FY2019 GDUFA Research Report: Abuse-Deterrent Opioid Drug Products

Summary of FY2019 Activities

In FY2019, several intramural and extramural research projects focused on enhancing our assessment of abuse-deterrent formulations (ADF) of opioid drug products.

Nasal insufflation studies in non-dependent recreational drug users are currently recommended for products with an abuse-deterrence (AD) claim via the nasal route. One contract (HHSF223201510138C) investigated the formulation design and manipulated ADF properties on opioid bioavailability following insufflation of milled ADF of oxycodone extended-release (ER) product. This study revealed that when the ADF oxycodone ER product was milled into fine particles (106-500 µm), the rate and extent of oxycodone absorption following insufflation were similar between an ER ADF (OxyContin®) and immediate-release (IR) ADF (Roxicodone®). Particle size had a significant effect on nasal pharmacokinetics (PK). However, for finely milled oxycodone ER, the polymer-to-drug ratio (PDR) did not significantly impact PK (See Figure 1).

One design for AD properties involves incorporation of opioid agonists and antagonists in the same dosage form, which presents unique challenges in AD assessments. A contract (HHSF2232016100041-HHSF22301002T) has been awarded to investigate nasal PK and pharmacodynamics (PD) of such combination ADF to evaluate product and design factors affecting the bioavailability of opioid agonists and antagonists following nasal insufflation of manipulated products as well as the consequent human abuse potential.

As in vivo studies are costly, efforts have been made to develop in vitro testing methods and in silico models to predict the bioavailability of manipulated ADF following various routes of abuse to aid in study design and minimize the reliance on in vivo studies. For the nasal route, FDA has established a dissolution method using USP Apparatus 4 and a realistic 3D nasal cavity model. The developed in silico model used in vitro dissolution data as input has so far predicted well for manipulated IR tablets (See Figure 2). The application of this model to the testing of ER products is ongoing. Similar integrated in vitro-in vivo efforts are also ongoing and working to predict bioavailability following chewing of ADF products. A grant (Grant 3UO1FD004275) has been awarded to produce a hydrocodone bitartrate ADF that will be studied in a future chewing PK study (Contract HHSF223201610004I/75F40119F19004). These studies will evaluate operation parameters for a chewing apparatus to mimic human chewing and a dissolution method previously established to generate dissolution profiles for “chewed” ADF to be put through physiologically-based PK (PBPK) modeling.

FDA internal studies have revealed the importance of considering AD as a property that can vary with product storage time and the need to identify relevant and robust surrogate properties/tests. Work is underway to understand the impact of storage temperate/humidity on AD properties. Additionally, the relationship between manufacturing processes, material attributes, and AD properties are also being investigated.

Research Highlights

Contract (HHSF223201510138C) research entitled "Pharmacokinetics Study of Opioid Drug Product Following Insufflation of Milled Drug Products":

This project included a randomized, 4-sequence, 4-period, 4-treatment, open-label, single-dose crossover study to evaluate the impact of particle size and formulation factors on PK and safety of milled ER oxycodone tablets (OxyContin) following intranasal insufflation in recreational opioid users under a naltrexone block. Specifically, the study assessed (1) PK of milled OxyContin compared to milled Roxicodone following intranasal insufflation, (2) the effects of ratio of release controlling excipient (polyethylene oxide) to active pharmaceutical ingredient on nasal bioavailability, and (3) the safety of milled OxyContin compared to milled Roxicodone following intranasal insufflation in non-dependent recreational opioid users.

Particle size distribution was a significant factor in PK following nasal insufflation (see Figure 1). Additionally, drug loss during physical manipulation and drug content in the associated particle size range in the manipulated product are also critical and should be measured in nasal insufflation studies.

Findings from this contract research have complemented FDA's internal research and provided valuable support to many regulatory activities, such as pre-ANDA meetings, and controlled correspondence and ANDA reviews, particularly with respect to characterization of physically manipulated ADF, study design, and data analysis for in vivo nasal insufflation studies.

An internal project to predict the impact of particle size distribution for manipulated products on PK following nasal insufflation:

FDA laboratories have established a dissolution method using a modified USP Apparatus 4 and are developing a method for measuring regional deposition with a 3D-printed anatomically realistic nasal cavity model. The in vitro dissolution and regional deposition study data generated are to be employed as inputs for an in silico model that incorporates both computational fluid dynamics (CFD) analysis and a drug disposition model to predict PK following nasal insufflation. The current in silico model has demonstrated reasonably good predictions of PK for nasal insufflation of manipulated IR tablets (as compared to the data observed in the contract study HHSF223201510138C) (see Figure 2). This in silico model is now being tested for manipulated ER products.

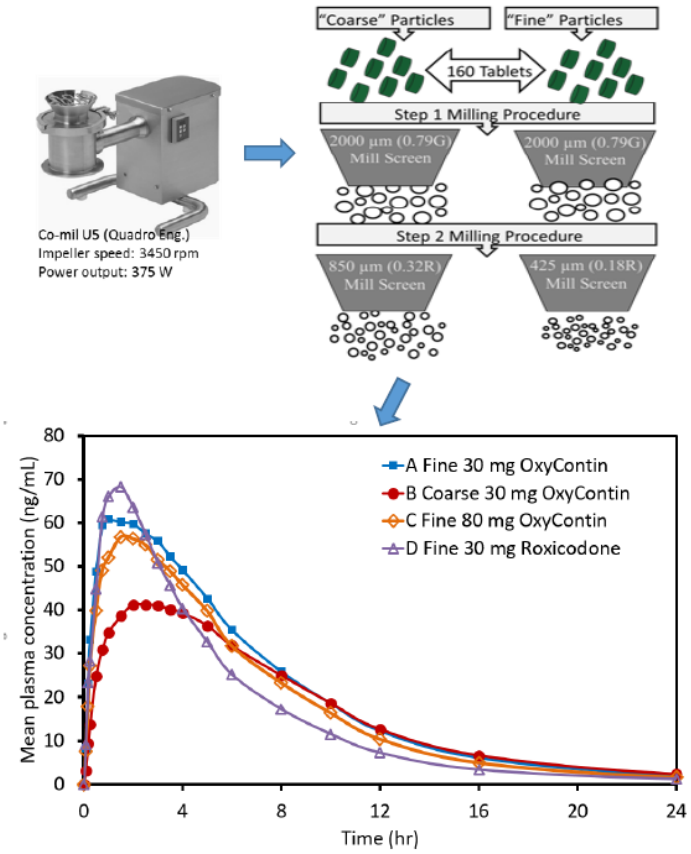


Figure 1: Physical manipulation (milling) of oxycodone HCl ER (OxyContin) and IR (Roxicodone) tablets into coarse (500-1000 µm) and fine particles (106-500 µm) (Upper Panel) and PK profiles following nasal insufflation of milled product at a quantity to contain 30 mg of oxycodone (Lower Panel; Data from Contract HHSF223201510138C presented by Dr. Bradley Vince at American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting in March 2019.)

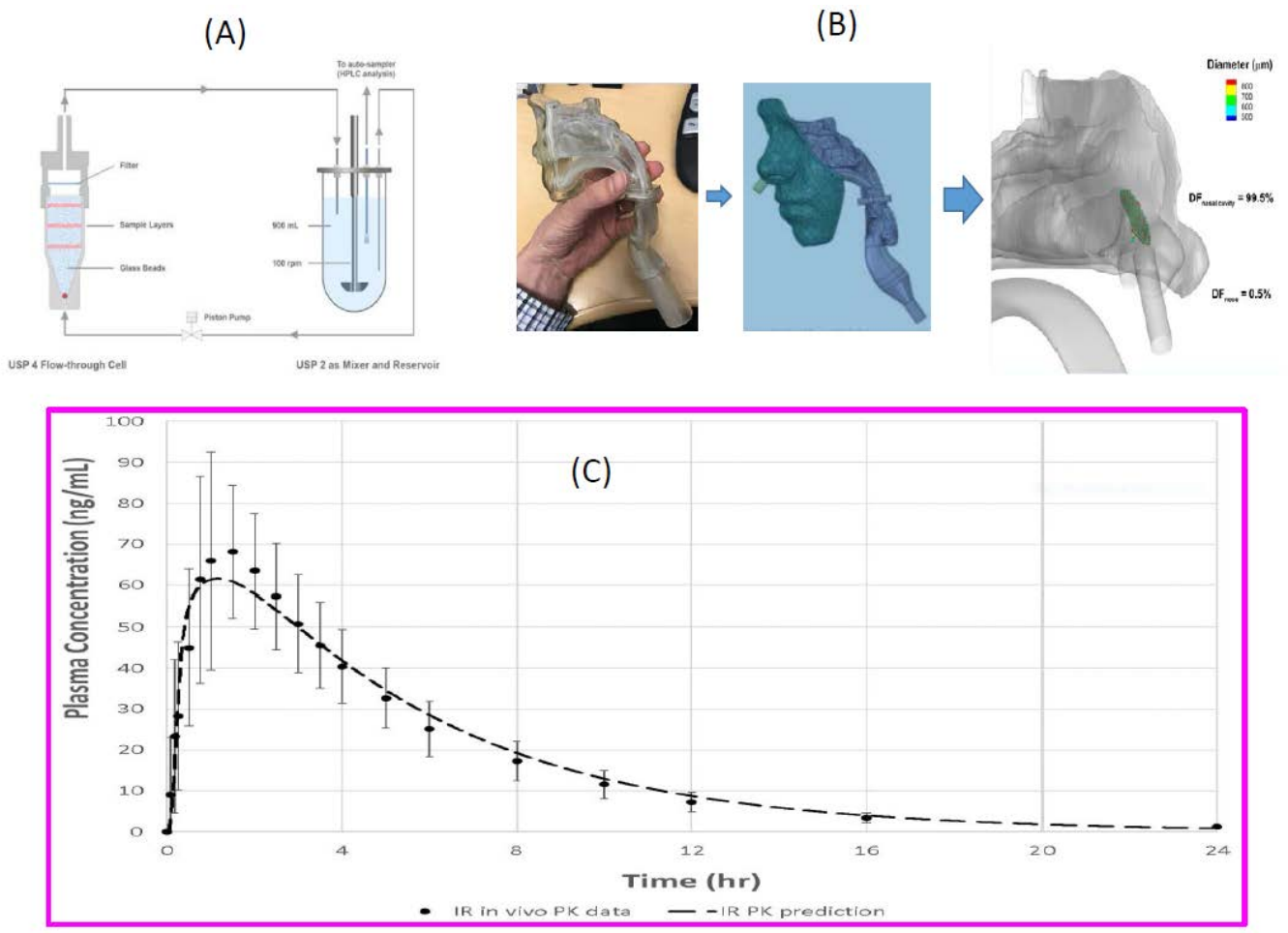


Figure 2: Simulation of PK profile following nasal insufflation of milled oxycodone product using in vitro dissolution data and an in silico CFD model paired with a drug disposition model. (A) Schematic diagram of the modified USP Apparatus 4 Flow Through Dissolution setup, (B) Anatomically realistic nasal cavity model and CFD predictions of regional deposition for nasally insufflated particles, and (C) Simulated vs. observed oxycodone PK profiles following nasal insufflation of milled IR oxycodone ADF.

Research Projects and Collaborations

New Grant and Contract

- Grant (3U01FD004275-075S1) *Formulation Development of Hydrocodone Bitartrate Opioid Drug Product Expected to Have Similar Rate and Extent of Release as HYSINGLA Intact Tablet but Designed to Have Higher Rate of Hydrocodone Release When Product is Chewed* with Vadim J. Gurvich at NIPTE
- Contract (HHSF223201610004I-75F40119F19004) *Pharmacokinetic (PK) Study of Opioid Drug Products Following Oral Ingestion of Chewed Products* with Kathleen Doisy at Biopharma Services USA Inc.

FY2019 GDUFA Science and Research Report

Continuing Grant and Contract

- Grant (3U01FD004275-07S1) *Formulation of Hydrocodone Bitartrate Opioid Tablet* with Vadim J. Gurvich at NIPTE
- Contract (HHSF2232016100041-HHSF22301002T) *Nasal Pharmacokinetic (PK)/Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Kathleen Doisy at Biopharma Services USA Inc.

Completed Contract

- Contract (HHSF223201510138C) *Pharmacokinetics Study of Opioid Drug Product Following Insufflation of Milled Drug Products* with Bradley Vince at Vince & Associates Clinical Research

Active FDA Research

- *Identification of Abuse-Deterrent Surrogates and Test for Abuse-Deterrent Performance Throughout the Shelf-Life*
- *Development of an In Vivo Predictive Method for Determining Opioid Availability Following Chewing of Solid Oral Opioids*
- *Development of In Vitro Methods for Nasal Abuse-Deterrent Opioids*
- *Development of a Standardized Method and a Predictive Model for Syringeability and Injectability Assessment for Abuse-Deterrent Formulations*
- *Understanding the Relationship Between Manufacturing Process, Material Attributes and Abuse-Deterrent Properties*
- *Quantitative Analysis of PKPD Relationship of Abuse Deterrent Opioid Products*
- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*

Outcomes

Articles

- Externbrink, A., Sharan, S., Sun, D., Jiang, W., Keire, D., and Xu, X. *An In Vitro Approach for Evaluating the Oral Abuse Deterrence of Solid Oral Extended-Release Opioids with Properties Intended to Deter Abuse Via Chewing*. International Journal of Pharmaceutics. (2019) **561**:305–313. doi: 10.1016/j.ijpharm.2019.03.017. PMID: 30862508
- Hsu, H., Yang Y., Pavuluri, V., Abraham, C., Naraharisetti, S., Ashraf, M., Al-Ghabeish, M. *Effect of Formulation Variables on the Nasal Permeability and Stability of Naloxone Intranasal Formulations*. AAPS PharmSciTech (2019) **20**:232. doi: 10.1208/s12249-019-1452-6. PMID: 31236738.
- Xu, X., Siddiqui, A., Mohammad, A., Srinivasan, C., Rahman, Z., Korang-Yeboah, M., Feng, X., Khan, M., Ashraf, M. *Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-melt Extrusion*. AAPS PharmSciTech (2019) **20**:230. doi: 10.1208/s12249-019-1448-2. PMID: 31227939.

Posters

- Feng, X., Zidan, A., Kamal, N., Xu, X., Sun, D., Walenga, R., Boyce, H., Cruz, C., and Ashraf, M. *A Flow-Through Dissolution Method for Evaluation of Drug Release from Manipulated Abuse Deterrent Formulations*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.

- Kamal, N., Zidan, A., Feng, X., Xu, X., Sun, D., Walenga, R., Boyce, H., Cruz, C., and Ashraf, M. *Development of In Vitro Permeation Method for Nasally Insufflated Abuse Deterrent Formulations*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Hsu, H., Pavuluri, V., Yang Y., Abraham, C., Naraharisetti, S., Ashraf, M., Al-Ghabeish, M. *Influences of Formulation Variables on Nasal Permeation and Stability of Naloxone in Intranasal Formulations*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Vaghasia, B., Aqueel, M., Siddiqui, A., Ashraf, M., Cruz, C. *Evaluation of the Internal and External Structure of Directly Compressed Polyethylene Oxide (PEO) Based Matrix Tablets Before and after Curing Using X-ray Micro-Computed Tomography*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Boyce, H. Sun, D., S. Raofi, M. Kinjo, Z. Meng, T. Li. *Preferential Drug Loss of Physically Manipulated Abuse-Deterrent (AD) Opioid Drug Products Prepared for Nasal Insufflation Studies.* Poster Presentation AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Boyce, H., Sun, D., Kinjo, M., Raofi, S., Frost, M., Luke, M., Kim, M., Lionberger, R., Vince, B., Kelsh, D., and Li, Z. *Pharmacokinetic Study of Physically Manipulated Oxycodone Hydrochloride Products Following Nasal Insufflation in Recreational Opioid Users.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 13, 2019.
- Sharan, S., Li, Z., Fang, L, Kim, MJ and Zhao, L. *Population Pharmacokinetic Modeling to Characterize the Impact of Oral Abuse After Administration of Manipulated Hydrocodone Bitartrate Extended Release Tablets.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 13, 2019.
- Kibria, G. and Cruz, C. *Stability of Abuse-deterrent Properties of PEO-based Abuse-deterrent Formulations*. Poster Presentation at 4th FDA/PQRI Conference on Advancing Product Quality: Patient-Centric Product Design, Drug Development, and Manufacturing. Received Best Poster Award (1st place). Rockville, MD, Apr. 11, 2019.

Presentations

- Vince, B.D. *Nasal PK Study of Abuse-Deterrent Opioid Products Following Insufflation of Physically Manipulated Products.* Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 15, 2019.
- Zhao, L. *Quantitative Analysis of Opioid ADF PK/ PD.* Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 15, 2019.
- Walenga, R.L. *Computational Fluid Dynamics Modeling of Nasally Administered Drug Products in Regulatory Science Research at the U.S. Food and Drug Administration.* Presentation at the 2019 Society for Computational Fluid Dynamics of the Nose and Airway (SCONA). Chicago, IL, Jun. 5, 2019.
- Fang, L. *PK/PD Meta-Analysis of Abuse Deterrent Opioid Drug Products: PSG Development, Research and ANDA Assessment.* Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop: Complex Drug Product Development, College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Complex Injectables, Formulations and Nanomaterials

Summary of FY2019 Activities

In FY2019, there were 2 external and 10 internal active GDUFA-funded research projects on complex injectable drug products that are manufactured to contain sub-micron formulation elements. These complex drug products that incorporate nanomaterials can include, but are not limited to, emulsions, liposomes, and iron colloid formulations where different arrangements of matter exist and can enhance the product performance. FY2019 GDUFA research projects focused on developing and testing new high-resolution analytical methods for assessing and comparing the nanoscale structural features of these complex products to support formulation equivalence between a proposed generic and its associated reference listed drug (RLD). This GDUFA research priority and associated FY2019 studies aim to assist both the generic drug industry's development and FDA regulatory review of these complex products. For example, an ongoing external study with the University of Maryland, Baltimore, (1U01FD005266) compared the physicochemical properties and conducted a comparative crossover pharmacokinetic (PK) bioequivalence (BE) study of two sodium ferric gluconate products, an approved generic and the brand name reference, to evaluate the feasibility of a crossover BE study compared to the current recommended parallel BE study design.

These research projects generally focused on the development and testing of new analytical methods to better characterize and understand the fundamental properties of liposomal drug products. This research included internal studies that examined an asymmetric flow field flow fractionation (AF4) method in combination with high-performance liquid chromatography ultra-violet-visible and charged aerosol detection to quantify lipid and active pharmaceutical ingredient (API) in different sizes of amphotericin B liposomes, a capillary electrophoresis (CE) method with UV-Vis detection to separate and quantify unencapsulated doxorubicin drug from liposome encapsulated drug, and a liquid chromatography-mass spectrometry-based analytical method to characterize cholesterol oxidation products in parenteral liposomal pharmaceutical formulations. A collaborative project between FDA and the National Institute of Standards and Technology (NIST) continues to develop nanoparticle tracking devices to improve the accuracy of characterizing the size and concentration of liposomal drug products. In addition, a novel dissolution method to characterize drug release from a complex multivesicular liposome (MVL) formulation was developed and published. The study also utilized imaging methods, such as cryogenic scattering electron microscopy (cryo-SEM), to characterize the external and internal MVL structures and changes to these structures during the dissolution process to better understand the drug release mechanism. Please refer to Chapter 3, Report on LAI Products, for more details regarding this project.

Research Highlight

An internal FDA research project focused on developing innovative analytical methods to quantify unencapsulated drug, excipients, and potential impurities in the liposome formulation. This collaborative research project resulted in three publications and received the 2019 FDA Excellence in Analytical Science Scientific Achievement Award.

Common methods to quantify unencapsulated (free) drug from the liposome-associated drugs involve two lengthy steps: first separation of unencapsulated drug from liposome-associated drugs off-line via solid-phase extraction, dialysis, and other methods; followed by quantification of the drug. Another limitation with these off-line separation methods are drug and liposome adsorption and drug leakage, which can lead to inaccurate quantification of unencapsulated drug and liposome-associated drug. To address this issue, a capillary electrophoresis method with UV-Vis detection was developed for a fast separation (10 min) and direct quantification of unencapsulated drug in liposome formulation while minimizing the drug leakage.

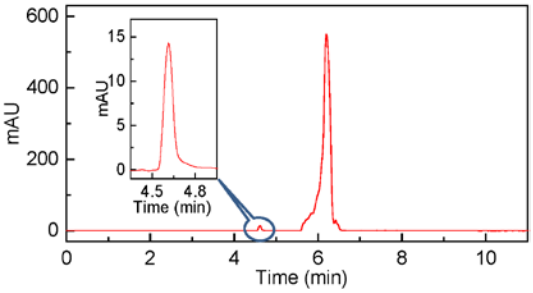


Figure A. Electropherogram of two-fold diluted liposomal doxorubicin formulation (DOX) with peaks at approximately 4.6 min and 6.2 min corresponding to free DOX and encapsulated liposomal DOX. Inset shows the zoomed in electropherogram corresponding to free DOX.

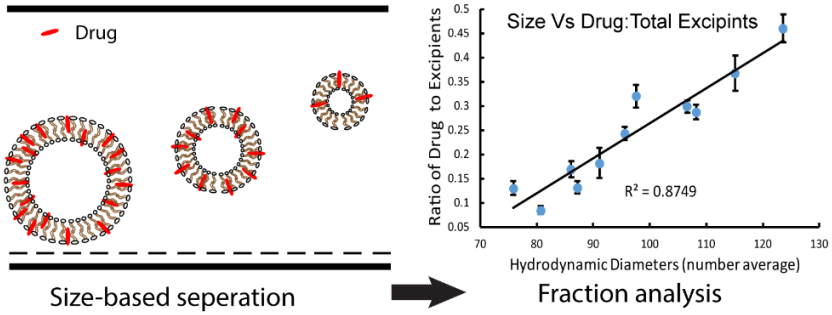


Figure B. Conventional quantitation of drug content in a liposome formulation involves breakdown of bulk liposomes, which ignores details on the distribution of the API and excipients in liposomes of different sizes. An AF4 method was developed for AmBisome, an amphotericin B liposomal formulation, and a HPLC-UV-CAD (Charged Aerosol Detection) method for simultaneous quantitation of the API (amphotericin B), phospholipids and cholesterol. The study results suggest that, for AmBisome, the drug to lipid ratio increases with the size of the liposome. This method provided a more in-depth characterization of liposomes, i.e., determining drug and excipient distributions in different sizes of liposomes, in a more efficient manner with more specific size-based composition information.

Cholesterol is a major structural constituent in a liposomal bilayer, which is susceptible to oxidation during manufacturing or storage. A liquid chromatography-mass spectrometry (LC-MS)-based analytical method was developed to measure cholesterol oxidation products present in liposomal formulations. This method was validated and can be used to ensure the quality and safety of these products.

