Prioritization and Optimization of Modified Release BE Guidances*

Outcomes

Product Specific Guidances

- *Revised Draft Guidance for Mesalamine Oral Capsule, Extended Release*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *Revised Draft Guidance for Sucralfate Oral Suspension*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.

Publications

- Del Moral Sanchez, J., Gonzalez Alvarez, I., Cerda Revert, A., Gonzalez Alvarez, M., Navarro Ruiz, A., Amidon, G., and M., B. S. *Biopharmaceutical Optimization in Neglected Diseases for Paediatric Patients by Applying the Provisional Paediatric Biopharmaceutical Classification System*. Br J Clin Pharmacol. (2018) **84**(10):2231–2241. doi: 10.1111/bcp.13650. PMID: 29846973.
- Gagne, J., Polinski, J., Jiang, W., Dutcher, S., Xie, J., Lii, J., Fulchino, L., and Kesselheim, A. *Correction To: Outcomes Associated with Generic Drugs Approved Using Product-Specific Determinations of Therapeutic Equivalence. Drugs.* (2018) **78**(4):523–4. doi: 10.1007/s40265-0180890-x. PMID: 29520639.

- 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.
- Hens, B. et al. *Low Buffer Capacity and Alternating Motility Along the Human Gastrointestinal Tract: Implications for In Vivo Dissolution and Absorption of Ionizable Drugs.* Mol Pharm. (2017) **14**(12):4281– 4294. doi: 10.1021/acs.molpharmaceut.7b00426. PMID: 28737409.
- Hens, B. et al. *Formulation Predictive Dissolution (Fpd) Testing to Advance Oral Drug Product Development: An Introduction to the US FDA Funded '21st Century BA/BE' Project.* Int J Pharm. (2018) **548**(1):120– 127. doi: 10.1016/j.ijpharm.2018.06.050.. PMID: 29944899.
- Hens, B., Bermejo, M., Tsume, Y., Gonzalez-Alvarez, I., Ruan, H., Matsui, K., Amidon, G. E., Cavanagh, K. L., Kuminek, G., Benninghoff, G., Fan, J., Rodriguez-Hornedo, N., and Amidon, G. L. *Evaluation and Optimized Selection of Supersaturating Drug Delivery Systems of Posaconazole (BCS Class 2b) in the Gastrointestinal Simulator (GIS): An In Vitro-in Silico-In Vivo Approach*. Eur J Pharm Sci. (2018) **115**:258–269. doi: 10.1016/j.ejps.2018.01.039. PMID: 29378253.
- Hens, B. et al. *Summary of the In Vivo Predictive Dissolution (IPD) Oral Drug Delivery (ODD) Conference 2018.* Dissolution Technologies. (2018) **25**(5):50–53. doi: 10.1208/s12248-018-0217-6.
- Hens, B., Talattof, A., Paixao, P., Bermejo, M., Tsume, Y., Lobenberg, R., and Amidon, G. *Measuring the Impact of Gastrointestinal Variables on the Systemic Outcome*. AAPS J. (2018) **20**(3):57. doi: 10.1021/ acs.molpharmaceut.7b00426. PMID: 29600330.
- Koenigsknecht, M. J. et al. *In Vivo Dissolution and Systemic Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract Under Fed and Fasted Conditions*. Mol Pharm. (2017) **14**(12):4295– 4304. doi: 10.1021/acs.molpharmaceut.7b00425. PMID: 28937221.
- Paixao, P. et al. *Gastric Emptying and Intestinal Appearance of Nonabsorbable Drugs Phenol Red and Paromomycin in Human Subjects: A Multi-Compartment Stomach Approach.* Eur J Pharm Biopharm. (2018) **129**:162–174. doi: 10.1016/j.ejpb.2018.05.033. PMID: 29857136.
- Purohit, H., Trasi, N., Sun, D., Chow, E., Wen, H., Zhang, X., Gao, Y., and Taylor, L. *Investigating the Impact of Drug Crystallinity in Amorphous Tacrolimus Capsules on Pharmacokinetics and Bioequivalence Using Discriminatory In Vitro Dissolution Testing and PBPK Modeling and Simulation*. J Pharm Sci. (2018) **107**(5):1330–41. doi: 10.1016/S1474-4422(16)00014-4. PMID: 29289674.
- Sinko, P., Gidley, D., Vallery, R., Lamoureux, A., Amidon, G., and Amidon, G. *In Vitro Characterization of the Biomimetic Properties of Poly(Dimethylsiloxane) to Simulate Oral Drug Absorption*. Mol Pharm. (2017) **14**(12):4661–4674. doi: 10.1021/acs.molpharmaceut.7b00798. PMID: 29120190.
- Talattof, A. and Amidon, G. *Pulse Packet Stochastic Model for Gastric Emptying in the Fasted State: A Physiological Approach.* Mol Pharm. (2018) **15**(6):2107–2115. doi: 10.1021/acs.molpharmaceut.7b01077. PMID: 29504768.
- Tsume, Y. et al. *In Vivo Predictive Dissolution and Simulation Workshop Report: Facilitating the Development of Oral Drug Formulation and the Prediction of Oral Bioperformance*. AAPS J. (2018) **20**(6):100. doi: 10.1208/s12248-018-0260-3. PMID: 30191341.
- Tsume, Y., Igawa, N., Drelich, A., Amidon, G., and Amidon, G. *The Combination of GIS and Biphasic to Better Predict In Vivo Dissolution of BCS Class IIb Drugs, Ketoconazole and Raloxifene*. J Pham Sci. (2018) **107**(1):307–316. doi: 10.1208/s12248-018-0260-3. PMID: 28919384.