FY2019 GDUFA Science and Research Report

Research Projects and Collaborations

New Contract

- Interagency Agreement (IAA, 75F40119S30028) *Nanofluidic Slit Devices for Measuring Nan-Particle Drug Concentration to Improve Complex Drug Regulation* with Patrick Hovis at NIST/CNST

Continuing Grant

- Grant (1U01FD005266) *Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate* with Sarah L. Michel at University of Maryland

Completed Contract

- Interagency Agreement (IAA-224-17-3008S) *Nanoparticle Tracking in Nanofluidic Slits* with Samuel Stavis at NIST

Active FDA Research

- *Physicochemical Characterization of Protein-Particle Nanotechnology Drug Products*
- *In Vivo Biodistribution and In Vitro Characterization of Iron Colloid Drug Products*
- *In Vivo Biodistribution Evaluation of Liposome Drug Products*
- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Methods to Characterize Bupivicaine Multivesicle Liposome Structure and Mechanism of Drug Release*
- *Improving In Vitro Drug Release Testing of Complex Drug Products Containing Nanomaterials using a Compendial USP II Apparatus*
- *Application of Cryo-electron Microscopy (cryo-EM) for Morphological Characterization of Complex Nano-drug Products to Improve the Review of In Vitro Bioequivalence Studies*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *Comparative Evaluation of Doxil® and Generic Liposomal Doxorubicin Formulations: Physicochemical Characterization, In Vitro Biocompatibility & In Vivo Efficacy and Biodistribution Evaluation*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Letermovir, Intravenous Solution*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Angiotensin II, Acetate IV Infusion*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Daptomycin IV, Powder for Solution*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Eravacycline Dihydrochloride, Intravenous Powder*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Fosnetupitant Chloride Hydrochloride; Palonosetron Hydrochloride, Intravenous Powder.* FDA Guidance Posting. May 15, 2019. Link to Posting.

- *New Draft Guidance for Chlorpromazine Hydrochloride, Oral Concentrate*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *New Draft Guidance for Hydroxyprogesterone Caproate, Intramuscular Solution*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *New Draft Guidance for Plazomicin Sulfate, Intravenous Solution*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.

Articles

- Ansar, S.M., Jiang, W., Mudalige, T. *Direct Quantification of Unencapsulated Doxorubicin in Liposomal Doxorubicin Formulations Using Capillary Electrophoresis.* International Journal of Pharmaceutics (2018) **549** (1-2), 109-114. doi: 10.1016/j.ijpharm.2018.07.019. PMID:29981410.
- Haute, D., Jiang, W., Mudalige, T. *Evaluation of Size-Based Distribution of Drug and Excipient in Amphotericin B Liposomal Formulation.* International Journal of Pharmaceutics. (2019) **569**: doi: 10.1016/j.ijpharm.2019.118603. PMID: 31401296.
- He, H., Liu, C., Liu, Y., Liu, X., Wu, Y., Fan, J., Zhao, L., Cao, Y. *Mathematical Modeling of the Heterogeneous Distributions of Nanomedicines in Solid Tumors. European* Journal of Pharmaceutics and Biopharmaceutics. (2019) **142**:153–164. doi:10.1016/j.ejpb.2019.06.005. PMID: 31226367
- Neu, H., Alexishin, S., Brandis, J., Williams, A., Li, W., Sun, D., Zheng, N., Jiang, W., Zimrin, A., Fink, J., Polli, J., Kane, M., and Michel, S. *Snapshots of Iron Speciation: Tracking the Fate of Iron Nanoparticle Drugs Via a Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometric Approach*. Molecular Pharmaceutics. (2019) **16**(3):1272–1281. doi: 10.1021/acs.molpharmaceut.8b01215. PMID: 30676753.
- Park, K. *Probing the Mechanism of Drug Release from Liposomes*. Journal of Controlled Release. (2019) **294**:390. Doi: 10.1016/j.jconrel.2019.01.003. PMID: 30660324.
- Park, K., Skidmore, S., Hadar, J., Garner, J., Park, H., Otte, A., Soh, B. K., Yoon, G., Yu, D., Yun, Y., Lee, B. K., Jiang, X., Wang, Y. *Injectable, Long-Acting PLGA Formulations: Analyzing PLGA and Understanding Microparticle Formation.* (2019) **304**:125–134. Doi: 10.1016/j.jconrel.2019.05.003. PMID: 31071374.
- Patil, S. M., Li, V., Peng, J., Kozak, D., Xu, J., Cai, B., Keire, D. A., and Chen, K. *A Simple and Noninvasive DOSY NMR Method for Droplet Size Measurement of Intact Oil-in-Water Emulsion Drug Products*. Journal of Pharmacuetical Science. (2019) **108**:815–820. Doi: 10.1016/j.xphs.2018.09.027. PMID: 30291851.
- Rivnay, B., Wakim, J., Avery, K., Petrochenko, P., Myung, J., Kozak, D., Yoon, S., Landrau, N., Nivorozhkin, A. *Critical Process Parameters in Manufacturing of Liposomal Formulations of Amphotericin B*. International Journal of Pharmaceutics. (2019) **565**:447–457. Doi: 10.1016/j.ijpharm.2019.04.052. PMID: 31071418.
- Soumyarwit, M., Wu, Y., Wang, Y., Koo, B., Chen, L., Petrochenko, P., Dong, Y., Choi, S., Kozak, D., Oktem, B., Xu, X., Zheng, J. *Probing the Mechanism of Bupivacaine Drug Release from Multivesicular Liposomes*. Journal of Controlled Release. (2019) **294**:279–287. Doi: 10.1016/j.jconrel.2018.12.029. PMID: 30576748.

- Vlieger, J., Crommelin, D., Tyner, K., Drummond, D., Jiang, W., McNeil, S., Neervannan, S., Crist, R., Shah, V. *Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: Drug Products, Including Biological Products, That Contain Nanomaterials*. The AAPS Journal. (2019) **21**(56): doi: 10.1208/s12248-019-0329-7.
- Wang, C., Siriwardane, D., Jiang, W., and Mudalige, T. *Quantitative Analysis of Cholesterol Oxidation Products and Desmosterol in Parenteral Liposomal Pharmaceutical Formulations*. International Journal of Pharmaceutics. (2019) **569**: doi: 10.1016/j.ijpharm.2019.118576. PMID: 31362094.
- Yuan, D., He, H., Wu, Y., Fan, J., and Cao, Y. *Physiologically Based Pharmacokinetic Modeling of Nanoparticles*. J. Pharm. Sci. (2019) **108**:58–72. Doi: 10.1016/j.xphs.2018.10.037. PMID:30385282.

Book Chapter

- Kapoor, M., Hughes, K.L., Tyner, K.M. *Regulatory Considerations for Cancer Drug Products Containing Nanomaterials.* Nanotheranostics for Cancer Applications, edited by Stephanie Morris and Rai Prakash, Springer, 2019.

Posters

- Siriwardane, D., Wang, C., Ansar, S., Jiang, W., and Mudalige, T. *Quantification of Lysophosphatidylcholines (Lpcs) and Free Fatty Acids (Ffas) in Parenteral Liposomal Formulations by Liquid Chromatography – Mass Spectrometry (LC-MS)*. Poster Presentation at 4th PQRI/FDA Conference on Advancing Product Quality. Rockville, MD, Apr. 9, 2019.
- Wang, C., Siriwardane, D., Jiang, W., and Mudalige, T. *Investigation of Cholesterol Oxidation Products (Cops) in Liposomal Drug Products*. Poster Presentation at 4th PQRI/FDA Conference on Advancing Product Quality. Rockville, MD, Apr. 11, 2019.
- Siriwardane, D., Wang, C., Ansar, S., Jiang, W., and Mudalige, T. *Quantitative Analysis of Cholesterol Oxidation Products and Desmosterol in Parenteral Liposomal Pharmaceutical Formulations.* Poster Presentation at 4th PQRI/FDA Conference on Advancing Product Quality, Rockville, MD. April 9-11, 2019.
- Haute, VD., Wenlei Jiang W., Mudalige, T. *Evaluation of size-based distribution of drug and excipient in amphotericin B liposomal formulation.* 4th PQRI/FDA Conference on Advancing Product Quality. Rockville, MD. April 9-11, 2019.

Presentations

- Feng, W. *Complex Particle Morphology in Propofol Emulsions: Effect of Manufacturing Process*. AAPS PharmSci 360. Washington DC, Nov 4-7, 2018.
- Manna, S. *Mechanistic Understanding of In Vitro Drug Release of Bupivacaine from Multivesicular Liposomes.* AAPS PharmSci 360. Washington DC, Nov 4-7, 2018.
- Jiang, W. *Advanced Analytical Methods to Characterize Liposome Drug Products.* Joint Eurpopean Commission Joint Research Center (JRC), National Institute of Standards and Technology (NIST) Workshop on Characterization Methods and Standards for Nanoparticles in Medical Products. Ispra, Italy. Dec. 3, 2018.

- Jiang, W. *Complex Injectable and Implantable Drug Products: Bioequivalence Considerations.* 4th FDA/PQRI Conference on Advancing Product Quality: Patient-Centric Product Design, Drug Development, and Manufacturing. Rockville, MD. April 9-11, 2019.
- Kozak, D. *Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives*. Presentation at FY2019 Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.
- Stavis, S.M., *A Multifunctional Microstructure for Microscope Calibration and Nanoparticle Characterization*. Conference on Electron, Ion, and Photon Beam Technology and Nanofabrication. Minneapolis, MN. May 29, 2019.
- Manna, S. *Significance of Cryo-Scanning Electron Microscopy (Cryo-SEM) in Evaluating the Morphology of Multivesicular Liposomes*. Presentation at Microscopy and Microanalysis. Portland, OR. Aug 2, 2019.
- Jiang, W. *Regulating Generic Nanotechnology Drug Products: Guidances and Standards.* Presentation at Global Summit for Regulatory Science. Lago Maggiore. Lago Maggiore, Italy. Sept. 25, 2019.
- Tyner, K. *Regulatory Research Supporting the Development of Drug Products Containing Nanomaterials: A US FDA Perspective*. Presentation at Global Summit for Regulatory Science. Lago Maggiore, Italy. Sept. 25, 2019.

FY2019 GDUFA Research Report: Complex Mixtures and Peptides

Summary of FY2019 Activities

Complex mixtures and therapeutic peptides represent a unique challenge from a quality perspective. The development of advanced analytical methods and strategies for the characterization and comparative analysis of these products are essential for linking product attributes to safety, quality, and clinical performance. In FY2019, we continued our research efforts in these areas with the focus on characterizing complex mixtures, peptides, and polymeric active ingredient drugs. Analytics are being developed for the evaluation and characterization of conjugated estrogens (CEs), teriparatide, and patiromer drug products.

PREMARIN cream contains a mixture of CEs obtained from pregnant mares' urine and was initially approved in 1946 (NDA 020216). Internally, studies are underway to optimize an existing ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS) method initially designed for the analysis of steroidal components in the active ingredient in CE tablet for the identification and quantification of both steroidal and non-steroidal components. In addition, the newly developed method will be optimized to ensure both sensitivity and reproducibility when applied to the analysis of the active pharmaceutical ingredient (API) in CEs cream formulations.

For peptide drugs, analysis of peptide-related impurities and assessment of their immunogenicity risk are important areas for GDUFA-supported research. Teriparatide is a peptide drug used in the treatment of osteoporosis. Through collaboration with FDA Labs, a UHPLC-MS/MS method was developed to characterize the impurity profile of teriparatide. Comparative analysis studies of the impurity profiles were performed for the reference listed drug (RLD) (NDA 021318) and generic synthetic peptide products. In addition, a UHPLC method was also developed to identify and quantify D-isomer impurities in the synthetic peptides. Both methods were validated and applied to the analysis of teriparatide drug substance and products. The identified peptide-related impurities are being evaluated using non-clinical assays and in silico tools for assessing their immunogenicity risk through several external research collaborations.

On the polymeric API characterization front, we have collaborated with the National Institute for Pharmaceutical Technology and Education (NIPTE) and have demonstrated that solid state Carbon-13 nuclear magnetic resonance (ss ^{13}CNMR) spectroscopy is a powerful tool to quantitatively analyze the structure and composition of patiromer, a synthetic polymeric drug used for hyperkalemia.

Research Highlight

A sensitive and reproducible analytical method for the analysis of the API from CEs, including steroidal and non-steroidal components, has been developed and validated. The UHPLC-MS method was applied to the analysis of several lots of drug substance collected over a two-year period to characterize lot-to-lot variability (Figure 1). The use of advanced analytical methods can help establish standards to demonstrate active ingredient sameness of CEs.

Peptide impurity profiles of teriparatide drug substance and product was characterized in the RLD and in generic products. Using UHPLC-MS, over 30 impurities were identified and quantified, including 16 impurities above the reporting threshold of 0.05%. These impurities could be categorized either as degradation products that accumulated over time or process impurities produced during the manufacturing process (Figure 2). In addition, isomerization was not observed in drug substances related to pending or marketed products. Results from these studies provide a useful benchmark for assessing current and future generic teriparatide applications. These studies also provide an insight into the analytical process and analysis necessary to ensure the safety and efficacy of the generic peptide drug products.

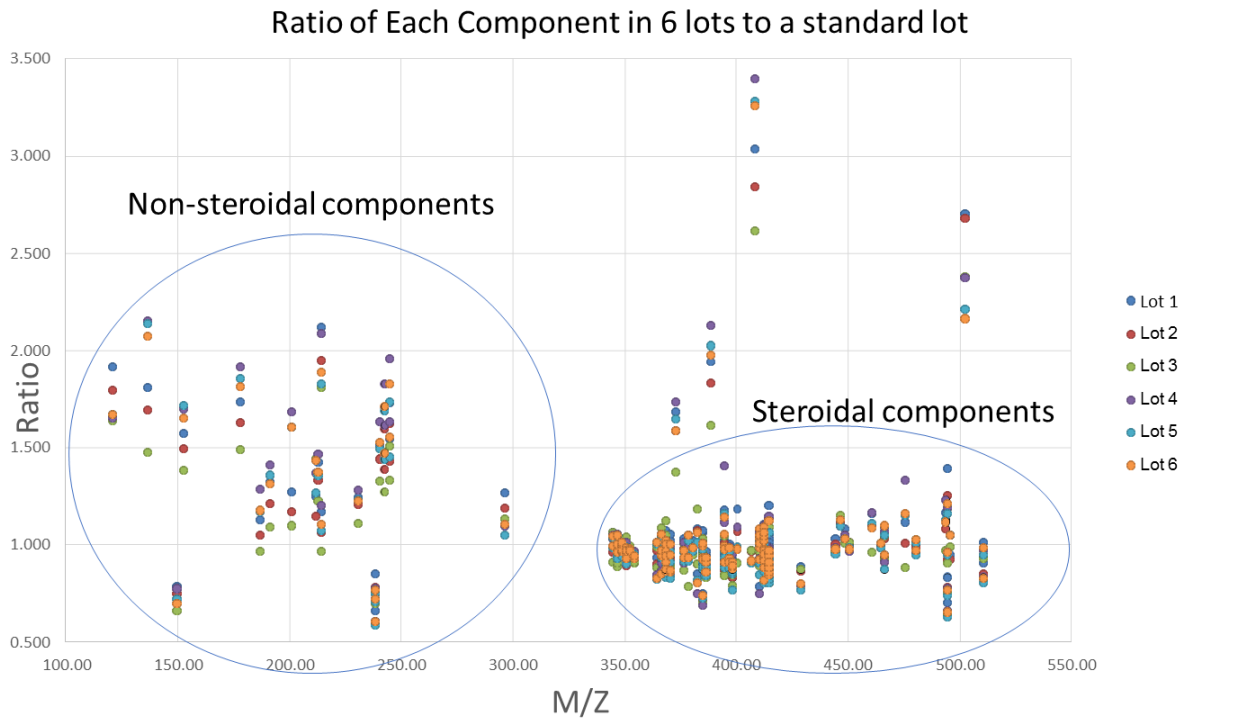


Figure 1. Component variability evaluation, in six drug substance lots for Conjugated Estrogens tablets, as a ratio to a standardized lot.

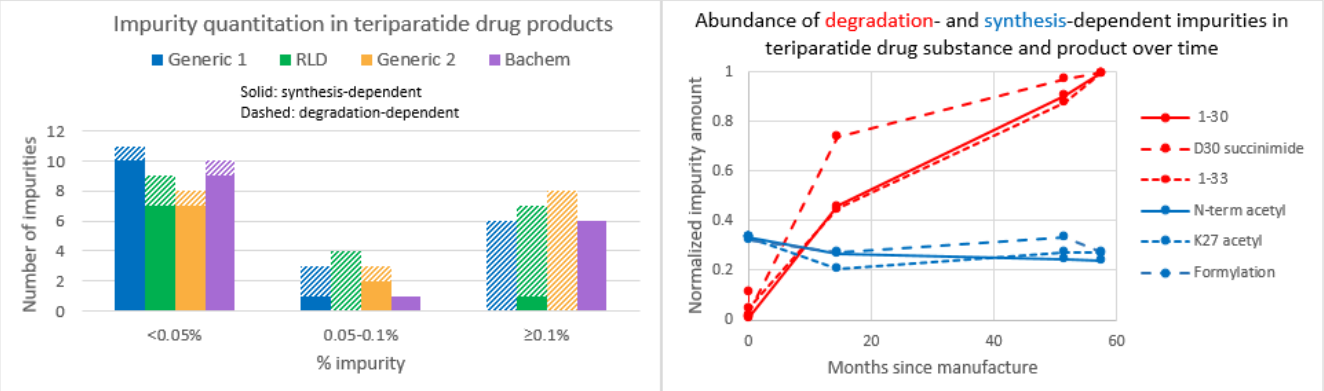


Figure 2. **A.** Distribution of impurities by % abundance category, in the RLD, two generic products, and a synthetic drug substance control purchased from Bachem. Synthesis-dependent impurities are shown in solid colors and degradation-dependent impurities in the corresponding dashed color. The three drug products are placed left to right by increasing age: Generic 1, RLD, Generic 2. **B**. Degradation impurities increase in abundance with increasing drug product age, while synthesis-dependent impurities remain roughly constant over time. 1-30 and 1-33: teriparatide truncation products.

Research Projects and Collaborations

New Contract

- Contract (IAA-224-19-3008S) *Evaluating Innate Immune Response of Generic Peptide Drugs and Associated Impurities using In Vitro Assays* with Marina Dobrovolskaia at National Cancer Institute

Continuing Grants and Contracts

- Grant (5U01FD004275-07) *Solid State NMR Analysis (NIPTE)* with Vadim Gurvich at NIPTE
- Contract (HHSF223201810186C) *In-Silico and in-Vitro Methods for Evaluating Generic Peptide Drug Immunogenicity* with Anne S. De Groot, Cara Depczynski at CUBRC & EpiVax, Inc.
- Contract (HHSF223201610114C) *Mass Spectrometry Profiling of Pentosan Polysulfate in Urine* with John Cort at Battelle Memorial Institute

Active FDA Research

- *Immunogenicity Assays for Peptide Drugs Physicochemical Characterization of Sucralfate Tablets to Support In Vitro BE Methods*
- *Impurity Profile Characterization in Synthetic Peptide Drug Products*
- *Developing Novel Regulatory Analytical Methods for Minor Glycan Control in mAb Therapeutics*
- *Characterization of Patiromer Drug Products*
- *Characterization of Conjugated Estrogens*
- *Evaluation of Humanized Mouse Model for Peptide Immunogenicity*
- *Characterization of Synthetic Oligonucleotides to Support Generic Drug Equivalence*

- *Characterization of Acthar Gel*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Fish Oil; Medium Chain Triglycerides; Olive Oil; Soybean Oil IV Emulsion*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Desmopressin Acetate Sublingual Tablet*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Colesevelam Hydrochloride Oral Powder for Suspension*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Plecanatide Oral Tablet*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Sucralfate Oral Tablet.* FDA Guidance Posting. Sept. 16, 2019. Link to Posting.

Presentations

- Jiang, X. *Follow Up Discussion on FDA Peptide Guidance after Public Comments*. Presentation at United States Pharmacopeia (USP) Workshop on Synthetic Therapeutic Peptides. Rockville, MD, Nov. 5, 2018.
- Kozak, D. *Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives*. Presentation at FY2019 Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.
- Zhang, D. *Characterization and Comparative Evaluation Strategies to Demonstrate Complex API Sameness.* Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop. College Park, MD, Sept. 25, 2019.

FY2019 GDUFA Research Report: Data Analytics

Summary of FY2019 Activities

In FY2019, the FDA continued to build data analytics capacities, including data management, big data toolsets, bioequivalence (BE) statistical methods, and data analysis methods for generic drug post-marketing surveillance, to support the mission of the Office of Generic Drugs (OGD).

OGD's data management efforts aim to promote data availabilityto facilitate generic drug development and regulatory review. For example, the Office of Research and Standards (ORS) under the OGD maintains a knowledge base regarding complexity of approved drug products to support research on complex generic drug development. Another example is that the ORS developed a Shiny-R-based application to facilitate the usability of received PK data for reviewers. Now this application is being expanded to further enhance the BE review efficiency by automating PK profile visualization, BE statistical analysis, and draft report generation.

Regarding the development of big data toolsets, the ORS has conducted time-to-event analysis based on machine learning (ML) to predict the time to the first submission of abbreviated new drug applications (ANDAs) referencing new chemical entities (NCEs). This research is important to inform ANDA workload and to prioritize research efforts. Current efforts focus on the prediction of the ANDA submission number. In addition, the ORS is developing a review-assistant tool based on text analysis and machine learning to enhance the development of product-specific guidances (PSGs).

To support BE statistical assessment, FDA has addressed complex statistical issues, including error control in adaptive study designs, dose-scale analysis for pharmacodynamics BE studies, equivalence of dissolution profiles from multiple batches, suitability of analysis of covariance (ANCOVA) method for BE assessment, and equivalence assessment of complex particle size distribution profiles using earth mover's distance (EMD) algorithm.

To facilitate generic drug post-marketing surveillance, a research grant funded by the FDA (U01FD005556) successfully developed a G-computation based analysis method for analyzing and comparing outcomes between generic and brand name drug products using real-world data. This novel method can account for the temporal and time-varying confounding factors that are pervasive, but seldomly accounted for, in most epidemiological studies. Another FDA-funded grant is developing an instrumental variable methodology for generic drug post-marketing study. This method will provide adjustment for the unobserved confounding factors in observational studies that cannot be addressed by conventional multivariate adjustment or propensity score analysis. Furthermore, FDA is utilizing the Sentinel tool to conduct post-marketing studies to compare the safety and effectiveness outcomes between generics and the brand name products.

Research Highlight

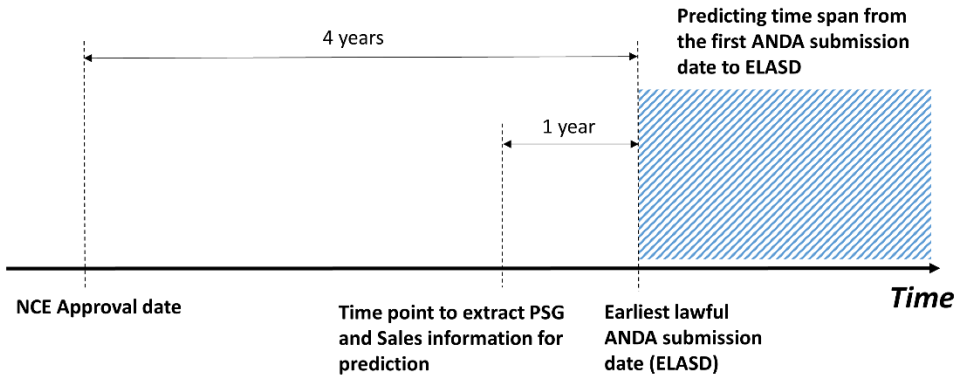
Predictive Analysis of Time to First ANDA Submission for New Chemical Entities Based on Machine Learning Methodology

The ANDA assessment and approval involve multiple offices across FDA. Forecasting ANDA submissions can critically inform resource allocation and workload management. The present study focuses on the prediction of the time to first ANDA submissions referencing new chemical entities (NCEs) following their earliest lawful ANDA submission dates. It facilitates timely development of product-specific guidance for generic firms and strategic planning to conduct regulatory research to fill in scientific gaps.

Data analysis on the time of occurrence of a certain event is typically referred to as the time-to-event analysis, also known as survival analysis, and a key feature of this analysis method is data censoring or the absence of an event in the study duration. One of the commonly used survival analysis methods is the Cox proportional hazard (PH) regression model. Although widely used, the Cox model has inbuilt model assumptions (e.g., proportional hazard and linear additive relationship between covariates) that are often oversimplified for real-world data. Random survival forest (RSF) is a well-established survival analysis approach based on ML method. Compared to traditional time-to-event analysis, such as Cox model, the RSF offers superior performance, especially for nonlinear relationships and high-order and high-dimension survival data, without imposing significant prior assumptions on the relationships. By leveraging drug product, regulatory, and pharmacoeconomic information (Figure 1), the developed time-to-event model by RSF can perform accurate predictions of the time to first ANDA submission referencing an NCE drug product (Figure 2) and identify the influential factors driving a submission. The developed RSF method, validated by internal and external datasets, showed superior predictive performance as opposed to the conventional Cox model.

This effort shows that ML-based time-to-event methodologies can be effective toolsets used for strategic workload and research planning in the regulatory setting.

Reference: Hu M, *et al.,* Clin Pharmacol Ther. 106(1):174-181, 2019. doi: 10.1002/cpt.1479.



$$\textit{Time span from the first ANDA submission date to ELASD} \sim f\left(\text{Drug Information, Regulatory Information, Pharmacoeconomic Information}\right)$$

Figure 1: Data model to delineate how the collected variables are used to establish the predictive model. The ANDA ELASD is the date of 4 years after the NCE approval date. The time span between the first ANDA submission date and the ELASD is used as the dependent variable, which is described by a function (f) of drug information, regulatory information, and pharmacoeconomic information. (Figure is from Hu M, *et al.,* Clin Pharmacol Ther. 106(1):174-181, 2019).

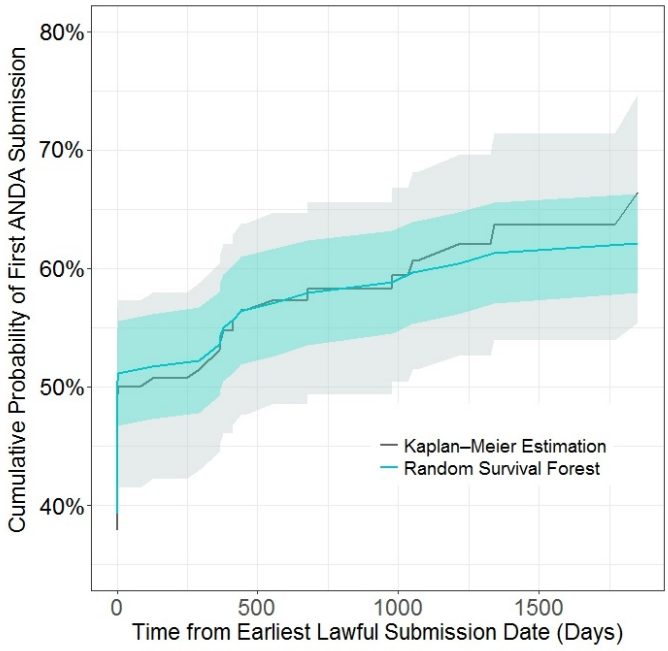


Figure 2: Kaplan-Meier survival plot of the all eligible data (black) and the predicted survival plot (green) based on random survival forest using the leave-one-out method. The shaded area refers to the 95% confidence intervals. (Figure is from Hu M, *et al.,* Clin Pharmacol Ther. 106(1):174-181, 2019).

FY2019 GDUFA Science and Research Report

Research Projects and Collaborations

New Contract

- Contract (75F40119C10106) *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency* with Hualou Liang at Drexel University

Continuing Grant

- Grant (1U01FD005938-01) *Bran Name and Generic Drugs to Treat Hypothyroidism* with Joseph Ross at Yale University and Nilay Shah at Mayo Clinic

Completed Grants

- Grant (1U01FD005556*) Structural Nested Models for Assessing the Safety and Effectiveness of Generic Drugs* with Ravi Varadhan at Johns Hopkins University
- Grant (1U01FD005555*) Novel Approaches for Confounding Control in Observational Studies of Generic Drugs* with Rishi Desai at Brigham & Woman Hospital
- Grant (1U01FD005875*) Generic Drug Substitution in Special Populations* with Jingjing Qian at Auburn Univeristy and Ilene Harris at IMPACT International

Active Internal Research

- *Development of the Earth Movers Distance for Particle Size Distribution Comparisons*
- *Development and Analysis of a Complex Product Database*
- *Data Analysis for Product Specific Guidances*
- *Machine Learning for Generic Drug Analysis*
- *Development of PK Data Warehouse for BE Analysis*

Outcomes

Articles

- Desai, R., Sarpatwari, A., Dejene, S., Khan, N., Lii, J., Rogers, J., Dutcher, S., Raofi, S., Bohn, J., Connolly, J.,Fischer, M., A, K., and Gagne, J. *Comparative Effectiveness of Generic and Brand-Name Medication Use: A Database Study of US Health Insurance Claims.* PLOS Medicine. (2019) **16**(3). doi: 10.1371/journal.pmed.1002763. PMID: 30865626.
- Gagne, J., Sarpatwari, A., and Desai, R. *Role of Authorized Generics in Postapproval Surveillance of Generic Drug Products.* Clinical Pharmacology & Therapeutics. (2019) **105**(2):313–315. doi: 10.1002/cpt.1283. PMID: 30593655.
- Gopalakrishnan, C., Gagne, J., Sarpatwari, A., Dejene, S., Dutcher, S., Levin, R., Franklin, J., Scheeweiss, S., and Desai, R. *Evaluation of Socioeconomic Status Indicators for Confounding Adjustment in Observational Studies of Medication Use.* Clinical Pharmacology & Therapeutics. (2019) **105**(6):1513–1521. doi: 10.1002/cpt.1348. PMID: 30659590.
- Hu, M., Babiskin, A., Wittayanukorn, S., Schick, A., Rosenberg, M., Gong, X., Kim, M.-J., Zhang, L., Lionberger, R., and Zhao, L. *Predictive Analysis of First Abbreviated New Drug Application*

Submission for New Chemical Entities Based on Machine Learning Methodology. Clinical Pharmacology & Therapeutics. (2019) **106**(1):174–181. DOI: 10.1002/cpt.1479. PMID: 31009066.

- Segal, J. B., Onasanya, O., Daubresse, M., Lee, C.-Y., Moechtar, M., Pu, X., Dutcher, S. K., and Romanelli, R. J. *Determinants of Generic Drug Substitution in the United States.* Therapeutic Innovation & Regulatory Science. (2019): e0113. doi: 10.1177/2168479018820050. PMID: 30636440.
- Woo, J., Luan, J., Li, Z., Grosser, S., Peters, J., and Chazin, H. *Abbreviated New Drug Applications: Generic Drug User Fee Amendments Act Analysis of Application Quality Metrics.* Therapeutic Innovation and Regulatory Science. (2018) **53**(5):696–700. doi: 10.1177/2168479018806192. PMID: 30360656.

Presentations

- Hu, M. *Equivalence Criteria for In Vitro BE Tests for Locally Acting Drug Products: The Earth Mover's Distance Approach.* Presentation at Scientists Advancing Affordable Medicines (SAAM) Conference. Rockville, MD, April 4, 2019.
- Rantou, E. *Statistical Issues with Aberrant IVRT/IVPT Data – FDA Perspective.* Presentation at Scientists Advancing Affordable Medicines (SAAM) Conference. Rockville, MD, April 4, 2019.
- Rantou, E. *Using R for Generic Drug Evaluation and SABE R-Package for Assessing Bioequivanlence of Topical Dermatological Products.* Presentation at R in Pharma Conference. Boston, MA, Aug. 2, 2019.
- Gong, X. *Regulatory Considerations on Dose-scale Analysis in Assessing Pharmacodynamic Equivalence*. Presentation at 2019 SBIA Complex Generic Drug Product Development Workshop. College Park, MD, September 26, 2019.

FY2019 GDUFA Research Report: Drug-Device Combination Products

Summary of FY2019 Activities

A continuing priority for the Food and Drug Administration is to advance research that involves drug-device combination products, some of which are considered complex products, as defined in the GDUFA II commitment letter.[1] Specifically, GDUFA regulatory science priorities for FY2019 include scientific research to inform new guidance and recommendations to support a demonstration of bioequivalence (BE) and substitutability for generic drug-device combination products.

One of the research initiatives related to this area was to evaluate the impact of differences identified in the user-interface of the product on the substitutability of generic drug-device combination products.[2] FDA awarded a contract to Research Triangle Institute (RTI) to conduct research in this area, with the goals of advancing FDA's understanding of patient and caregiver attitudes toward generic drug-device combination product substitution and building an evidence base to inform policy. This contract is currently underway, and a survey of the literature has been completed to examine existing research on patient and caregiver generic drug-device combination product substitution. This research seeks to gather patients' and caregivers' in-depth perceptions of generic drug-device combination products and to elicit reactions to generic substitutions. A better understanding of these issues can assist applicants in the development of complex generic drug-device combination products.

Also ongoing during FY2019 was an FDA contract to a group at the Imperial College London to further assess whether certain identified differences may impact the clinical effect or safety profile of generic drug-device combination products when compared to reference listed drug (RLD) counterparts. The researchers on this project have drafted a literature review on the evaluation of reported airflow resistances for dry powder inhalers (DPIs) approved in the United States and Europe and conducted focus group sessions with experts and patient representatives to help inform drafting the study questionnaire, clinical study protocol, and informed consent documentation.

Another area of focused interest has involved topical and transdermal delivery systems (collectively referred to as TDS). A sustained focus of FY2019 research in the area of TDS products has been to develop in vitro tools that may have the potential to be predictive of in vivo heat effects with TDS products. Over the last several years, multiple in vitro and/or in vivo (clinical) studies have been completed with TDS products containing nicotine, fentanyl, buprenorphine, lidocaine, and, during FY2019, studies with TDS products containing oxybutynin and rivastigmine have been initiated and are ongoing. Some of the research in this area is described in the Research Highlight.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022. https://www.fda.gov/media/101052/download

[2] U.S. Food and Drug Administration (FDA). GDUFA Regulatory Science Priority Initiatives for Fiscal Year 2019. https://www.fda.gov/media/119040/download

Research Highlight

An in vitro study with rivastigmine TDS sought to 1) explore the feasibility of using an in vitro permeation test (IVPT) to characterize the rate and extent of rivastigmine permeation, 2) optimize the IVPT study conditions for evaluating the delivery of rivastigmine across human skin using an IVPT study, and 3) characterize the effects of heat on the transdermal delivery of rivastigmine through human skin in vitro. Exelon® (rivastigmine) TDS, 9.5 mg/24 h (reference listed drug (RLD)), and a generic TDS, 9.5 mg/24 h (Alvogen) were evaluated. Studies were performed either at a normal skin surface temperature (32 ± 2°C), or under continuous or transient exposure to elevated skin surface temperature (42 ± 2°C). Both the generic and RLD TDS exhibited an increase in the rate and extent of drug delivery in vitro when exposed to an elevated temperature, involving continuous or transient heat. The time to reach J_{max} was also shorter for both TDS, relative to baseline condition, when heat was applied. Results suggest that carefully designed and optimized IVPT studies using excised human skin may have the potential to compare changes in the rate and extent of drug delivery from generic and RLD rivastigmine TDS under the influence of heat. Additional IVPT studies using an identical study design but different human skin donors are currently underway, and a corresponding clinical study has been initiated. The data from these studies will be used to evaluate an in vitro-in vivo correlation between IVPT and serum pharmacokinetic data from human subjects, and will help to evaluate the effectiveness of an IVPT study as a tool for comparing bioavailability of rivastigmine from different rivastigmine TDS under the influence of heat.

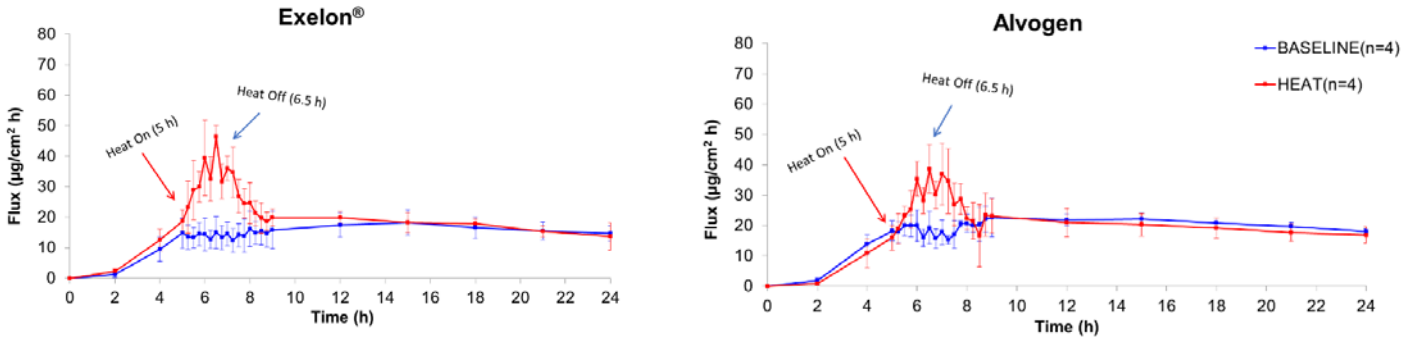


Figure 1: IVPT flux values (µg/cm^2·h) for human skin from one of the donors in the study at baseline and transient heat (1.5 h) conditions (n=4 replicates/treatment) [Mean ± SD] for Exelon® TDS (Left) and Alvogen's rivastigmine TDS (Right). Time points obtained: 2, 4, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 12, 15, 18, 21, and 24 h.

Research Projects and Collaborations

Continuing Grant and Contracts

- Grant (1U01FD004955) *Heat Effect on Generic Transdermal Drug Delivery Systems* with Audra L. Stinchcomb at University of Maryland

- Contract (HHSF223201710072C) *Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London
- Contract (HHSF223201810113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Vanessa Boudewyns at RTI International

Active FDA Research

- *Characterization of Transdermal Drug Delivery System by Coupled Scanning Electron Microscopy-Raman Spectroscopy*
- *Snowflakes in Transdermal Systems: Influence of Drug Crystallization on Drug Permeation and Quality of TDS*
- *Development of a Novel Bio-Relevant In Vitro Skin Permeation Test (IVPT) for Hydrophobic Drugs Using in-Line Flow Through Diffusion Cells (FTC) Development of New BE Methods for Transdermal Adhesion*
- *Development of New BE Methods for Transdermal Irritation and Sensitization*
- *Development of New BE Methods for Transdermal Adhesion*
- *In Vitro Performance Testing of Soft Mist Inhalers*

Outcomes

General Guidances

- *Draft Guidance for Industry: Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs,* Oct. 2018. Link to Posting.
- *Draft Guidance for Industry: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*, Oct. 2018. Link to Posting.

Product-Specific Guidances

- *Revised Draft Guidance for Buprenorphine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *New Draft Guidance for Capsaicin Topical Patch*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Clonidine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Diclofenac Epolamine Topical Patch*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Estradiol Transdermal Film, Extended Release (NDA 019081)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Estradiol Transdermal Film, Extended Release (NDAs 020375 and 021674)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Estradiol Transdermal Film, Extended Release (NDA 020538)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Estradiol Transdermal Film, Extended Release (NDA 203752)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *New Draft Guidance for Estradiol; Norethindrone Acetate Transdermal Film, Extended Release (NDA 020870)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.

- *Revised Draft Guidance for Ethinyl Estradiol; Norelgestromin Transdermal Film, Extended Release (NDAs 200910 and 021180)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.

- *Revised Draft Guidance for Fentanyl Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Granisetron Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Lidocaine Topical Patch*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Menthol; Methyl Salicylate Topical Patch*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Methylphenidate Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Nicotine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Nitroglycerin Transdermal Film, Extended Release (NDA 020144)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Nitroglycerin Transdermal Film, Extended Release (NDA 020145)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Oxybutynin Transdermal Film, Extended Release (NDA 021351)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Oxybutynin Transdermal Film, Extended Release (NDA 202211)*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Rivastigmine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Rotigotine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Scopolamine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Selegiline Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Testosterone Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *New Draft Guidance for Estradiol Transdermal Gel*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Beclomethasone Dipropionate Inhalation Aerosol, Metered*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Estradiol; Levonorgestrel Transdermal Film, Extended Release (NDA 021258)*. FDA Guidance Posting. May 15, 2019. Link to Posting.

Article

- Sun, W., Grosser, S., Kim, C., Raney, SG. *Statistical Considerations and Impact of the FDA Draft Guidance for Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs*, J. Biopharm. Stat., Sept. 8, 2019. doi 10.1080/10543406.2019.1657440, PMID: 31495266

Posters

- Thomas, S., Shukla, S., Hammell, D., Hassan, H., and Stinchcomb, A. *In Vitro and In Vivo Evaluation of Two Lidocaine Topical Delivery Systems With or Without the Influence of Transient Heat Exposure*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Sun, W., Zhang, Z., Zhou, L., Grosser, S., Li, B., Yim, S., Raney, S., Ghosh, P., Kim, C., and Wang, R. *Effect of Adhesion on Pharmacokinetics (PK) of Transdermal (TDS) Topical Products*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Zhang, Q., Ghosh, P., Raney, S., Hammell, D., Hassan, H., and Stinchcomb, A. *Assessment of Bioavailability of Rivastigmine from Two Rivastigmine Transdermal Delivery Systems with and Without Exposure to Heat Using In Vitro Permeation Test (IVPT)*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Barenie, R., Kesselheim, A., Gagne, J., Campbell, E., Dutcher, S., Jiang, W., and Sarpatwari, A. *Does Variation in the Physical Characteristics of Generic Drugs Affect Patient Adherence? Results from National Surveys Of pharmacists and Patients*. Poster Presentation at Academy Health Organization Annual Research Meeting. Washington, DC, June 2-4, 2019.
- Thomas, S., Hammell, D., Hassan, H., and Stinchcomb, A. *A Pharmacokinetic Study of Two Oxybutynin Trandermal Formulations with Transient Heat Exposure*. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.

Presentations

- Conti, D. *Overview of Complex Generic Inhalation, Nasal and Auto- Injector Drug-Device Combination Products.* Presentation at 2018 FDA/DIA Complex Generic Drug-Device Combination Products Workshop. Silver Spring, MD, Oct. 9, 2018.
- Luke, M. Horizon Scanning for Generic Combination Drug-Device Products. Presentation at 2018 FDA/DIA Complex Generic Drug-Device Combination Products Workshop. Silver Spring, MD, Oct. 10, 2018.
- Lionberger, R. *Closing Remarks*. Presentation at 2018 FDA/DIA Complex Generic Drug-Device Combination Products Workshop. Silver Spring, MD, Oct. 10, 2018.
- Sharan, S. *Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits for Long Acting Intrauterine Product.* Presentation at 2018 FDA/DIA Complex Generic Drug-Device Combination Products Workshop. Silver Spring, MD Oct. 0, 2018
- Kozak, D. *Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives*. Presentation at FY2019 FDA Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.
- Rodriguez, J. *Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products.* Presentation at FY2019 FDA Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.
- Witzmann, K. *Comparative Analyses: Device and User Interface Considerations*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Inhalation and Nasal

Summary of FY2019 Activities

FY2019 research activities are continuing the Agency's efforts for addressing the challenges to generic orally inhaled and nasal drug product development, assessment, and approval. For instance, developing generic dry powder inhalers (DPIs) remains challenging due to uncertainty with the relationship between in vitro study results and in vivo performance at the local site of action, the lungs. Two research projects are ongoing that aim to characterize DPI microstructure (drug and excipient particles, as well as their interaction) to better understand how these properties impact their aerosolization and subsequent deposition within the lungs. Using a novel in vitro technique, Morphology Directed Raman Spectroscopy (MDRS), research contracted from the University of Bath (HHSF223201710116C) has shown that the type of drug-drug and drug-excipient agglomerates can vary between strengths of the same product (Figure 1), as well as across different products (Figure 2), which may affect drug dissolution following deposition. Separate research contracted with the University of Texas at Austin (HHSF223201810169C) has begun evaluating whether certain in vitro parameters are more sensitive to variability between batches of the same DPI product. Collectively, the goal of these projects is to determine whether certain in vitro studies can sufficiently characterize the critical features of the DPI microstructure that may influence aerosolization, deposition and dissolution, which may provide a foundation to help ensure equivalence at the local site of action and so potentially contribute to alternative bioequivalence (BE) approaches in lieu of conducting a comparative clinical or pharmacodynamic endpoint BE study.

Research is also ongoing with developing a systematic way to evaluate patient perception of DPI airflow resistance, assess patient preferences for a particular airflow resistance range, and determine if the patient preference for the range varies with severities of diseases or classes of drug products. Contracted researchers at the Imperial College London (HHSF223201710072C) have completed two meetings with both patient representatives for inhalation products and questionnaire development experts to identify concepts related to patient perception of airflow resistance that should be included in the questionnaire as it is developed. The goal of this research is to further assess whether certain identified differences may impact the clinical effect or safety profile of generic DPI products when compared to reference listed drug (RLD) counterparts. Through better understanding of these issues, we hope to assist potential applicants in the development of complex generic DPI products.