- Yu, A., Jackson, T., Tsume, Y., Koenigsknecht, M., Wysocki, J., Marciani, L., Amidon, G., Frances, A., Baker, J., Hasler, W., Wen, B., Pai, A., and Sun, D. *Mechanistic Fluid Transport Model to Estimate Gastrointestinal Fluid Volume and Its Dynamic Change Over Time*. AAPS J. (2017) **19**(6):1682–1690. doi: 10.1016/j.addr.2003.10.012. PMID: 28980204.

Presentations

- Fan, J. *Potential Impact of Gastric pH On Generic Drug Bioequivalence Evaluation*. Presentation at In Vivo/Formulation Predictive Dissolution Conference 2018. Lake Tahoe, NV, Mar. 6, 2018.
- Jiang, W. *Exclusion of Pharmacokinetic Data in Bioequivalence Assessment.* Presentation at the 3rd GBHI Conference. Amsterdam, Netherlands, Apr. 12, 2018.
- Jiang, W. *In Vivo Relevance of Dissolution*. Presentation at 58th Annual Land O'Lakes Pharmaceutical Analysis Conference. Madison, WI, Aug. 7, 2018.
- Lee, S.-C. *Establishing Bioequivalence for Generic Oral Modified-Release Products: Regulatory Considerations and Utility of In Vivo Predictive Dissolution.* Presentation at In Vivo/Formulation Predictive Dissolution Conference 2018. Lake Tahoe, NV, Mar. 9, 2018.
- Zou, L. *Interactions of Azo Dyes Commonly Used in Oral Drug Products with the Organic Anion Transporting Polypeptide 2B1 (OATP 2B1) and Human Gut Bacteria.* Presentation at ASCPT Annual Meeting. Orlando, FL, Mar. 22, 2018.
- Stamatopoulos, K. *In Silico Tools to Simulate Differences of Regional Differences of Regional Differences of the Human GI tract*. Presentation at UNGAP Meeting. Leuven, Belgium, Mar. 9, 2018.
- Zhang, L. *Influx Intestinal Transporters: A Missing Piece in the Puzzle?* Presentation at ACCP Annual Meeting. Bethesda, MD, Sept. 22, 2018.
- Giacomini, K. *The Effects of Excipients on Intestinal Drug Transporters*. Presentation at ACCP Annual Meeting. Bethesda, MD, Sept. 22, 2018.

Posters

- Al-Ghabeish, M., Feng, X., Mohammad, A., Lionberger, R., Faustino, P., and Ashraf, M. *In Vitro Evaluation of the Performance of a Locally Acting Gastrointestinal Drug, Sucralfate.* Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Feng, X., Al-Ghabeish, M., Lionberger, R., Cruz, C., and Ashraf, M. *Development of an in-Vitro Protein Binding Method for the Evaluation of Bioequivalence of Sucralfate Suspension*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Gao, Z., Ngo, C., Ye, W., Rodriguez, J., Keire, D., Sun, D., Wen, H., and Jiang, W. *Mechanical Response of Nifedipine Extended-Release Tablet During In Vitro Dissolution Testing.* Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Hens, B. et al. *Dynamic Change in Ph by Low Buffer Capacity of Gastrointestinal Fluids Along the Human Gastrointestinal Tract: Implications for In Vivo Dissolution and Absorption of Ionizable Compounds.* Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.
- Hens, B., Bermejo, M., Tsume, Y., Gonzalez-Alvarez, I., Ruan, H., Matsui, K., Amidon, G., Cavanagh, K., Kuminek, G., Rodriguez-Hornedo, N., and Amidon, G. L. *Exploring Dissolution, Supersaturation and Precipitation of Posaconazolein the Gastrointestinal Simulator (GIS) in Parallel with Visualization of Precipitated Drug by Microscopy Studies*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.

- Khalaf, A., Hoad, C., Menys, A., Mudie, D., Wright, J., Heissam, K., Abrehart, N., Gowland, G., Amidon, P., Spiller, R., Amidon, G., and Marciani, L. *Fasted and Fed Motility of the Undisturbed Small Bowel: Development of Novel MRI Methods to Advance In Vivo Predictive Dissolution Studies.* Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.
- LeMerdy, M., Sun, D., Ni, Z., Babiskin, A., Lee, S.-C., Zhao, L., and Fan, J. *Physiologically-Based Pharmacokinetic Modeling Approach to Identify the Drug-Drug Interaction Mechanism of Nifedipine and a Proton Pump Inhibitor, Omeprazole*. Poster Presentation at American College of Clinical Pharmacy. Bethesda, MD, Sept. 24, 2018.
- Liu, D., Jamei, M., and Turner, D. *A New Particle Population Balance Model (PPB) for PBPK Modelling of Orally Dosed Drugs Accounting for Two Solid States*. Sept. 11, 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.
- Zou, L., Spanogiannopoulos, P., Ni, Z., Tsakalozou, E., Zhang, L., Turnbaugh, P., and Giacomini, K. *Interactions of Azo Dyes Commonly Used in Oral Drug Products with the Organic Anion Transporting Peptide 2b1 and Human Gut Bacteria.* Poster Presentation at ASCPT Annual Meeting. Orlando, FL, Mar. 21, 2018.