Internally, the Agency has continued its development of tools and methodologies for assessing the performance characteristics of oral inhalation powders, as well as more recently approved oral inhalation sprays and nasal powders. FDA is assessing device characteristics like airflow resistance, as well as critical performance parameters (e.g., delivered dose uniformity and aerodynamic particle side distribution) that can impact the Agency's assessment process of generic inhalation powders. Close collaboration between researchers and reviewers has included evaluation of particle sizing techniques, such as laser diffraction, for both oral inhalation sprays and nasal powders. Results from these evaluations may be used to support the Agency's recommendations for establishing bioequivalence with these products, as well as the internal assessment process of abbreviated new drug applications (ANDAs).

Research Highlight

To address challenges with conducting the comparative clinical endpoint BE study for metered dose inhaler (MDI) products, research projects were conducted to identify and develop more predictive, clinically relevant in vitro methodologies for characterizing the aerosolized particles, their deposition and dissolution, as well as new computational modeling and simulation approaches to correlate these results with the delivered dose measured in vivo. Three research projects (Grants# 1U01FD004953, 1U01FD004950, and 1U01FD004941[3]) developed in vitro dissolution methods that identified critical features that can impact discrimination between different MDI products, such as sample collection, apparatus, dissolution media, physicochemical properties of drug, device and formulation characteristics. Also, to better understand the impact of the anatomical features of mouth and throat on drug delivery, research projects outside (Grant# 1U01FD005231)[4] and within the Agency[5] evaluated different mouth-throat models, as well as the available compendial option from the United States Pharmacopoeia (USP), and their potential to better predict drug delivery in vivo. Moreover, results from outside research projects on computational approaches to develop predictive lung deposition models (Grants# 1U01FD004570, 1U01FD005837) and predictive lung absorption and pharmacokinetic models of pulmonary drug delivery (Grant# 1U01FD005214), as well as internal research on computational approaches to model droplet evaporation from solution-based MDIs, facilitated a better understanding of in vitro assessments and their impact on BE. As a result of these research projects, on May 2019, the Agency posted the first product-specific guidance (PSG) for a solution-based MDI product (Beclomethasone Dipropionate) that provides an option for conducting additional in vitro, in vivo, and/or in silico studies as an alternative approach for establishing BE, in lieu of conducting the recommended comparative clinical endpoint BE study, in the context of the weight-of-evidence.[6]

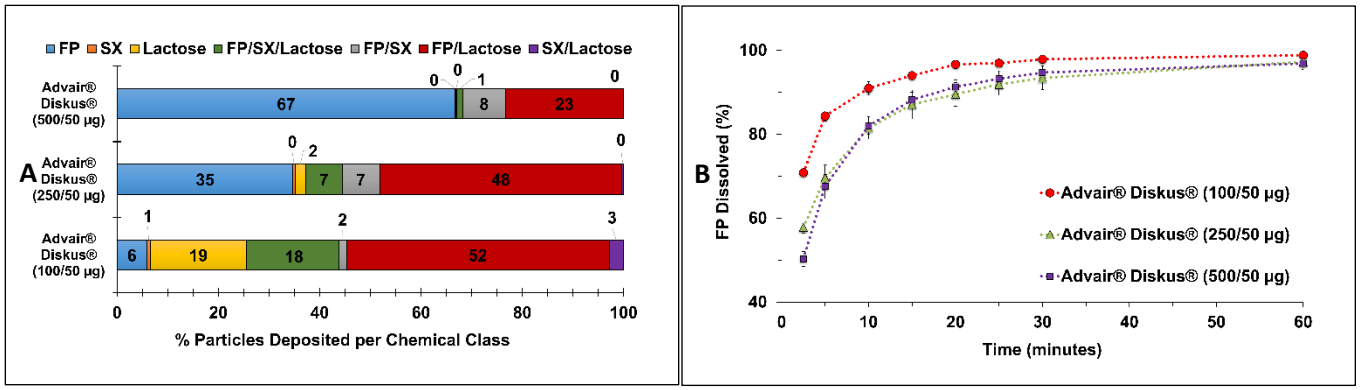


Figure 1: (A) Particles deposited per chemical class (%) of the impactor-sized mass (ISM) of Advair® Diskus® (Fluticasone Propionate (FP)/Salmeterol Xinafoate (SX); 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). The results are presented as mean ± standard deviation (n=5). (B) FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circles, Advair® Diskus® (250/50 µg)

[3] Sakagami M, Li H, Venitz J. In Vivo-Relevant Transwell Dish-Based Dissolution Testing for Orally Inhaled Corticosteroid Products. Pharmaceutical research. 2019 Jul 1;36(7):95.

[4] Wei X, Hindle M, Kaviratna A, Huynh BK, Delvadia RR, Sandell D, Byron PR. In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth–Throat Models and In Vitro—In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler. Journal of aerosol medicine and pulmonary drug delivery. 2018 Dec 1;31(6):358-71.

[5] Kaviratna A, Tian G, Liu X, Delvadia R, Lee S, Guo C. Evaluation of Bio-relevant Mouth-Throat Models for Characterization of Metered Dose Inhalers. AAPS PharmSciTech. 2019 Apr 1;20(3):130.

[6] FDA Product-specific Guidance for Beclomethasone Dipropionate Inhalation Aerosol Metered. Posted May 2019. Available at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

as Green Triangles, and Advair® Diskus® (500/50 µg) as Purple Squares. The results are presented as mean ± standard deviation (n=2).

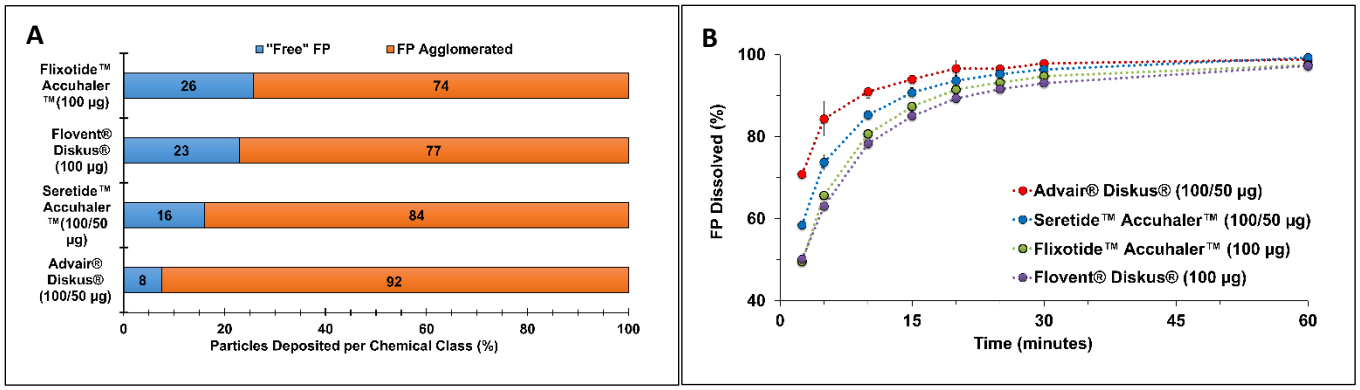


Figure 2: (A) Fluticasone Propionate dissolved (%) from the impactor-sized mass (ISM) of Advair® Diskus® (100/50 µg) as Red Circles, Advair® Diskus® (250/50 µg) as Green Triangles, and Advair® Diskus® (500/50 µg) as Purple Squares. The results are presented as mean ± standard deviation (n=2). (B) FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide™ Accuhaler™ (100 µg), Flovent® Diskus® (100 µg), and Seretide™ Accuhaler™ (100/50 µg). The results are presented as mean ± standard deviation (n=2).

Research Projects and Collaborations

New Contracts

- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Predication of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffry Schroeter at Applied Research Associates, Inc.
- Contract (75F40119C10154) *Systematic evaluation of the ex-throat plume properties of MDI formulations* with Guenther Hochhaus at University of Florida.

Continuing Grants and Contracts

- Grant (5U01FD004943) *Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance* with Guenther Hochhaus at University of Florida
- Grant (1U01FD006514) *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery* (U01) with Sankaran Sundaresan at Princeton University
- Grant (1U01FD006525) *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery* (U01) with Kim Chan at University of Sydney
- Grant (1U01FD006537) *Three-Dimensional Approach for Modeling Nasal Mucociliary Clearance Via Computational Fluid Dynamics (CFD)* (U01) with Clement Kleinstreuer at North Carolina State University Raleigh
- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-long Li at University of Iowa

- Contract (HHSF223201310220C) *Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical Properties of the Active in Suspension Nasal Products for Local Action* with Guenther Hochhaus at University of Florida
- Contract (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price at University of Bath
- Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches* with Robert Price; Jag Shur at University of Bath
- Contract (HHSF223201710072C) *Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation
- Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers* with Hugh D C Smyth at University of Texas at Austin
- Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition in Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University

Completed Grants and Contracts

- Completed Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation (CFDRC)
- Completed Contract (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price at University of Bath, UK
- Completed Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers using Orthogonal Analytical Approaches* with Robert Price (PI) and Jag Shur (CI) at University of Bath
- Completed Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition in Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University
- Completed Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers* with Hugh D. C. Smyth at The University of Texas at Austin, College of Pharmacy
- Completed Contract (HHSF223201610004I-HHSF22301002T) *Agonist-Antagonist Combination Products (Embeda) In Vivo PK* with Kathleen Doisy at Biopharma

Active FDA Research

- *In Vitro Performance Testing of Soft Mist Inhalers*
- *Product Quality and Performance Evaluation of Tiotropium Bromide Inhalation Powder Drug Products*
- *In Vitro Performance Testing of Nasal Powder Drug Products by Laser Diffraction with Chi Square Ratio Analysis of Aerodynamic Particle Size Distribution (APSD) by Multiple-Stage Cascade Impactor*
- *CFD Models of Droplet Formulation from MDI*

- *CFD Models of Soft Mist Inhalers*
- *Batch to Batch Variability of Inhalation Products*
- *Upper and Lower Human Airway Deposition Predictions of Solution-based MDIs*
- *Physiologically-Based Pharmacokinetic (PBPK) Model Development for Locally-acting Nasal Drug Products*
- *Assessment of Variability and Dose Sensitivity of FEV1 in Comparative Clinical Endpoint BE Studies of OIDPs*

Outcomes

Product-Specific Guidances

- *Revised Draft Guidance for Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered.* FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *Revised Draft Guidance for Fluticasone Propionate Nasal Spray, Metered.* FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *Revised Draft Guidance for Mometasone Furoate Nasal Spray, Metered*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *Revised Draft Guidance for Triamcinolone Acetonide Nasal Spray, Metered*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *Revised Draft Guidance for Mometasone Furoate Nasal Spray, Metered*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Beclomethasone Dipropionate Inhalation Aerosol, Metered*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Budesonide Nasal Spray, Metered*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Fluticasone Furoate Nasal Spray, Metered*. FDA Guidance Posting. May 15, 2019. Link to Posting.

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Posters

- Mangal, S., Conti, D., Delvadia, R., Oguntimein, M., Shur, J, Price, R. *Microstructural Mapping of Dry Powder Inhalers (DPIs) Using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Walenga, R. L., Conti, D. S., Oguntimein, O., Delvadia, R. R., Rygg, A. D, Babiskin, A. H. *Droplet Evaporation from a Solution-Based Metered Dose Inhaler: A Computational Approach*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Drescher, S. et al. *Assessing Central and Peripheral Pulmonary Deposition of Three Fluticasone Propionate Dry Powder Inhaler Formulations with Different Aerodynamic Particle Size Distributions in Healthy Subjects Via Population Pharmacokinetics Modeling.* Poster Presentation at Drug Delivery to the Lungs. Edinburgh, UK, Dec. 13, 2018.
- Choi, J., Choi, S., Li, F., Hoffman, E., Castro, M., Goss, C., Hall, C., Mceleney, S., Sieren, J, Lin, C.-L. *Cluster-Guided Image Matching Analysis of Multiscale Lung Response to Bronchial Thermoplasty.* Poster Presentation at American Thoracic Society 2019 International Conference. Dallas, TX, May 19, 2019.
- *Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J, Hochhaus, G. The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler performance. Poster Presentation at FDA Science Forum. Silver Spring, MD, Sept. 11, 2019.*

- Boc, S., Conti, D., Chen, M., Jiao, Y., Kurumaddali, A., Oguntimein, O., Delvadia, R., Saluja, B., Lee, S., Shur, J., Price, R., Hindle, M., Bulitta, J, Hochhaus, G. *Investigation of Pharmacokinetic Sensitivity to Lung Deposition of Locally-Acting Orally Inhaled Drug Products*. Poster Presentation atFDA Science Forum. Silver Spring, MD, Sept. 11, 2019.
- Hosseini, S., Schuman, T., Walenga, R., Babiskin, A, Golshahi, L. *Assessment of Internal Nasal Valve Using Anatomically-Accurate 3d Airway Models*. Poster Presentation at American Rhinologic Society. New Orleans, LA, Sept. 13, 2019.

Presentations

- Conti, D. *Overview of Complex Generic Inhalation, Nasal and Auto-Injector Drug-Device Combination Products.* Presentation at FDA/DIA Complex Generic Drug-Device Combination Products Workshop 2018. Silver Spring, MD, Oct. 9, 2018.
- Hochhaus, G. and Bulitta, J. *Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers*. Presentation at FDA/DIA Complex Generic Drug-Device Combination Products Workshop 2018. Silver Spring, MD, Oct. 9, 2018.
- Byron, P. *Bioequivalence Assessment for Inhalation Products*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- *Schroeter, J. D. Local and Systemic Absorption Predictions of Nasal Inhaled Corticosteroids: A Combined Approach. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.*
- *Hochhaus, G. Regulatory Implications of Device Changes Later in Drug Development. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.*
- *Schoroeter, J. Exploring the Relationship Between Suspension and Solution MDI Formulation Variables and Predicted Lung Deposition. Presentation at RDD Asia 2018. Kerala, India, Nov. 16, 2018.*
- *Choi, J., Choi, S., Hoffman, E., O'Shaughenessy, P., Castro, M., Delvadia, R., Walenga, R., Babiskin, A., and Lin, C. Assessment of Effects of Selective Airway Luminal Expansion on Inhaled Particle Deposition in Severe Asthmatic Human Lungs - A Numerical Study. Presentation at Georgia World Congress Center. Atlanta, GA, Nov. 19, 2018.*
- *Drescher, S. Characterizing the Time-Course of Lung Absorption Via Population Pharmacokinetic Modeling. Presentation at Drug Delivery to the Lungs Conference. Edinburgh, UK, Dec. 13, 2018.*
- *Witzmann, K. Critical Importance of Excipients in Generic Product Development- Now and in the Future. Presentation at Drug Delivery to the Lungs Conference. Edinburgh, Scotland, Dec. 13, 2018.*
- *Lin, C.-L. CFD Lung Models for Drug Delivery. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.*
- *Hochhaus, G., Bulitta, J., Price, R., Shur, J., and Hindle, M. Using PBPK to Link Systemic PK to Local Delivery in the Lung. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.*
- *Walenga, R. Impact of Orally Inhaled and Nasal Drug Product PBPK Models on Product Development and Regulatory Decision Making. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.*
- *Bulitta, J. and Hochhaus, G. Studies to Further Establish PK As Central Tool for a Streamlined Approval of Generic Inhalation Drugs. Presentation at FY2019 FDA Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.*

- *Kozak, D. Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives. Presentation at FY2019 FDA Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.*
- *Rodriguez, J. Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products. Presentation at FY2019 FDA Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.*
- *Conti, D. Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products. Presentation at 2019 American Thoracic Society (ATS) International Conference. Dallas, TX, May 19, 2019.*
- *Luke, M., K., W., and Conti, D. Generic Drug Development for Respiratory Products, US Food and Drug Administration Update. Presentation at 2019 American Thoracic Society (ATS) International Conference. Dallas, TX, May 19, 2019.*
- *Kurumaddali, A. A Semi-Physiological Approach for Evaluating the Sensitivity of Pharmacokinetics to Detect Differences in Regional Lung Deposition of Orally-Inhaled Drug Products (OIDPs). Presentation at American College of Clinical Pharmacology (ACCP) Annual Meeting. Chicago, IL, Sept. 16, 2019.*
- Conti, D. *Considerations for Pre-ANDA Meeting Requests for Orally Inhaled and Nasal Drug Products.* Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.
- Newman, B. PSG *Recommendations and Updates for OINDPs.* Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.
- Walenga, R. *Credibility Establishment for Computational Fluid Dynamics Models of Complex Generic Drug Delivery.* Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Locally-Acting Physiologically-Based Pharmacokinetic Modeling

Summary of FY2019 Activities

The main goal of the locally-acting physiologically-based pharmacokinetic (PBPK) modeling research program is to develop and advance mechanistic models that incorporate biopharmaceutical/formulation properties of drug products and human physiology/anatomy to support alternative bioequivalence (BE) approaches for locally-acting drug products.

Leveraging outcomes from GDUFA I-funded research, FDA has moved towards adopting a more focused approach regarding the development of quantitative modeling and simulation tools for locally-acting drug products. Twelve external projects were funded by the end of FY2018. Among the 12 projects:

- In the topical dermatological area, three grants (Figure 1) were awarded for dermal PBPK modeling of topically-applied dosage forms, focusing on incorporating formulation attributes (including in vitro testing methodologies), excipient effects and characteristics of dermal absorption in diseased skin, such as psoriasis, acne, and atopic dermatitis, to the models.
- In the pulmonary area, two grants and one contract were awarded to develop computational fluid dynamics (CFD) models of dry powder inhalers and further develop an existing lung PBPK model created by Grant 1U01FD005214. A continuing grant focusing on predicting evaporation of volatile aerosols and subsequent impact on pulmonary deposition was awarded.
- In the nasal area, a grant was awarded to incorporate a three-dimensional approach for modeling mucociliary clearance via CFD. A contract was awarded to develop a set of in vitro nasal models using combination of in vitro and CFD methods to characterize inter-subject variability.
- In the ocular delivery area, to further incorporate product attributes and more complex ophthalmic dosage forms into the modeling platforms, two contracts were awarded to advance ocular PBPK models previously developed in GDUFA I projects.
- A contract was awarded to generate new data via in vitro, ex vivo, and human clinical studies to develop a PBPK model for the female reproductive tract.
- A grant and a continuing grant were awarded to improve virtual BE techniques by leveraging Bayesian and other population-based algorithms for PBPK-based methods.

Internally, FDA continues to investigate the currently available modeling platforms, specifically researching the relationship between clinical response (as governed by local and systemic exposure) and specific product characteristics. For example, one project focusing on Respimat®-type inhalation devices uses a combination of in vitro and CFD methods to understand how in vitro metrics are best collected with this type of product, and how these metrics may affect regional lung deposition (Figure 2). Two case studies involving cyclosporine emulsion and dexamethasone suspension (see Research Highlight in Chapter 1 – Ophthalmic) were published. In FY2019, locally-acting PBPK and CFD models were submitted within abbreviated new drug applications (ANDAs) and pre-ANDA meetings in the dermal, inhalation, and ocular areas. In addition, an FDA co-sponsored pre-conference workshop at the 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting titled “PBPK Modeling for the Development and Approval of Locally Acting Products” was held on March 13, 2019 that highlighted research, knowledge gaps, regulatory utility, and implementation challenges of these models and included presentations from several GDUFA I external collaborators (see Presentation outcomes below for a list of presentations from these collaborators and FDA staff).

Research Highlight

A PBPK model that allowed the quantitative description of drug absorption through the skin was utilized to support the approval of a generic topical gel product referencing Voltaren® (diclofenac sodium) topical gel, 1% (Reference Listed Drug [RLD] - NDA 022122) indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment , such as the knees and those of the hands. The generic formulation was qualitatively and quantitatively similar to the RLD and showed similar physical and structural characteristics as the RLD. The applicant demonstrated systemic BE to the RLD based on an acceptable in vivo BE study with PK endpoints. In lieu of conducting the product-specific guidance recommended in vivo BE study with comparative clinical endpoints, the applicant developed product-specific dermal PBPK models which considered differences in formulation attributes between the two drug products. The performance of the modeling platform and the product-specific models were assessed by comparing model predictions with observed data on systemic and local exposure (various skin layers including synovial fluid) from various sources. The product-specific dermal PBPK models were further refined internally within the Agency to adequately predict diclofenac concentrations at the presumed site of action (synovial fluid), and the refined models were utilized to show BE between the RLD and the generic diclofenac sodium topical gel, 1% based on population predictions of exposure at the presumed site of action supporting the product approval.

The dermal PBPK modeling platform, Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) model (Simcyp® Simulator v17), was used to support this ANDA. Development and advancements of the modeling platform have been partially supported by 1U01FD005225 (Grant funded under GDUFA I) and 1U01FD006521/1U01FD006522 (Grants funded under GDUFA II). Knowledge (technical and otherwise) gained by FDA assessors and scientists through interactions and collaborations formed as part of the previously mentioned grants/contracts on the area of dermal PBPK modeling (GDUFA I and II), contributed to an efficient assessment process.

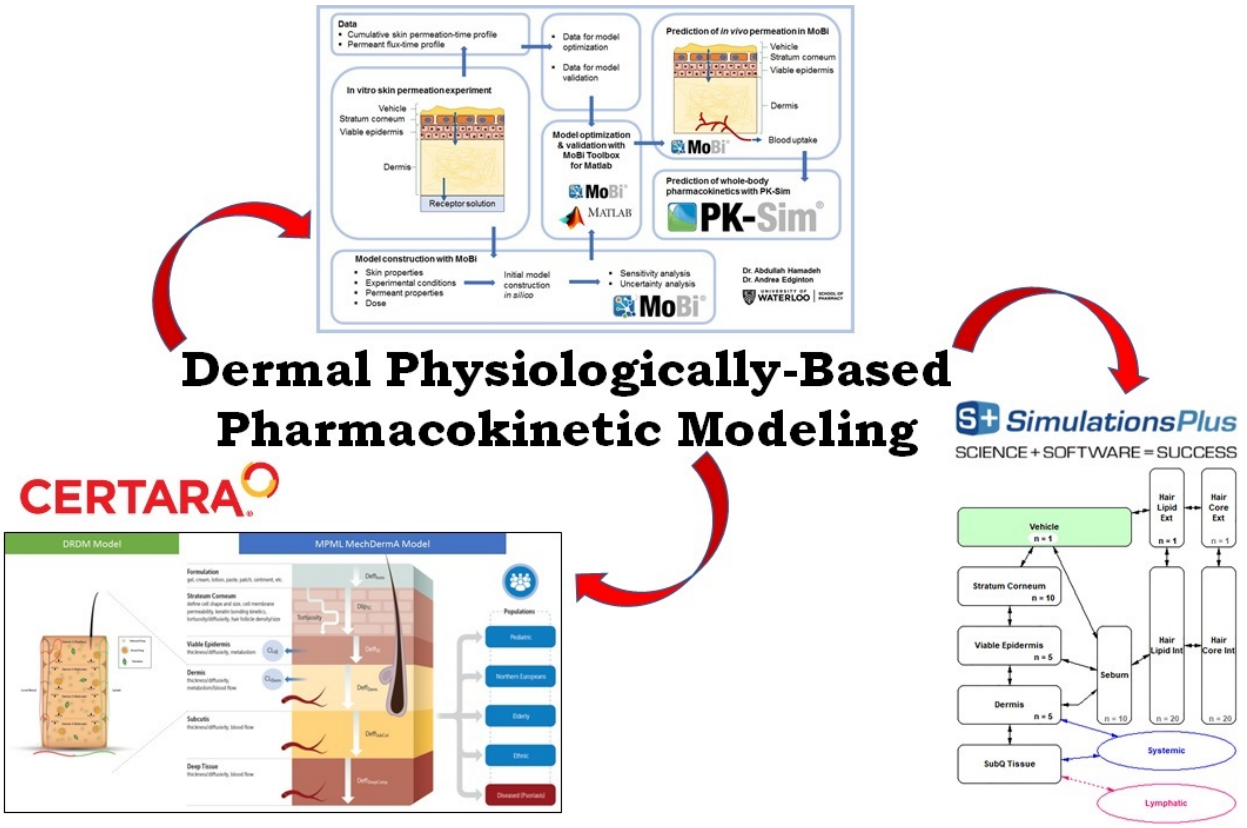

Figure 1: Skin absorption of pharmacologically active drug substances can be described by performing dermal physiologically-based pharmacokinetic modeling implemented in several software platforms including (in alphabetical order) the Multi-Phase, Multi-Layer MechDermA model within the Simcyp® Simulator by Certara (Grant #1U01FD006521), a skin model within PK-Sim®/MoBi® developed by Children's Hospital of Los Angeles (Grant #1U01FD006549) and the Transdermal Compartmental Absorption & Transit™ within Gastroplus™ by Simulations Plus (Grant #1U01FD006526). Recent enhancements in these modeling and simulation tools allow for a mechanistic understanding of the processes that govern permeation through the skin of drug substances applied on the skin of healthy and diseased populations as transdermal delivery systems and semisolid topical dosage forms.

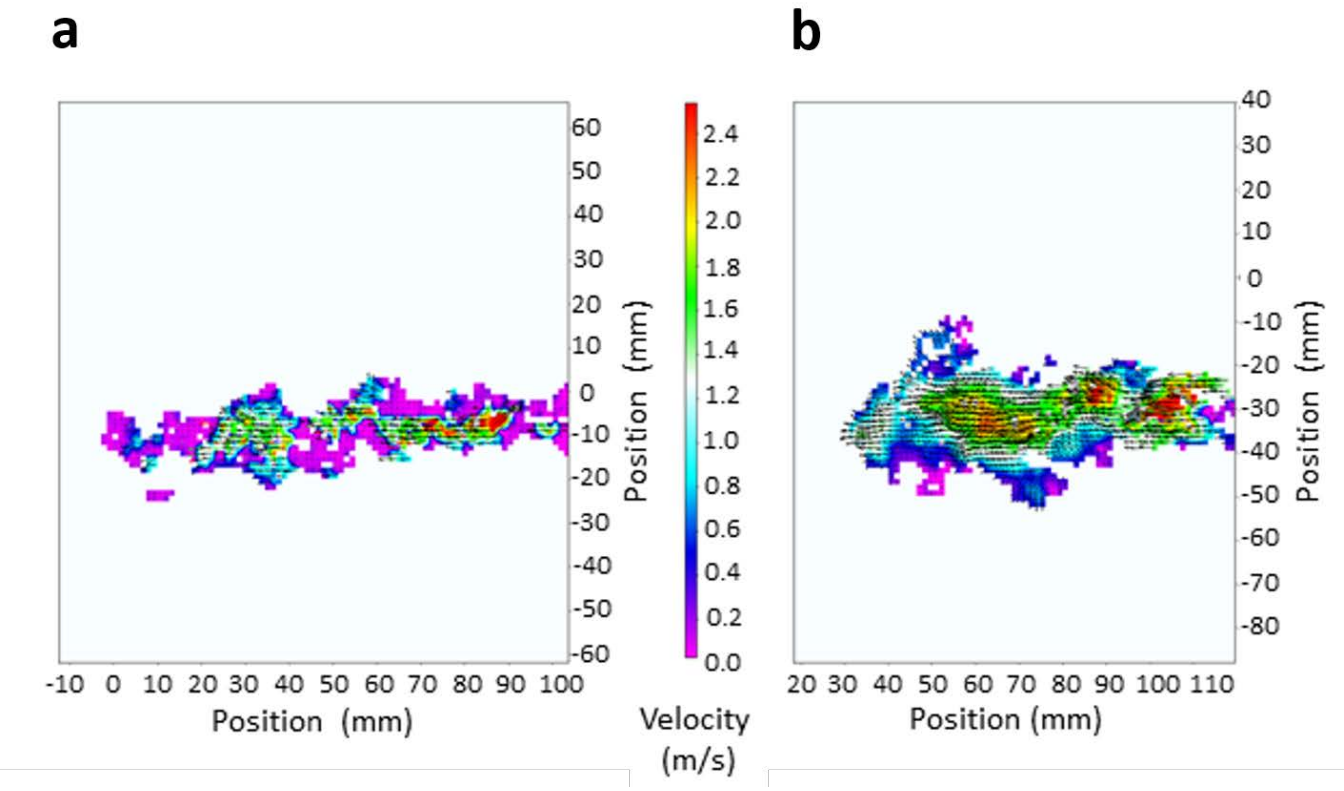

Figure 2: Particle image velocimetry (PIV) data demonstrating plume initiation and local velocity for Striverdi® Respimat® (olodaterol hydrochloride) inhalation metered spray taken 0.074 s after device actuation in (a) stable quiescent air and in (b) air with a physiologically-relevant co-flow condition of 28.3 L/min.

Research Projects and Collaborations

New Contracts

- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Predication of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffry Schroeter at Applied Research Associates
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie L.S. Au at Institute of Quantitative Systems Pharmacology (IQSP)

Continuing Grants and Contracts

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at University of Iowa
- Grant (1U01FD005838) *Enhancing the Reliability, Efficiency, and Usability of Bayesian Population PBPK Modeling* with Brad Reisfeld at Colorado State University

- Grant (1U01FD006521) *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations* with Sebastian Polak at Simcyp, Ltd.
- Grant (1U01FD006514) *Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery* with Sankaran Sundaresan at Princeton University
- Grant (1U01FD006525) *Development of Computational Models to Predict Delivery of Inhalation Drug Powders: from Deagglomeration in Devices to Deposition in Airways* with Kim Chan at the University of Sydney
- Grant (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael Neely at Children's Hospital of Los Angeles
- Grant (1U01FD006522) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems* with Michael Roberts at University of Queensland, Australia
- Grant (1U01FD006526) *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations* with Jessica Rose Spires at Simulations Plus, Inc.
- Grant (1U01FD006537) *Nasal Mucociliary Clearance Affecting Local Drug-Absorption in Subject-Specific Geometries* with Clement Kleinstreuer at North Carolina State University Raleigh
- Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition In Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drug*s with Narender Singh at CFD Research Corporation (CFDRC)
- Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert R. Bies at University at Buffalo
- Contract (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation
- Contract (HHSF223201810255P) *GastroPlus™ Ocular Compartmental Absorption and Transit (OCAT™) Model Extension and Validation* with Jessica Spires at Simulations Plus, Inc.

Completed Grants and Contracts

- Grant (1U01FD005232) *Physiologically Based Biopharmaceutics and Pharmacokinetics of Drug Products for Dermal Absorption in Humans* with Michael Roberts at University of South Australia
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation (CFDRC)
- Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition in Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth UniversityContract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert R. Bies at University at Buffalo

Active FDA Research

- *Manufacture of Ophthalmic Suspension Test Formulations with Meaningful Variations in Viscosity and Particle Size*

- *Impact of Soft Mist Inhaler In Vitro Characteristics on Human Airway Deposition: A Combined In Vitro-In Silico Approach*
- *Laser Diffraction of Soft Mist Inhalers*
- *Dissolution Testing of Nasally Insufflated OxyContin Using an In Vitro Method*
- *In Vivo Biodistribution Evaluation of Ophthalmic Suspension Drug Products*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*
- *CFD Models of Droplet Formulation from MDI*
- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*
- *CFD Analysis of Spreadability of Topical Formulations*
- *CFD Models of Soft Mist Inhalers*
- *Internally Implement PBPK Model Development for Locally-Acting Nasal Drug Products*
- *Ocular PBPK Model Development and Verification*

Outcomes

Product-Specific Guidances

- *Draft Guidance for Beclomethasone Dipropionate, Aerosol, Metered Inhalation*. FDA Guidance Posting. May 15, 2019. Link to Posting.

Articles

- Bai JPF, Musante CJ, Petanceska S, Zhang L, Zhao L, Zhao P. *American Society for Clinical Pharmacology and Therapeutics 2019 Annual Meeting Pre-Conferences*. CPT: Pharmacometrics & Systems Pharmacology. **8**(6):333-335, 2019. doi 10.1002/psp4.12424 PMID: 31087531 PMCID: PMC6617844
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- Choi, S., Yoon, S., Jeon, J., Zou, C., Choi, J., Tawhai, M., Hoffman, E., Delvadia, R., Babiskin, A., Walenga, R., and Lin, C. *1-D Network Stimulations for Evaluating Regional Flow and Pressure Distributions in the Healthy and Asthmatic Human Lungs*. Journal of Applied Physiology. (2019) **127**(1):122–133. doi: 10.1152/japplphysiol.00016.2019. PMID: 31095459.
- He, H., Liu, C., Liu, Y., Liu, X., Wu, Y., Fan, J., Zhao, L., and Y, C. *Mathematical Modeling of the Heterogeneous Distributions of Nanomedicines in Solid Tumors*. European Journal of Pharmaceutics and Biopharmaceutics. (2019) **142**:153–164. doi: 10.1016/j.ejpb.2019.06.005. PMID: 31226367
- Le Merdy, M., Fan, J., Bolger, MB., Lukacova, V., Spires, J., Tsakalozou, E., Patel, V., Xu, L., Stewart, S., Chockalingam, A., Narayanasamy, S., Rouse, R., Matta, M., Babiskin, A., Kozak, D., Choi, S., Zhang, L., Lionberger, R., Zhao, L. *Application of Mechanistic Ocular Absorption Modeling and Stimulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study Using Dexamenthasone Suspension*. AAPS J. (2019) **21**(4):65. doi:

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- Walenga R., Babiskin A., Zhao L. *In Silico Methods for Development of Generic Drug–Device Combination Orally Inhaled Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2019) **8**(6):359-370. doi: 10.1002/psp4.12413. PMID: 31044532.
- Yuan, D., He, H., Wu, Y., Fan, J., and Cao, Y. *Physiologically Based Pharmacokinetic Modeling of Nanoparticles*. J. Pharm. Sci. (2019) **108**:58–72. DOI: 10.1016/j.xphs.2018.10.037. PMID: 30385282.
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- Zhao, L., Kim, MJ., Zhang, L., and Lionberger, R. *Generating Model Integrated Evidence for Generic Drug Development and Assessment*. Clin Pharmacol Ther. (2019) **105**(2):338–349. doi: 10.1002/cpt.1282. PMID: 30414386.

Posters

- Walenga, R., Conti, D., Oguntimein, O., Delvadia, R., Rygg, A., and Babiskin, A. *Droplet Evaporation from a Solution-Based Metered Dose Inhaler: A Computational Approach*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Tsakalozou, E., Le Merdy, M., Babiskin, A., and Zhao, L. *Development of an Ocular Physiologically-Based Pharmacokinetic Model to Describe the Impact of Formulation Attributes on the Disposition of an Antibiotic Applied on the Rabbit Eye*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Hsieh, N., Reisfeld, B., and Chiu, W. *Pksensi: An R Package to Apply Sensitivity Analysis in Pharmacokinetic Modeling*. Fort Collins, CO, Mar. 10, 2019.
- Reisfeld, B., Chiu, W., Hsieh, N., Olschanowsky, C., Bois, F., and Ghosh, S. *Popkat: A Framework for Bayesian Population PBPK Analysis*. Fort Collins, CO, Mar. 11, 2019.
- Le Merdy, M., Fan, J., Babiskin, A., and Zhao, L. *Physiologically-Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development*. Poster Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Tsakalozou, E., Ni, Z., Babiskin, A., and Zhao, L. *Advancements in the Dermal Physiologically-Based Pharmacokinetic (PBPK) Modeling Under the Generics Drug User Fee Amendments (GDUFA) Program*. Poster Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Le Merdy, M., Fan, J., Babiskin, A., and Zhao, L. *Physiologically-Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development*. Poster Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 14, 2019.
- Choi, J., Choi, S., Li, F., Hoffman, EA., Castro, M., Goss, C., Hall, C., Mceleney, S., Sieren, JP, and Lin, CL. *Cluster-guided Image Matching Analysis of Multiscale Lung Response to Bronchial Thermoplasty*. Poster Presentation at the American Thoracic Society 2019 International Conference, Dallas, TX, May 19, 2019.

- Hosseini, S., Schuman, T., Walenga, R., Babiskin, A., and Golshahi, L. *Assessment of Internal Nasal Valve Using Anatomically-Accurate 3d Airway Models*. Poster Presentation at American Rhinologic Society. New Orleans, LA, Sept. 13, 2019.

Presentations

- Singh, N. *A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery*. Presentation at ACoP9. San Diego, CA, Oct. 10, 2018.
- Schroeter, J. D. *Local and Systemic Absorption Predictions of Nasal Inhaled Corticosteroids: A Combined Approach*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Choi, J., Choi, S., Hoffman, E., O'Shaughnessy, P., Castro, M., Delvadia, R., Walenga, R., Babiskin, A., and Lin, C. *Assessment of Effects of Selective Airway Luminal Expansion on Inhaled Particle Deposition in Severe Asthmatic Human Lungs - A Numerical Study*. Presentation at the 71st Meeting of the American Physical Society, Division of Fluid Dynamics. Atlanta, GA, Nov. 19, 2018.
- Babiskin, A. *Use of PBPK Model to Evaluate Impact of Ophthalmic Drug Product's Critical Quality Attributes on BA/BE Assessment.* Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington DC, Mar. 13, 2019.
- Bolger, M. *Developing PBPK for Ocular Delivery.* Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington DC, Mar. 13, 2019.
- Lin, CL. *CFD Lung Models for Drug Delivery*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Lionberger, R. *Critical Roles for Locally Acting PBPK in Regulatory Decisions*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Patel, N. *PBPK Modeling of Dermally Applied Drug Products to Support Clinical Development and Regulatory Assessment.* Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Przekwas, A., German, C., and Garimella, T. *An Integrated Multiscale-Multiphysics Modeling Ocular Drug Delivery and Pharmacokinetics Pharmacological Protection and Treatment*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Roberts, M. *PBPK Models of the Skin*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Tsakalozou, E. *Physiologically-Based Pharmacokinetic Modeling for the Development of Dermatological Drug Products and Its Regulatory Impact*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Walenga, R. *Impact of Orally Inhaled and Nasal Drug Product PBPK Models on Product Development and Regulatory Decision Making*. Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development

and Approval of Locally Acting Products., Washington, DC, Mar. 13, 2019.

- Walenga, R. *Role of Computational Fluid Dynamics and Physiologically-Based Pharmacokinetic Modeling in Development of Orally Inhaled and Nasal Drug Products*. Presentation at Design of Medical Devices Conference. Minneapolis, MN, Apr. 16, 2019.
- Walenga, R. *Computational Fluid Dynamics Modeling of Nasally Administered Drug Products in Regulatory Science Research at the U.S. Food and Drug Administration*. Presentation at Society for Computational Fluid Dynamics of the Nose and Airway (SCONA) 2019. Chicago, IL, June 5, 2019.
- Tsakalozou, E. *Physiologically-based Pharmacokinetic Modeling and Simulation Approaches: Best Practices for Regulatory Applications Related to Locally-acting Generic Drugs.* Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.
- Walenga, R. *Credibility Establishment for Computational Fluid Dynamics Models of Complex Generic Drug Delivery.* Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Long-Acting Injectable and Implants

Summary of FY2019 Activities

Long-acting injectables and implants cover a wide range of dosage forms and complexity, from systemic acting injectable particles and implants to local acting particles, as well as intrauterine systems and intravaginal rings. Each of these dosage forms has its own unique complexity in formulation design, which leads to various challenges in generic drug product development.

In FY2019, OGD had three grants, five contracts, and one internal collaboration related to long-acting injectables and implants. Although each project has different short-term goals, they all share a common long-term goal, which is to improve current scientific understanding on these products and provide new approaches to facilitate generic drug product development and regulatory approval. In brief, the short-term goals include:

1) developing new analytical tools for characterizing poly (lactide-co-glycolide) (PLGA) polymers;
2) investigating potential peptide polymer interactions in PLGA-based microparticles;
3) exploring in vitro and in vivo correlation of long-acting injectable suspensions;
4) developing a novel in vitro drug release testing method and using advanced imaging-based techniques to further understand multivesicular liposomes (MVLs);
5) developing new modeling tools to facilitate formulation design of PLGA-based microparticles; and
6) developing real time and accelerated in vitro drug release testing methods for intrauterine systems.

A considerable amount of progress was made in each of these projects and several projects had significant publications. For example, the FDA internal research team, which involves scientists in the Office of Generic Drugs and the Office of Pharmaceutical Quality in CDER and the Center for Devices and Radiological Health, published a paper in the Journal of Controlled Release describing the development of a novel in vitro drug release testing method for MVLs. The method involved a USP 2 apparatus (e.g., reverse dialysis setup inside the traditional USP 2 apparatus), where in situ UV-Vis probes were inserted in the dialysis cartridges for continuous monitoring of the drug concentration during release. This proposed setup along with other state-of-the-art physicochemical characterization techniques, such as cryo-scanning electron microscope (Cryo-SEM), laser diffraction, and confocal microscopy, were used to reveal the underlying mechanisms of drug release from MVLs. As MVL drugs are relatively new, the drug release mechanisms are not yet fully understood and guidance on in vitro drug release testing and physicochemical characterization is lacking. The published findings will be helpful in developing generic MVLs. The significance of these findings has been recognized by the chief editor of the journal and a cover story on this research paper was published in January 2019.

Research Highlight

Most approved long-acting injectable microparticles and implants use PLGAs as the rate controlling excipient. Since these products are parenteral, by regulation, generic versions must show qualitative (Q1) and quantitative (Q2) sameness to the reference products for excipients, including PLGAs. However, PLGAs are complex in nature and their properties can be altered during manufacturing, which can make reverse engineering difficult and assessment of Q1/Q2 sameness challenging. For example, glucose-star shaped PLGAs are relatively new and have not been well studied compared to other linear PLGAs. Based on our current understanding, comparative characterization data on polymer molecular weight/weight distribution, monomer ratio, and polymer structure (linear vs. branched) is critical for assessing Q1 sameness. However, there are no readily available methodologies for evaluating the structure of glucose-PLGAs. In addition, the conventional gel permeation chromatography-based characterization method is reference standard-dependent and direct comparisons between methods by different labs and/or firms cannot be made. Moreover, the reference standards that have been used do not have the branched structure, which can be problematic. To facilitate generic drug product development and regulatory assessment of long-acting drugs containing glucose-PLGA, FDA collaborated with Akina, Inc. to develop new analytical tools for characterizing glucose-PLGAs and to improve current understanding of polymer properties. In FY2019, the research team successfully developed and validated an analytical technique using a series of in-house synthesized branched-PLGA standards. The method was used to determine the branching parameters of glucose-PLGA extracted from Sandostatin LAR, as well as glucose-PLGAs obtained from three different suppliers in the United States. Detailed descriptions of method development, validation, and study results were published in the Journal of Controlled Release in May 2019. This project supports the evaluation of generic drug applications referencing Sandostatin LAR and will continue to benefit generic drug product development and regulatory assessment of glucose-PLGA-based drugs.

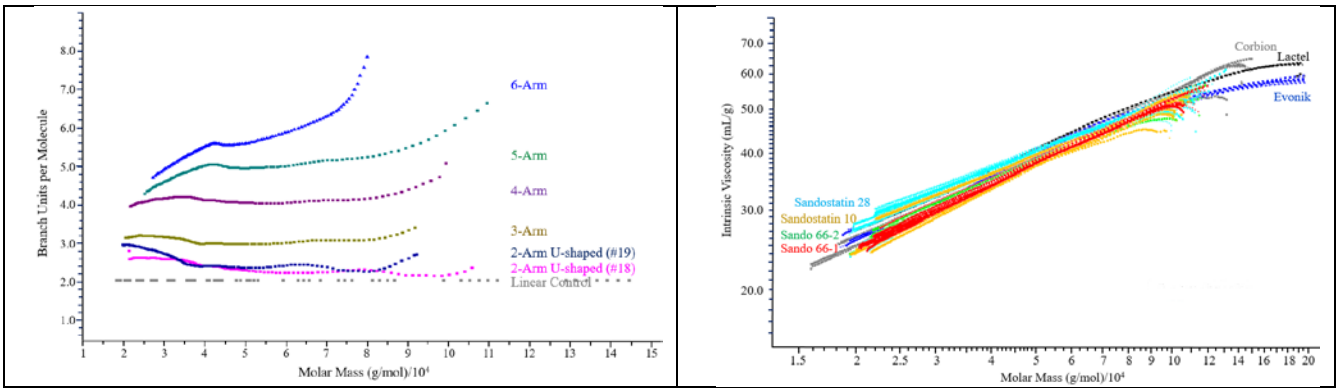

Figure 1: **(Left)** The branch units per molecule as a function of the molar mass of branched PLGAs with branch units ranging from 2 to 6; **(Right)** Mark-Houwink plots of glucose-PLGAs of Sandostatin LAR, glucose-PLGAs purchased from Corbion, Evonik, and DURECT Corporation (LACTEL®).

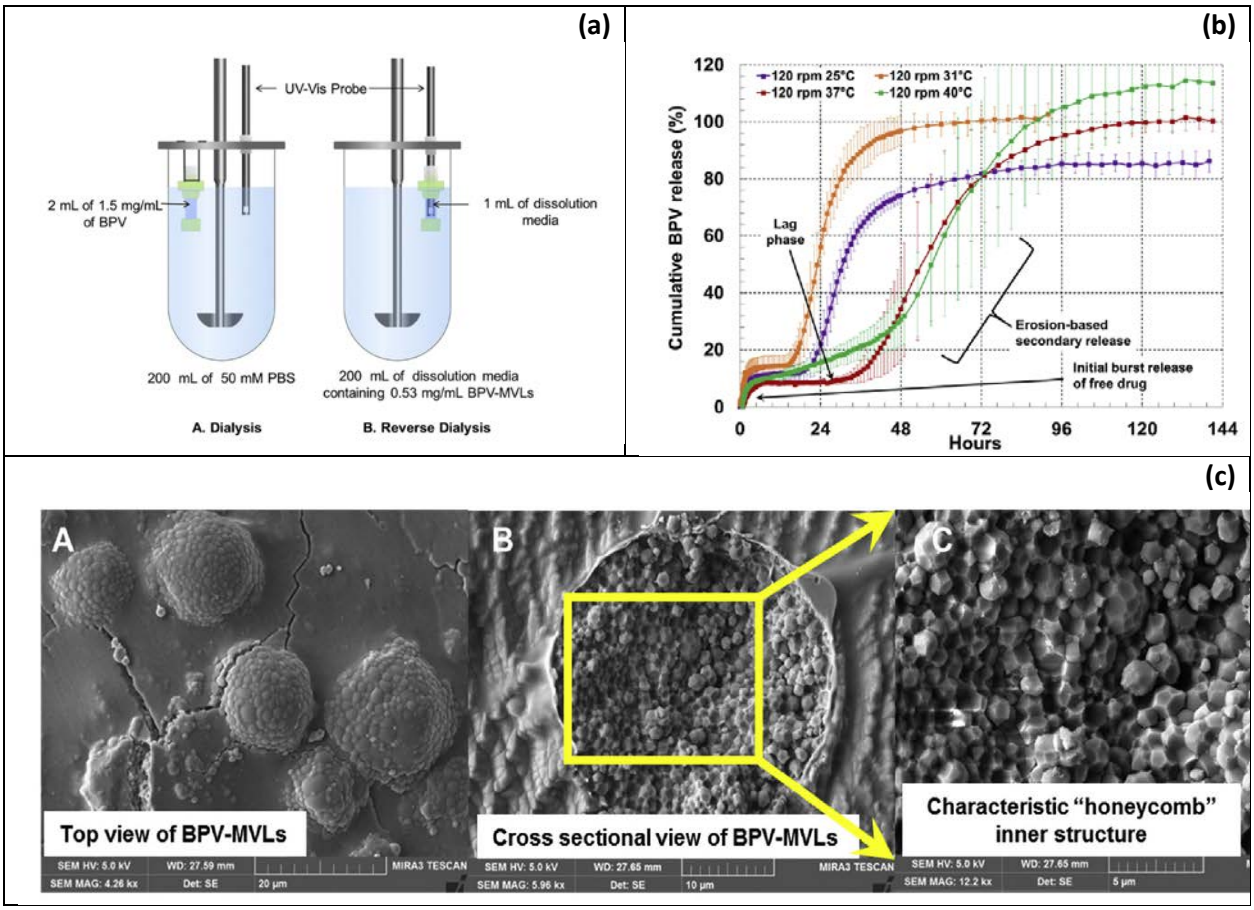

Figure 2: **(a)** In vitro release setup involving (A) dialysis and (B) reverse dialysis configuration; **(b)** bupivacaine release profiles from reverse dialysis set-up, detected with in situ fiber optic UV (IFO-UV) under different temperatures (Mean ± SD, n=3) **(c)** CryoSEM images showing (A) Top view; (B) Cross-sectional view; and (C) Inner structure of the MVLs prior to dissolution.

FY2019 GDUFA Science and Research Report

Research Projects and Collaborations

New Contracts

- Contract (75F40119C10096) *New Analytical Methods for Complex Sameness of Injectable, Long-Acting PLGA Formulations* with Haesun Park at Akina, Inc.
- Contract (75F40119C10157) *Microstructure Characterization with Micro-Imaging and Image-Based Analytics: A New Tool to Characterize Complex Polymer-Based Long Acting Drug Products* with Shawn Zhang at DigiM Solutions, LLC

Continuing Grants and Contracts

- Grant (1U01FD005442) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Robert Ward at University of Utah
- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane Jane Burgess at University of Connecticut
- Grant (1U01FD005847) *Investigation of Peptide-polymer Interactions in PLGA Microspheres* with Steven Schwendeman at University of Michigan
- Grant (1U01FD005447) *Biorelevant Dissolution Methods for Particulate dosage forms in the periodontal pocket* with Lisa Rohan at Magee-Women's Research Institute and Foundation
- Contract (HHSF223201710123C) *Development of Analysis Technique for Structural Characterization of Star-shaped Polyesters Used for Drug Delivery* with Kinam Park at Akina, Inc.
- Contract (HHSF223201610091C) *Advanced Analytical Techniques for Mixed Polymer Drug Delivery Systems* with Kinam Park at Akina, Inc.

Completed Contracts

- Contract (HHSF223201810115C) *Impact of Polymer Source Variations on Parenteral Microsphere Drug Product Performance* with Diane Jane Burgess at University of Connecticut
- Contract (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at University of Michigan
- Contract (HHSF223201710135C) *In vitro-In vivo Correlation of the Long-acting Injectable Suspensions Improve Scientific Approaches to Evaluate Generic Drugs* with Diane Jane Burgess at University of Connecticut

Active FDA Research

- *Bupivicaine Multivesicle Liposomes*

Outcomes

Articles

- *Andhariya, J., Jog, R., Shen, J., Choi, S., Wang, Y., Zou, Y., and Burgess, D. Development of Level A*

*In Vitro-In Vivo Correlations for Peptide Loaded PLGA Microspheres. Journal of Controlled Release. (2019) **308**:1–13. doi: 10.1016/j.jconrel.2019.07.013. PMID: 31301338.*

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Posters

- Andhariya, J., Jog, R., Shen, J., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Development of In Vitro-In Vivo Correlation for Complex Parenteral Microsphere Drug Products – Effect of Burst Release*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Andhariya, J., Jog, R., Shen, J., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Development of In Vitro-In Vivo Correlation of Peptide Microspheres – Possibility and Challenges*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Bao, Q., Zou, Y., Wang, Y., Choi, S., Kozak, D., and Burgess, D. *In Vitro Release Testing Methods for Long-Acting Intrauterine Systems*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Suh, M., Kastellorizios, M., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Effect of Implant Formation on Drug Release of in Situ Forming Implants*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Zhou, J. *Development and Characterization of Composition-Equivalent Formulations to the One-Month Lupron Depot*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018
- Garner, J., Hadar, J., Skidmore, S., Park, H., Park, K., Qin, B., Jiang, X., and Wang, Y. *Effect of Solvents and Their Isomers on Dissolution of PLGAs with Different Lactide:Glycolide (L:G) Ratios*. Poster Presentation at CRS Annual Meeting. Valencia, Spain, July 21, 2019.

- Garner, J., Hadar, J., Skidmore, S., Park, H., Park, K., Qin, B., Jiang, X., and Wang, Y. *Separation and Analysis of Poly(Lactide-Co-Glycolide) in Trelstar 22.5 Mg Formulation.* Poster Presentation at CRS Annual Meeting. Valencia, Spain, July 21, 2019.
- Hadar, J., Garner, J., Skidmore, S., Park, H., Park, K., Qin, B., Jiang, X., and Wang, Y. *Analysis of the Branch Units of Glucose-Poly(Lactide-Co-Glycolide) in Sandostatin LAR Formulation*. Poster Presentation at CRS Annual Meeting. Valencia, Spain, July 21, 2019.
- Hadar, J., Garner, J., Skidmore, S., Park, H., Park, K., Qin, B., Jiang, X., and Wang, Y. *Compositional Analysis of Glucose-Poly(Lactide-Co-Glycolide) in Sandostatin LAR Formulation.* Poster Presentation at CRS Annual Meeting. Valencia, Spain, July 21, 2019.

Presentations

- Kozak, D. *Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives*. Presentation at FY2019 Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.
- Fang, L. *Model-Informed Drug Development for Long-Acting Injectable Products*. Presentation at ACCP Annual Meeting. Chicago, IL, Sept. 16, 2019.
- Karlsson, M., Chen, X., and Hooker, A. *Development of Model-Informed Bioequivalence Evaluation Strategies for Long-Acting Injectable Products (LAI)*. Presentation at ACCP Annual Meeting. Chicago, IL, Sept. 16, 2019.
- Qin, B. *Characterization and Comparative Evaluation Strategies to Demonstrate Complex Excipient Sameness*. Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 25, 2019.
- Wang, Y. *Bioequivalence Approaches for Long-Acting Drug Products: Regulatory and Scientific Considerations*. Presentation at 2019 Small Business and Industry Assistance (SBIA), Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Ophthalmic

Summary of FY2019 Activities

In FY2019, there were three external and nine internal active GDUFA-funded research projects on locally-acting complex ophthalmic products (e.g., emulsion, ointment, and suspension). These research projects focused on developing and testing new high-resolution analytical methods to characterize formulation properties and on in silico modeling to better understand how differences in formulation properties impact the ocular pharmacokinetics and/or pharmacodynamics. This GDUFA research priority and these associated FY2019 studies aim to address challenges in the development and selection of appropriate criteria to facilitate the approval of bioequivalent complex generic ophthalmic drug products.

Eight FY2019 research projects focused on the development and testing of new physicochemical analytical testing methods to better characterize and understand the fundamental properties of ophthalmic emulsions and ointments. An external collaborative study (HHSF223201810114C) between researchers at the University of Connecticut and Virginia Commonwealth University explored new dissolution and in vitro characterization methods that can identify and characterize two active ingredients (dexamethasone and tobramycin) present as particulates formulated in an ointment. Internal studies also demonstrated the impact that viscosity modifying ingredients such as carbomer can have on particle size measurements, as well as the increased analytical sensitivity of Asymmetrical-Flow Field Flow Fractionation (AF4) for characterizing polydisperse dispersion formulations, such as ophthalmic emulsions. As shown in Figure 1, AF4 is able to separate and characterize the distribution of different particulate populations in a formulation, which are not resolved by more conventional particle analysis methods. A new method has also been developed internally to evaluate the impact of formulation and manufacturing process variations on drug distribution and release in ophthalmic emulsions. Methodology to employ Tip-Enhanced Raman Spectroscopy as an analytical technique for formulations such as ophthalmic emulsions has also been developed internally.

Four FY2019 research projects focused on developing ocular physiologically-based pharmacokinetic (PBPK) in silico models to predict how formulation properties may affect ocular retention and PK as well as tear film break-up time. Two external contracts (HHSF223201810151C and HHSF223201810255P) were awarded to CFD Research Corporation and Simulations Plus, Inc., respectively. These contracts aim to advance ocular PBPK models previously funded in GDUFA I, focusing on further incorporation of product attributes and more complex ophthalmic dosage forms into the modeling platforms. An internal study was published related to the prediction of cyclosporine ophthalmic emulsion ocular drug bioavailability and tear film breakup time for human subjects as a function of the vehicle physicochemical properties viscosity, surface tension, and osmolality for products that are formulated qualitatively and quantitatively the same. Another internal study for dexamethasone ophthalmic suspension is described in the Research Highlight.

Research Highlight

A key focus of FY2019 ophthalmic research was the development of ocular PBPK models to better predict how formulation properties can impact in vivo performance. In FY14, a collaborative project was initiated with Simulations Plus under Grant 1U01FD005211 to further develop the mechanistic Ocular Compartmental Absorption and Transit (OCAT™) model within GastroPlus™. Improvements of the model have been, and continue to be, made available in the commercial software package. Internally, we continue to investigate whether the PBPK tool could explain how modifications to ophthalmic suspension formulation properties impact ocular bioavailability. The investigation is currently limited to modeling rabbit ocular PK due to data availability; although such tools may support drug development and serve as a base for extrapolation from the rabbit model to a human model. In 2019, we published an internally developed OCAT model for dexamethasone ophthalmic suspensions that was developed and validated using published and in-house-generated rabbit PK data. The model was then used to simulate the ocular drug PK profiles of dexamethasone formulations that are qualitatively and quantitively similar but have differences in drug particle size, formulation viscosity, and strength. The model describes the dose-dependent (0.01 to 0.1%) non-linear PK in ocular tissues and illustrates that ocular bioavailability is dictated by the interplay between formulation properties and physiological clearance, through drainage and tear turnover rates in the pre-corneal compartment. As shown in Figure 2, the OCAT model was used predict the increasing ocular exposure of dexamethasone in formulations with viscosities ranging from 1.67 to 72.9 cP and the decreasing ocular exposure of dexamethasone in formulations with particle sizes from 5.5 to 22 µm (22 µm omitted in the figure).

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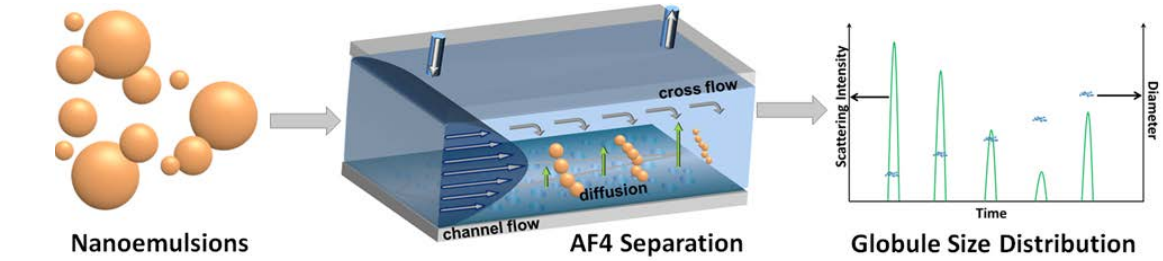

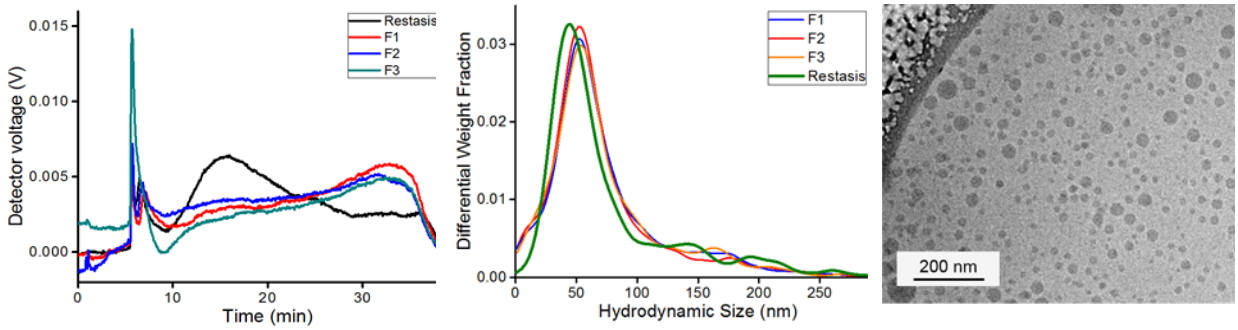

Figure 1: Asymmetrical-flow field flow fractionation (AF4) method for determining the particle size distribution of polydisperse ophthalmic emulsions. **Top Graph** is a schematic illustration of AF4 separation and characterization of a polydisperse emulsion. **Bottom Left Graph** is AF4 fractograms of RESTASIS®, cyclosporine, ophthalmic emulsion, and in-house formulations manufactured under different conditions. **Bottom Middle Graph** is respective globule size distribution based on the AF4 refractive index (dRI) detector. **Bottom Right** is a cryo-Transmission Electron Micrograph of RESTASIS® illustrating globule size and polydispersity.

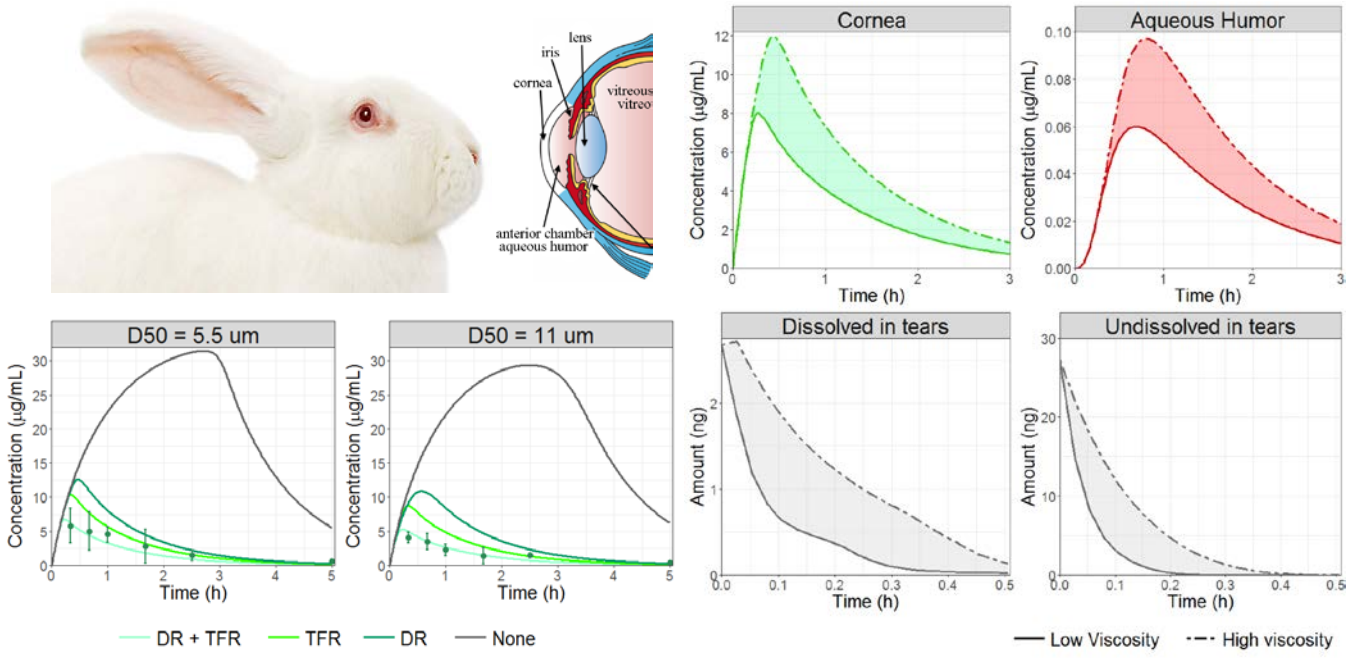

Figure 2: Rabbit ocular physiologically-based pharmacokinetic (PBPK) model to predict how differences in drug particle size and formulation viscosity of a topical ophthalmic suspension drop affect the ocular pharmacokinetics. **Lower left graphs** are cornea concentrations of dexamethasone following the administration of a dexamethasone 0.1% ophthalmic suspensions with different median particle sizes (D50; 5.5 or 11 microns) to rabbit eye. Lines represent simulations for different elimination mechanisms from ocular surface; DR = drainage rate, TFR = tear flow rate. Green dots represent observed data. **Graphs on the right** are cornea and aqueous humor concentration as well as dissolved and undissolved amounts of dexamethasone in tear fluid following the administration of a dexamethasone 0.1% ophthalmic suspensions with different viscosities (low ~ 17 cP or high~ 75 cP).

Research Projects and Collaborations

New Contracts

- New IDIQ Contract Task Order (75F40119D10024-75F40119F19001) *In Vitro and Non-Clinical Evaluation of Locally-Acting Topical Dermal and Ophthalmic Formulation Properties* with Glenwood Gum at Absorption Systems, Inc.

FY2019 GDUFA Science and Research Report

Continuing Grants and Contracts

- Grant (HHSF223201810151C) *An Integrated Multiscale-multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation
- Grant (HHSF223201810255P) *GastroPlus™ Ocular Compartmental Absorption and Transit (OCAT™) Model Extension and Validation* with Jessica Spires at Simulations Plus, Inc.
- Contract (HHSF223201810114C) *In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence* with Xiuling Lu at University of Connecticut

Active FDA Research

- *Physicochemical Characterization of Topical Ophthalmic Emulsion Products*
- *Physicochemical Characterization of Topical Ophthalmic Suspension Products*
- *Manufacture of Ophthalmic Test Formulations with meaningful variations in viscosity and particle/globule size*
- *Development of biphasic diffusion method to understand impact of formulation and manufacturing process variables on drug distribution and release in ophthalmic emulsion products*
- *In Vivo Biodistribution Evaluation of Ophthalmic Suspension Drug Products*
- *Ophthalmic Antimicrobial Kill Rate Study*
- *Development of the Earth Movers Distance for Particle Size Distribution Comparisons*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations Assessing and Predicting Ocular Bioavailability with Changes in Critical Formulation Ingredients (Preservatives) and Properties*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Latanoprostene Bunod Ophthalmic Solution, Drops*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Lifitegrast Ophthalmic Solution, Drops*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Netarsudil Dimesylate Ophthalmic Solution, Drops*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *Revised Draft Guidance for Dexamethasone; Tobramycin Ophthalmic Suspension Drops (NDA 050818)*. FDA Guidance Posting. February 22, 2019. Link to Posting.
- *Revised Draft Guidance for Dexamethasone; Tobramycin Ophthalmic Suspension Drops (NDA 050592)*. FDA Guidance Posting. February 22, 2019. Link to Posting.
- *New Draft Guidance for Benoxinate Hydrochloride; Fluorescein Sodium Ophthalmic Solution, Drops*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Betaxolol Hydrochloride Ophthalmic Suspension Drops.* FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Brimonidine Tartrate Ophthalmic Solution, Drops.* FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Brimonidine Tartrate; Brinzolamide Ophthalmic Suspension Drops.* FDA Guidance Posting. May 15, 2019. Link to Posting.

- *Revised Draft Guidance for Brinzolamide Ophthalmic Suspension Drops.* FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Cyclosporine Ophthalmic Solution, Drops.* FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Prednisolone Acetate Ophthalmic Suspension Drops*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Timolol Maleate Ophthalmic Solution, Drops*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Tobramycin Ophthalmic Ointment.* FDA Guidance Posting. May 15, 2019. Link to Posting.
- *New Draft Guidance for Fluorometholone Acetate Ophthalmic Suspension Drops*. FDA Guidance Posting. September 16, 2019. Link to Posting.
- *New Draft Guidance for Loteprednol Etabonate Ophthalmic Gel.* FDA Guidance Posting. September 16, 2019. Link to Posting.
- *New Draft Guidance for Loteprednol Etabonate Ophthalmic Suspension Drops.* FDA Guidance Posting. September 16, 2019. Link to Posting.

Articles

- *Chockalingam, A., Xu, L., Stewart, S., LeMerdy, M., Tsakalozou, E., Fan, J., Patel, V., and Rouse, R. Protocol for Evaluation of Topical Ophthalmic Drug Products in Different Compartments of Fresh Eye Tissues in a Rabbit Model. Journal of Pharmacological and Toxicological Methods. (2019)* ***96****:9–14. doi: 10.1016/j.vascn.2018.12.002. PMID: 30552958.*
- Dong, Y., Hengst, L., Patel, D., Hunt, R., Qu, H., Choi, S., Ashraf, M., Cruz, C.N., Xu, X. *A Kinetic Approach to Determining Drug Distribution in Complex Biphasic Systems*. Journal of Pharmaceutical Sciences (2019). 108(6), pp 2002-2011. doi: 10.1016/j.jconrel.2019.09.010. PMID: 31536731.
- Merdy, M. Fan, J., Bolger, M.B., Lukacova, V., Spires, J., Tsakalozou, E., Patel, V., Xu, L., Stewart, S., Chockalingam, A., Narayanasamy, S., Rouse, R., Matta, M., Babiskin, A., Kozak, D., Choi, S., Zhang, L., Lionberger, R., Zhao, L. *Application of Mechanistic Ocular Absorption Modeling and Stimulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study Using Dexamethasone Suspension*. AAPS J. (2019): 10.1208/s12248-019-0334-x. PMID: 31111305.
- *Walenga, R., Babiskin, A., Zhang, X., Absar, M., Zhao, L., and Lionberger, R. Impact of Vehicle Physicochemical Properties on Modeling-Based Predictions of Cyclosporine Ophthalmic Emulsion Bioavailability and Tear Film Breakup Time. Journal of Pharmaceutical Sciences. (2019)* ***108****(1):620–629. doi: 10.1016/j.xphs.2018.10.034 PMID: 30385283.*
  Patil, S. M., et al. *A Simple and Noninvasive DOSY NMR Method for Droplet Size Measurement of Intact Oil-In-Water Emulsion Drug Products*. Journal of Pharmaceutical Sciences, (2019) 108(2), 815-820. PMID: 30291851.

Posters

- Dong, Y., Hengst, L., Patel, D., Hunt, R., Qu, H., Choi, S., Ashraf, M., Cruz, C.N., Xu, X. *Understanding Drug Partition through Biphasic Diffusion*. AAPS PharmSci 360, Washington DC, Nov 4-7, 2018. **AAPS Poster Award.
- Tsakalozou, E., M, L., A, B., and L., Z. *Development of an Ocular Physiologically-Based Pharmacokinetic Model to Describe the Impact of Formulation Attributes on the Disposition of an Antibiotic Applied on the Rabbit Eye*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Merdy, M., Fan, J., Babiskin, A., and Zhao, L. *Physiologically-Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT) Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Le Merdy, M., Fan, J., Babiskin, A., and Zhao, L. *Physiologically-Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development*. Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 14, 2019.
- Qu, H., Patel, D., Kozak, D., Walenga, R., Choi, S., Ashraf, M., Faustino, P., Cruz, C., and Xu, X. *Asymmetrical-Flow Field Fractionation to Assess the Impact of Manufacturing process Variables on the Globule Size of Distribution of Cyclosporine Emulsions*. ACS Annual Meeting Silver Spring, MD, Mar. 28, 2019.
- Wood. E., Tyner K., *Tip-Enhanced Raman Spectroscopy as a Novel Method for Supporting the Physicochemical Sameness of Ophthalmic Emulsions.* Poster Presentation at FDA Science Forum, Silver Spring, MD, Sept. 11, 2019.

Presentations

- Urtti, A. *Bioequivalence Assessment for Complex Ophthalmic Products*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Kozak, D. *Generic Ophthalmic Drug Products, Physical Characteristics, And Bioequivalence*. Presentation at Association for Ocular Pharmacology and Therapeutics. New Orleans, LA, March 10, 2019.
- Luke, M. *Generic Drugs and Their Role in Bringing Next Generation Products: An FDA Perspective.* Presentation at Association for Ocular Pharmacology and Therapeutics. New Orleans, LA, March 10, 2019.
- Babiskin, A. *Use of PBPK Model to Evaluate Impact of Ophthalmic Drug Product's Critical Quality Attributes on BA/BE Assessment.* Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington DC, Mar. 13, 2019.
- Bolger, M. *Developing PBPK for Ocular Delivery.* Presentation at 2019 American Society for Clinical Pharmacology and Therapeutics (ASCPT), Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington DC, Mar. 13, 2019.
- *Przekwas, A., German, C., and Garimella, T. An Integrated Multiscale - Multiphysics Modeling Ocular Drug Delivery and Pharmacokinetics Pharmacological Protection and Treatment. Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and*

Therapeutics (ASCPT) Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.

- *Kozak, D. Advantages and Challenges in Implementing New Analytical Methods That Arise from Regulatory Science Initiatives. Presentation at FY2019 Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.*
- *Rodriguez, J. Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products. Presentation at FY2019 Generic Drug Research Public Workshop. Silver Spring, MD, May 1, 2019.*

FY2019 GDUFA Research Report: Oral Absorption Models and Bioequivalence (BE)

Summary of FY2019 Activities

In FY2019, intramural and extramural projects related to oral absorption models have objectives which fall into three major categories: (1) development of biorelevant dissolution testing, (2) enhancement of physiologically-based pharmacokinetic (PBPK) modeling capabilities, and (3) assessment of bioequivalence (BE) approaches and standards for global harmonization.

The intramural research includes, among others, investigations to (a) development of innovative in vitro dissolution methods for accurate dissolution determination in real time for nanocrystal drugs, (b) identification of differences in the approval basis for generic oral solution products among regulatory agencies to facilitate global harmonization, and (c) establishment of a framework to determine the need for fed BE studies for immediate-release drug products.

The extramural projects have focused on a wide range of issues, including: (a) crystallinity in amorphous solid dispersions (ASD), (b) use of PBPK model to predict the impact on PK, and (c) interaction potential of excipients with gastrointestinal (GI) transporters as further described below.

1. Formulation, Processing and Performance Interrelationships for ASD:
This project aimed to identify critical process parameters and quality attributes for ASD drug products and develop biopredictive dissolution methods for ASDs prepared by hot melt extrusion (HME).

2. Phase Behavior and Transformation Kinetics of Poorly Water Soluble Weakly Basic Drugs upon Transit from Low-to-high pH Conditions:
The aim was to evaluate the landscape of precipitation outcomes and kinetics for a poorly water-soluble base, posaconazole, to provide input values for PBPK modeling. Nucleation induction time was found to vary with the degree of supersaturation, the amount of colloidal amorphous drug present in the supersaturated solution, and the presence of undissolved free base.

3. Design, Development, Implementation and Validation of a Mechanistic PBPK Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug Product:
This project was conducted to develop, test and implement nucleation model, dynamic in vivo fluid volume/osmotic gradient model, enabling formulations/excipients, food effects, in vitro-in vivo correlation (IVIVC) tools for supersaturating drug products.

4.Wireless Sampling Pill to Measure In Vivo Drug Dissolution in GI Tract and Computational Model to Distinguish Meaningful Product Quality Differences and Ensure BE in Patients:
This project aimed to develop a wireless pharmaceutical analysis device (WPAD) for sampling GI fluid that contains drug particles and/or dissolved drug at various locations in the GI tract. Hardware was developed that will identify the location of the WPAD as it travels through the GI tract.

5. Effects of Excipients in Generic Drug Products on Intestinal Drug Transporters:
The aim was to enhance our understanding of pharmaceutical excipients by screening oral molecular excipients (136 in total) for interactions with intestinal drug transporters to help provide a scientific

foundation for expansion of Biopharmaceutics Classification System (BCS) Class 3 waivers to non-Q1/Q2 formulations.

Research Highlights

An intramural project is ongoing to 1) systematically compare different regulatory agencies' requirements regarding BE demonstration of oral solution products (e.g., when a biowaiver may be granted), and 2) evaluate the approval basis of U.S. generic oral solution products, especially the ones which contain poorly soluble active pharmaceutical ingredients (APIs). A total of 928 oral solution products were examined. The outcomes of this study can provide a summary about the approval basis of U.S. generic oral solution products and help identify potential areas for specific guideline development and global harmonization regarding the waiver of oral solution products. Preliminary findings are shown in Figure 1.

For one GDUFA-funded project on ASDs, earlier research found that degree of crystallinity of an ASD may be impacted during the manufacture of a drug product and upon storage, altering the dissolution profile (Figure 2, Left Panel). A physiologically-based pharmacokinetic (PBPK) model developed through a contract predicts that increase in crystallinity can result in bioinequivalence (Figure 2, Right Panel).

Criteria for Waiver of In Vivo BE Studies for Oral Solution Products	
U.S. FDA	Test product contains (i) the same active drug ingredient in the same concentration and dosage form as the reference listed drug (RLD); and (ii) no inactive ingredient or other change in formulation from the RLD that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed (per 21CFR 320.22).
Health Canada	Test product should be qualitatively the same and quantitatively essentially the same.
European Medicines Agency (EMA)	Test product contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, and the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance.
Therapeutic Goods Administration (TGA Australia)	Test product both: – contains the same drug substance(s) in the same concentration as a currently registered oral solution – does not contain excipients that may significantly affect gastric passage or absorption of the drug substance(s) in vivo solubility or in vivo stability of the drug substance.

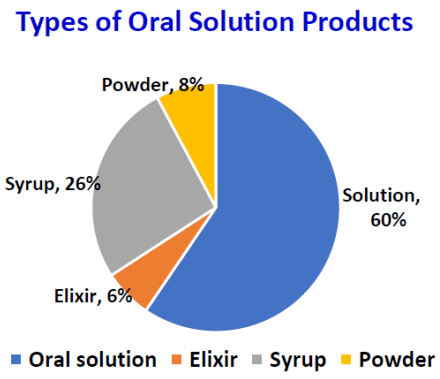

Figure 1: Criteria for waiver of in vivo BE studies for oral solution products among global agencies (Left Panel) and different types of oral solution products (Right Panel).

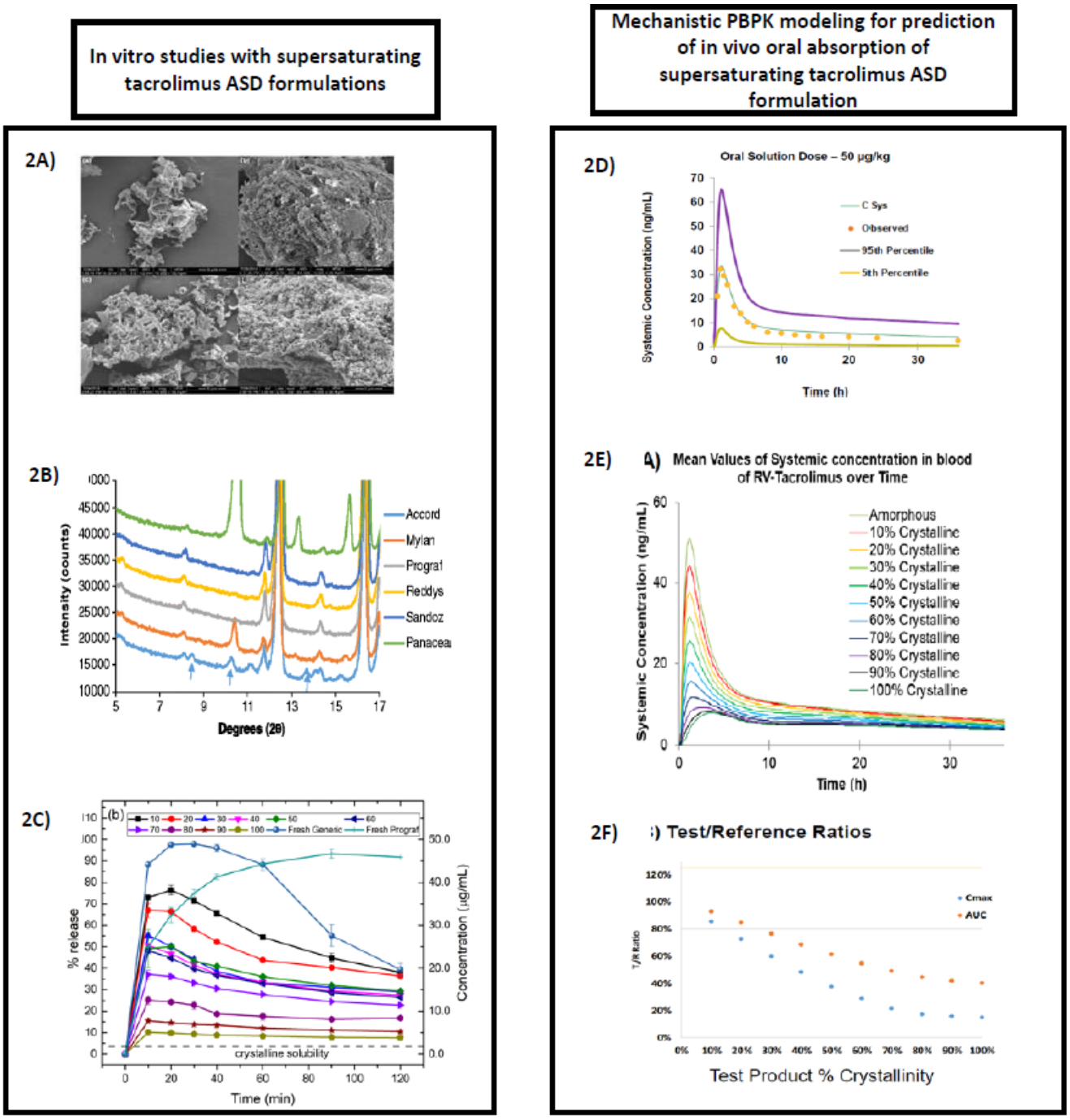

Figure 2: Prediction of the In Vivo Behavior of Supersaturating Drug Product Using PBPK Modeling.
2A) Scanning electron microscope image: Upper left and right panels show the residue obtained after dissolving powder contents of a brand and generic ASD product of tacrolimus. Lower left and right panels show the residue from tacrolimus-lactose dispersion and tacrolimus-Hydroxypropyl Methylcellulose (HPMC) dispersion, respectively. Brand residue is similar to tacrolimus-HPMC whereas the generic residue is similar to tacrolimus-lactose dispersion (Trasi NS, *et al*, Pharm Res, 2017, funded by 1U01FD005259);

2B) X-ray powder diffraction $_{patterns}$ showing evidence of crystallinity for various tacrolimus products following stressed storage condition of 40°C/75% RH (Trasi NS, *et al,* Pharm Res, 2017, funded by 1U01FD005259);

2C) The dissolution performance of ASD varies with degree of crystallinity in ASD formulation. The dissolution profiles of fresh reference product and generic tacrolimus ASD capsules containing varying levels of crystallinity in USP I medium 100 mL (Purohit HS, *et al*, J Pharm Sci, 2018, funded by 1U01FD005259);

2D) Simulated vs. observed PK profiles of tacrolimus utilizing a mechanistic PBPK model using Simcyp V18. A Particle Population Balance (PPB) model implemented in this version provides mechanistic models for simultaneous handling of two solid states (amorphous and crystalline) within the dosage;

2E) Simulated systemic exposure to tacrolimus at varying degrees of crystallinity in the dosage form utilizing the PBPK model from 2D;

2F) Virtual BE simulations (2-way crossover) evaluating the PK metrics (C_{max} and AUC_{0-t}) of 50 healthy subjects comparing 100% amorphous product (reference) with varying proportions of crystalline drug (10-100%) in the test drug product. This indicates crystallization within the tacrolimus drug product could potentially lead to bioinequivalence. PBPK models can be a good tool in identifying formulation design space (Fig. 2D-2F, Arora S, *et al*, Controlled Release Society Annual Meeting, Spain 2019, funded by 1U01FD005225-01).

Research Projects and Collaborations

New Contracts

- Contract (75F40119C10127) *Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2* with Chris Bode at Absorption Systems Inc.
- Contract (75F40119C10106) *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency* with Hualou Liang at Drexel University

Continuing Grants and Contract

- Grant (1U01FD005978-P2) *Effect of Excipient Transporter Interactions on BCS Class Drugs* with Kathleen M Giacomini at University of California San Francisco
- Grant (1U01FD005865) *Design, Development, Implementation and Validation of a Mechanistic Physiologically-Based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug Products* with David Barnes Turner at Simcyp, Ltd.
- 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 BE in Patients* with Duxin Sun at University of Michigan

Completed Grant and Contracts

- Grant (1U01FD005259) *Formulation, Processing and Performance Interrelationship for Amorphous Solid Dispersions* with Lynne Taylor at Purdue University

- 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
- Contract (HHSF223201510157C) *In Vivo Predictive Dissolution (IPD) to Advance Oral Product BE Regulation* with Gordon Amidon at University of Michigan

Active FDA Research

- D*issolution 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 BE*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *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 Guidance Development*
- *Analysis of the Predictability of BE in the Fed State*
- *Comparison of Steady State and Single Dose BE Studies for MR Product*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Desmopressin Acetate Sublingual Tablet*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Mesalamine Oral Capsule, Extended Release*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.

Articles

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- Moseson, D., Mugheirbi, N., Stewart, A., and Taylor, L.S. *Nanometer-Scale Residual Crystals in a Hot Melt Extruded Amorphous Solid Dispersion: Characterization by Transmission Electron Microscopy.* Crystal Growth & Design. (2018) **18**(12):7633–7640. doi: 10.1021/acs.cgd.8b01435.
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- Paixao, P. et al. *Linking the Gastrointestinal Behavior of Ibuprofen with the Systemic Exposure Between and Within Humans-Part 2: Fed State.* Mol Pharm. (2018) **15**(12):5468–5478. doi: 10.1021/acs.molpharmaceut.8b00736. PMID: 30417648.
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Posters

- Moseson, DE., and Taylor, LS. *Exploiting Melting Point Depression for Hot Melt Extrusion Processing of Amorphous Solid Dispersions*. Poster Presentation at Center for Pharmaceutical Processing Research (CPPR) Meeting, Purdue University, West Lafayette, IN, Oct. 16, 2018.
- Heissam, K. et al.; *Measuring Fasted State Gastric Motility Before and After a Standard BA/BE 8 OZ Drink of Water: Validation of New MRI Imaging Protocols Against Concomitant Perfused Manometry in Healthy Participants*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 4, 2018.
- Van Duong, T., Turner, DB., Taylor, LS. *Phase Behavior and Transformation Kinetics of a Poorly Water Soluble Weakly Basic Drug Upon Transit from Low to High Ph Condition.* Poster presentation at AAPS Pharmsci 360. Washington DC, Nov. 4, 2018.
- Amidon, G. *Remaining Challenges and New Initiatives in Oral Biopharmaceutics.* Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Duong, T., Turner, D., and Taylor, L. *Phase Behavior and Transformation Kinetics of a Poorly Water Soluble Weakly Basic Drug Upon Transit from Low to High PH Conditions*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Gao, Z., Yi, W., Tian, L., and Rodriguez, J. *Effect of Simulated Gastrointestinal Contraction on Drug Release of Nifedipine Extended-Release Tablet*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Tian, L., Ye, W., Rodriguez, J., Sun, D., Jiang, W., Lin, HP., and Gao, Z.; *Dissolution Testing of Nifedipine ER Tablet Using the USP Flow-Through Method*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Moseson, DE., and Taylor, LS. *The Application Of Temperature-Composition Phase Diagrams For Hot Melt Extrusion Processing Of Amorphous Solid Dispersions To Prevent Residual Crystallinity*. Poster Presentation at College of Pharmacy Graduate Students Research Symposium, Purdue University, West Lafayette, IN, Nov. 14, 2018.
- Turner, D. et al.; *Advanced Dynamic Bile Salt Model.* Poster Presentation at UNGAP In Vivo Tools Meeting. Greifswald, Germany, Feb. 24, 2019.

- Bajaj, R., Chong, LB., Zhou, L., Tsakalozou, E., Ni, Z., Giacomini, KM., Kroetz, DL.; *In vitro Evaluation of Excipient Dyes as Inhibitors of Human Intestinal P-glycoprotein Function.* ASPET Annual Meeting, Orlando, FL, Apr. 6-9, 2019.
- Arora, S., Patel, N., Jamei, M., and Turner, D. Modelling Framework. Poster Presentation at Controlled Release Society Annual Meeting. Valencia, Spain, July 21, 2019.
- Tian, L., Box, K., Swoboda, M., Tang, F., Lin, H., Jiang, W., Ruzicka, C., Rodriguez, J., and Gao, Z. *Exploring Factors Affecting Nifedipine Biphasic Dissolution Profile Using an Inform Platform*. Poster Presentation at 2019 FDA Science Forum. Silver Spring, MD, Sept. 11, 2019.

Presentations

- Amidon, G. *Keynote: Advancing the Science of Oral Solid Dosage Form Development and Performance*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Zhang, L*. Regulatory Science Issues in the Effect of Microbiomes on Bioequivalence Determination for Generic Drug Products.* Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 16, 2019.
- Zhao, L. *Use of Modeling and Simulation to Support New BE Approaches*. Presentation at Scientists Advancing Affordable Medicines (SAAM) Conference. Rockville, MD, Apr. 5, 2019.
- Zhang, L. *Drug-Drug Interactions and Generic Drugs.* Presentation at 22nd International Conference on Drug-Drug Interactions. Seattle, WA, Jun. 20, 2019.

FY2019 GDUFA Research Report: Patient Substitution

Summary of FY2019 Activities

To better understand the substitutability of generic drug products in patients who use drugs, FDA supports research projects funded in this area. Our research program looks at generic substitution in various ways, including clinical studies of substitution in patients, analyzing medical informatics data to evaluate generic utilization and substitution, and patient and provider perceptions impacting generic substitution.

FDA funded two additional studies - *Educating Groups Influencing Generic Drug Use* (Auburn University) (Grant 1U01FD005486) and *Identifying Messages to Promote Value and Education of Generic Prescribing* (University of Chicago) (Grant 1U01FD005485). The Auburn University study results showed that 93% of the patients/caregivers had positive perceptions about generic drug safety and effectiveness after reading a handout developed by FDA. After reading the handout, 52% of participants self-reported an improved opinion of generic drug safety, effectiveness, and cost. The University of Chicago study results found that 70% of health care providers agreed that after watching the educational module developed by the research team they plan to discuss and prescribe generic oral contraceptives. In addition, over 95% of health care providers correctly identified certain facts about generics presented in the module. The results from this study helped inform educational outreach messages targeting health care providers and patients.

Research Highlight

In FY2019, FDA funded a research project to assess the patient substitution of generic approved dry powder inhalers, with the Sentinel group. This project is ongoing; the data parameters have been established and the project protocol has been drafted. This project seeks to assess patient use data (number of users, and duration of use and time) as well as switch patterns of generic inhaled pulmonary products and its impact on the safety and effectiveness of these products compared to the reference listed drug counterparts.

Research Projects and Collaborations

New Grant

- Grant (1U01FD005938-A11) *Characterizing Safety and Efficacy of Brand and Generic Drugs Used to Treat Hypothyroidism Among Patients Who Switch Therapy Formulation* with Joseph Ross and Nilay Shah at Yale-Mayo CERSI

Continuing Grants and Contract

- Grant (1U01FD005938-A10) *Use of Instrumental Variable Approaches to Assess the Safety and Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross and Nilay Shah under Yale- Mayo CERSI
- Grant (1U01FD005271) *Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes Adherence and Immune Responses* with Suphamai Bunnapradist at the University of California at Los Angeles

- Grant (1U01FD005240) *Pharmacokinetic Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder* with Thomas J. Spencer at Massachusetts General Hospital
- Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Robert Ward at University of Utah
- Contract (HHSF223201610004I) *Base IDIQ for Postmarket Bioequivalence Study* with David Moreton at Biopharma Services USA

Completed Grants

- Grant (1U01FD005274) *The Transplant Outcomes Using Generic and Brand Name Immunosuppressants (TOGBI) Study* with Alan Leichtmann at Arbor Research Collaborative for Health
- Grant (1U01FD005486) *Educating Groups Influencing Generic Drug Use* with Jingjing Qian at Auburn University
- Grant (1U01FD005485) *Identifying Messages to Promote Value and Education of Generic Prescribing* with Vineet Arora with University of Chicago

Active FDA Research

- *Surveillance of Cardiovascular Generic Drug Products Using High-Throughput Preemptive Measures*

Outcomes

Articles

- Basu, S., Yang, H., Fang, L., Gonzalez-Sales, M., Zhao, L., Trame, M., Lesko, L., and Schmidt, S. *Physiologically Based Pharmacokinetic Modeling to Evaluate Formulation Factors Influencing Bioequivalence of Metoprolol Extended-Release Products.* Journal of Clinical Pharmacology. (2019) **59**(9):1252–1263. doi: 10.1002/jcph.1017. PMID: 31087553.
- Brown, J., Henriksen, C., Vozmediano, V., and Schmidt, S. *Real-World Data Approaches for Early Detection of Potential Safety and Effectiveness Signals for Generic Substitution: A Metoprolol Extended-Release Case Study.* Journal of Clinical Pharmacology. (2019) **59**(9):1275–1284. doi: 10.1002/jcph.1436. PMID: 31087552.
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- Kharasch, E. D., Neiner, A., Kraus, K., Blood, J., Stevens, A., Schweiger, J., Miller, J. P., and Lenze, E. J. *Bioequivalence and Therapeutic Equivalence of Generic and Brand Bupropion in Adults with Major Depression: A Randomized Clinical Trial*. Clin Pharmacol Ther. (2019) **105**(5):1164–1174. doi: 10.1002/cpt.1309. PMID: 30460996.
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- Sarpatwari, A., Gagne, J., Lu, Z., Campbell, E., Carman, W., Enger, C., Dutcher, S., Jiang, W., and Kesselheim, A. *A Survey of Patients' Perceptions of Pill Appearance and Responses to Changes in Appearance for Four Chronic Disease Medications*. Journal of General Internal Medicine. (2019) **34**(3):420–428. doi: 10.1007/s11606-018-4791-1. PMID: 30632102.
- *Segal, J. B., Onasanya, O., Daubresse, M., Lee, C.-Y., Moechtar, M., Pu, X., Dutcher, S. K., and Romanelli, R. J. Determinants of Generic Drug Substitution in the United States. Therapeutic Innovation & Regulatory Science. (2019): e0113. doi: 10.1177/2168479018820050. PMID: 30636440.*

Posters

- Farhan, N., Basu, S., Kim, S., Lingineni, K., Vozmediano, V., Ait-Oudhia, S., Fang, L., Zhao, L., Lesko, L., and Schmidt, S. *Application of Physiologically-Based Oral Absorption & Pharmacokinetic Modeling to Investigate Formulation Factors Influencing the Pharmacokinetics of Novel Oral*

Anticoagulants. Poster Presentation at Annual Meeting of the American Conference on Pharmacometrics (ACoP) 9, San Diego, CA, Oct. 8-10, 2018

- Kim S, Sharma VD, Lingineni K, Farhan N, Fang L, Zhao L, Brown JD, Cristofoletti R, Vozmediano V, Ait-Oudhia S, Lesko LJ, Trame MN, Schmidt S. *A Model- and Systems-Based Approach to Assess Impact of Potential Pharmacokinetic Differences on Pharmacodynamics and Questions Regarding Generic Substitution: A Case Study on Metoprolol Extended-Release Tablets*. Poster Presentation at Annual Meeting of the American Conference on Pharmacometrics (ACoP) 9, San Diego, CA, Oct. 8-10, 2018.
- Mosley, S., Frye, R., Langaee, T., Schmidt, S., Schmidt, S., Gong, Y., Binkley, P., Johnson, J., and Cavallari, L. *Determination of CYP2D6 Phenotyping for Metoprolol Using the Genotype-Derived Activity Score.* Poster Presentation at American College of Clinical Pharmacy (ACCP) Annual Meeting. Seattle, WA, Oct. 20, 2018.
- Thomas C.D., Monsely S.A., El Rouby N., Kim S., Lingineni K., Langaee T., Gong Y.; Johnson J.A., Schmidit S.O., Fyre R.F., Cavallari L.H. *Determination of CYP2D6 Phenotyping for Metoprolol Using CYP2D6 Genotype-Derived Activity Score: Results from a Prospective, Clinical Trial.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 13, 2019.
- Kitabi, E., Ivaturi, V., Liang, Z., Fang, L., Gobburu, J., and Gopalakrishnan, M. *A Tool for Prioritization of Investigation of Generic Drug Ineffectiveness Complaints.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 15, 2019.

FY2019 GDUFA Research Report: Quantitative Clinical Pharmacology

Summary of FY2019 Activities

Quantitative Clinical Pharmacology (QCP) is a quantitative platform that describes drug disposition, drug action, and associated variability in humans. In generic drug product development and regulatory assessment, 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 approaches are used in various regulatory activities including consultations, citizen petitions, controlled correspondences, abbreviated new drug application (ANDA) reviews related to complex products, pre-ANDA meetings, and development of product-specific guidances (PSGs). For instance, long-acting injectable (LAI) products is an area where QCP tools are applied to support the evaluation of alternate study designs considering the challenges in conducting BE studies due to their long duration and high dropout rate. In addition, pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations have been employed to assess the sensitivity of dose-scale approach for bronchoprovocation and bronchodilatation studies as recommended in the PSG for albuterol metered dose inhaler (MDI). The analysis results showed that, depending on the study design and data, dose-scale approach based on bronchodilatation studies may be insensitive to detect the clinically meaningful differences in relative bioavailability among albuterol MDIs. As such, a bronchoprovocation study may provide more sensitive means of demonstrating BE between test and reference albuterol MDI products.

As part of our continued work to encourage drug developers to bring safe, effective, and high-quality generic abuse-deterrent formulation (ADF) opioid products to the market, the Food and Drug Administration (FDA) issues PSGs describing current thinking and expectations on how to develop generics therapeutically equivalent to abuse-deterrent opioid products. QCP analysis supports the recommendation of partial area under the curve (AUC) for comparative abuse-deterrence evaluation of the test and reference opioid products. Therefore, FDA recommends that, in addition to maximum concentration (C_{max}) and AUC as primary PK metrics, generic applicants submit partial AUCs (pAUCs) (e.g., $pAUC_{0\text{-}3hr}$ and $pAUC_{0\text{-}4hr}$) as supportive data for abuse-deterrence assessment. The upper 95% confidence bound of the Test/Reference (T/R) ratio for C_{max} and AUC should be no more than 125.00%, while point estimates of the T/R ratio for pAUC should be no more than 125.00%. Furthermore, FDA is collaborating with external experts to advance the development of novel model-based BE approaches. One research topic has focused on nonlinear mixed-effect modeling (NLME) to assess BE with sparse PK data under certain circumstances such as patient PK studies. These model-based BE analysis methods demonstrated high power without compromising type I error, serving as a promising tool for future BE study analysis with sparse sampling (refer to Research Highlight for more information).

Research Highlight

Evaluation and Development of Model-Based Bioequivalence Analysis Strategies

Two projects were conducted to evaluate new approaches for assessment of bioequivalence (BE) in PK study designs with sparse sampling. In the first project, nonlinear mixed-effect modeling (NLME) approach was evaluated. NLME for drug PK is a promising tool to handle sparse data for BE analysis compared to non-compartment analysis (NCA) that requires rich sampling. However, NLME may suffer from inflated type I error, hindering its application in evaluating BE studies. In this work, model-based BE analysis methods were developed based on a single PK model and then extended it to multiple pre-defined PK model approaches via model averaging. A new method with Sampling Importance Resampling (SIR) as a tool for model parameter uncertainty estimation was developed. Two model averaging methods were developed and assessed as compared to the bootstrap NCA method as defined in the PSG for some ophthalmic drug products. The evaluated model averaging methods include conventional model averaging using Akaike Information Criterion (AIC)-based weighting, and bootstrap model selection, where one model was selected for each bootstrapped dataset. In the simulation studies for ophthalmic product BE data that only had one PK sample per subject, both model averaging methods indicated controlled overall type I error (based on inference tests of AUC_{last} and C_{max}) and higher power than the bootstrap NCA method. Significantly higher power for the model averaging approaches was observed for C_{max}. In this work, the bootstrap model selection method is preferred with lower type I error compared to the conventional model averaging method. In summary, the model-based BE analysis methods developed in this project demonstrated high power without compromising type I error (Figure 1), serving as a promising tool for future BE study analysis with sparse sampling.

In the second project, the following model-based alternative approaches were studied: 1) bootstrap standard errors (SE), 2) Gallant correction, and 3) 90% confidence interval derived from the posterior distribution (post) to avoid asymptomatic SE using the Stan software. A new bioequivalence optimal test (BOT) based on folded-normal distribution was proposed. For parallel studies and products with low variability (e.g., CV < 30%), all proposed alternatives corrected for the type I error inflation. For products with high variability (e.g., CV=50%), model-based two one-sided test (TOST) proved to be too conservative while model-based BOT maintained a type I error close to the conventionally accepted significant level of 0.05 (Figure 2). For crossover studies, all proposed alternatives corrected for the type I error inflation and TOST worked well. In conclusion of this work, model-based BE approach can be applied for study design with sparse sampling but the posterior distribution should be used instead of asymptotic SE and the BOT test instead of the TOST for highly variable drug products with parallel study design.

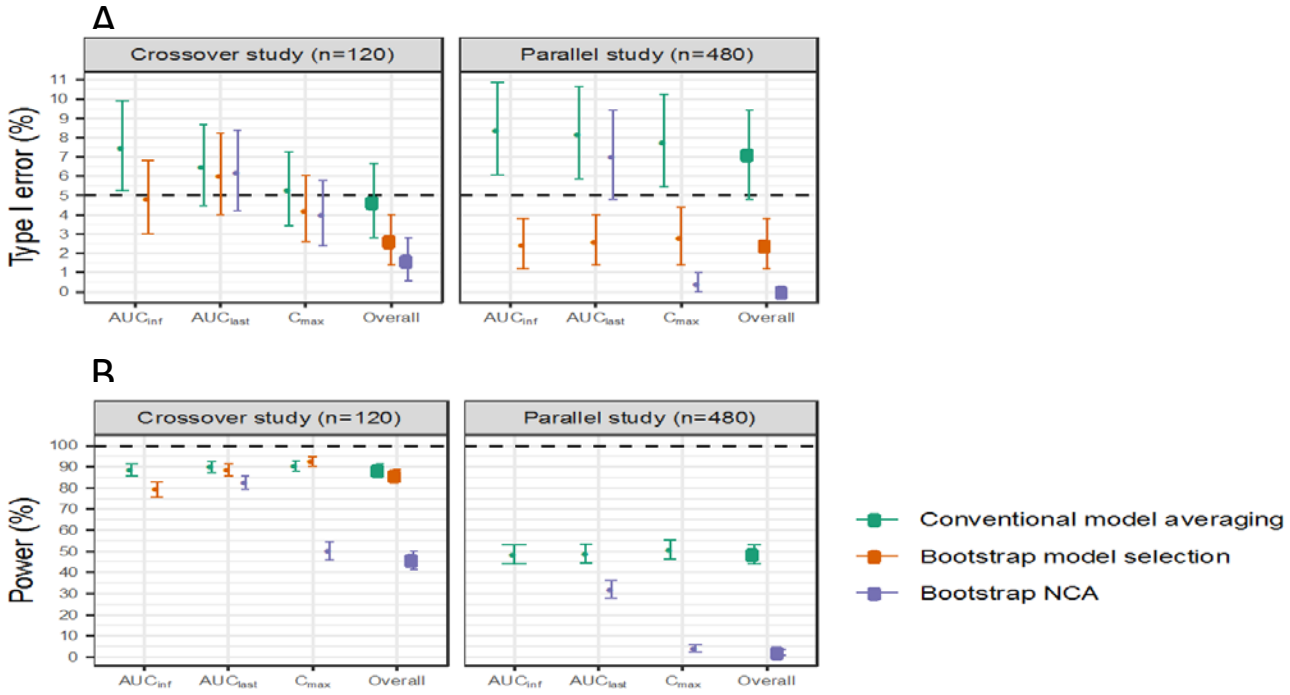

Figure 1: Simulation results for an ophthalmic drug product using model averaging approaches and the standard bootstrap NCA method for a crossover study with 120 subjects and a parallel study with 480 subjects. Type I errors (A) and power (B) were estimated when true treatment effect on bioavailability was set at 1.25 and 0.9, respectively, and for specific PK metrics (AUC_{inf}, AUC_{last}, and C_{max}) and overall BE (i.e., the final conclusion based on BE results for AUC_{last}, and C_{max}).

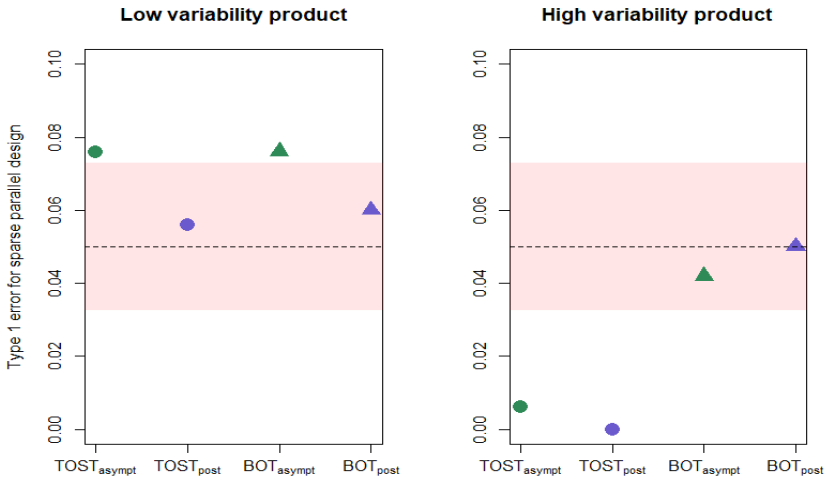

Figure 2: Type I errors for model-based BE TOST and BOT for parallel study designs with sparse sampling without (asymptotic) and with (posterior) SE correction. Pink area is the 95% prediction interval around 5% for 500 replicates.

FY2019 GDUFA Science and Research Report

Research Projects and Collaborations

New Contracts

- Contract (HHS223201975F40119C10018) *Development of Model- Informed Bioequivalence Evaluation Strategies for Long-Acting Injectable Products* with Mats O. Karlsson at Uppsala University
- Contract (75F40119C10111) *Evaluation of Model-Based Bioequivalence (MBBE) Statistical Approaches for Sparse Designs PK Studies* with France Mentre at Inst Nat Sante Et La Recherche Medicale (INSERM)
- Contract (75F40119C10068) *Batch-to-Batch Variability: Exploring Solutions for Generic BE Pathway* with Joga Gobburu at University of Maryland

Continuing Grants and Contracts

- Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Robert M. Ward at University of Utah
- Grant (1U01FD005240) *Pharmacokinetic Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder* with Thomas J. Spencer at Massachusetts General Hospital
- Grant (1U01FD005442) Pharmacometric *Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Robert M. Ward at University of Utah
- Grant (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael Neely at Children's Hospital of Los Angeles
- 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, UK
- Contract (HHSF223201710015C) *Evaluation and Development of Model-Based Bioequivalence Analysis Strategies* with Andrew Hooker at Uppsala University
- Contract (HHSF223201610110C) *Evaluation of Model-Based BioEquivalence (MBBE) Statistical Approaches for Sparse Designs PK Studies* with France Mentre at Inst Nat Sante et La Researche Medicale (INSERM)

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*
- *Model-Based Assessment on Bioequivalence Limits for Anticoagulants*
- *Assessment of Variability and Dose Sensitivity of FEV1 in Comparative Clinical Endpoint BE Studies of OIDPs*
- *Model-Based Adaptive Learning Design in BE Assessments*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*

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Outcomes

Product-Specific Guidances

- *Revised Draft Guidance for Scopolamine Transdermal Film, Extended Release*. FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *New Draft Guidance for Amphetamine Oral Suspension, Extended Release*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.

Articles

- Basu, S., Yang, H., Fang, L., Gonzalez-Sales, M., Zhao, L., Trame, MN., Lesko, L., Schmidt, S. *Physiologically Based Pharmacokinetic Modeling to Evaluate Formulation Factors Influencing Bioequivalence of Metoprolol Extended-Release Products.* J Clin Pharmacol. (2019) **59**(9):1252–1263. doi: 10.1002/jcph.1017. PMID: 31087553.
- Brown, J., Henriksen, C., Vozmediano, V., and Schmidt, S. *Real-World Data Approaches for Early Detection of Potential Safety and Effectiveness Signals for Generic Substitution: A Metoprolol Extended-Release Case Study.* J Clin Pharmacol. (2019) **59**(9):1275–1284. doi: 10.1002/jcph.1436. PMID: 31087552
- Gomeni, R., Fang, L., Bressolle-Gomeni, F., Spencer, TJ., Faraone, SV., and Babiskin, A. *General Framework for Assessing IVIVC As a Tool for Maximizing the Benefit-Risk Ratio of a Treatment Using a Convolution-Based Modeling Approach*. CPT: Pharmacometrics & Systems Pharmacology. (2019) **8**(2):97–106. doi: 10.1002/psp4.12378. PMID: 30659771.
- *Hohmann, N.S., Garza, K.B., Surry, D., Hansen, R.A., Harris, I., Kiptanui, Z., Oguntimein, O., Frost, M.M., and Qian, J. Communicating Benefits and Risks of Generic Drugs to Consumers: Patient and Caregiver Opinions of Two FDA-Developed Educational Materials. Res Social Adm Pharm. (2019): doi: 10.1016/j.sapharm.2019.01.013. PMID: 30744957.*
- Jayachandran, P., Okochi, H., Frassetto, LA., Park, W., Fang, L., Zhao, L., Benet, LZ. *Evaluating Within-Subject Variability for Narrow Therapeutic Index Drugs.* Clin Pharmacol Ther. (2019) **105**(2):411–416. doi:10.1002/cpt.1293. PMID: 30652304.
- Kim, H., Fang, L., Yu, J., Meng, Z., Trame, MN., Schmidt, S., Lesko, LJ., Zhao, L. *Is Bioequivalence Established Based on the Reference Scaled Average Bioequivalence Approach Relevant to Chronic Administration of Phenytoin? Perspectives Based on Population Pharmacokinetic Modeling and Simulations.* J Clin Pharmacol. (2019) **59**(8):1061–1069. doi:10.1002/jcph.1380. PMID: 30716169.
- Kim, S., Sharma, V.D., Lingineni, K., Farhan, N., Fang, L., Zhao, L., Brown, JD., Cristofoletti, R., Vozmediano, V., Ait-Oudhia, S., Lesko, LJ., Trame, MN., Schmidt, S. *Evaluating the Clinical Impact of Formulation Variability: A Metoprolol Extended-Release Case Study.* J Clin Pharmacol. (2019) **59**(9):1266–1274. doi:10.1002/jcph.1433. PMID: 31087554.
- *Lesko, L., Fang, L., Schmidt, S., and Trame, M. An Integrated Bioinformatics and Quantitative Modeling Approach to Investigate Potential Claims of Oral Generic Drug Product Bioinequivalence: Introduction. J Clin Pharmacol. (2019) **59**(9):1245–1248. doi: 10.1002/jcph.901. PMID: 31087551.*
- Zhao, L., Kim, MJ., Zhang, L., and Lionberger, R. *Generating Model Integrated Evidence for Generic Drug Development and Assessment*. Clin Pharmacol Ther. (2019) **105**(2):338–349. doi: 10.1002/cpt.1282. PMID: 30414386.

Posters

- Farhan, N., Basu, S., Kim, S., Lingineni, K., Vozmediano, V., Ait-Oudhia, S., Fang, L., Zhao, L., Lesko, L., and Schmidt, S. *Application of Physiologically-Based Oral Absorption & Pharmacokinetic Modeling to Investigate Formulation Factors Influencing the Pharmacokinetics of Novel Oral*

Anticoagulants. Poster Presentation at American Conference on Pharmacometrics (ACoP) 9 Meeting, San Diego, CA, Oct. 8-10, 2018.

- Kim, S., Sharma, V., Lingineni, K., Farhan, N., Fang, L., Zhao, L., Brown, J., Cristofoletti, R., Vozmediano, V., Ait-Oudhia, S., Lesko, L., Trame, M., and Schmidt, S. *A Model- and Systems-Based Approach to Assess Impact of Potential Pharmacokinetic Differences on Pharmacodynamics and Questions Regarding Generic Substitution.* Poster Presentation at American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 8-10, 2018.
- *Mosley, S., Frye, R., Langaee, T., Schmidt, S., Schmidt, S., Gong, Y., Binkley, P., Johnson, J., and Cavallari, L. Determination of CYP2D6 Phenotyping for Metoprolol Using the Genotype-Derived Activity Score. Poster Presentation at ACCP Annual Meeting. Seattle, WA, Oct. 20, 2018.*
- Thomas CD., Monsely SA., El Rouby N., Kim S., Lingineni K., Langaee T., Gong Y., Johnson JA., Schmidit SO., Fyre RF., and Cavallari LH. *Determination of CYP2D6 Phenotyping for Metoprolol Using CYP2D6 Genotype-Derived Activity Score: Results from a Prospective, Clinical Trial*. Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Orlando, FL, Mar. 13, 2019.
- Sharan, S, Li, Z, Fang, L, Kim, MJ and Zhao, L, *Population Pharmacokinetic Modeling to Characterize the Impact of Oral Abuse After Administration of Manipulated Hydrocodone Bitartrate Extended Release Tablets.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington DC, Mar. 14, 2019.
- Kitabi, E., Ivaturi, V., Liang, Z., Fang, L., Gobburu, J., and Gopalakrishnan, M. *A Tool for Prioritization of Investigation of Generic Drug Ineffectiveness Complaints*. Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington DC, Mar. 15, 2019.
- Miao, L., Wu, F., Yang, X, Ramamoorthy A, Lee S, Raines K, Zhang L, Seo P. *Application of Dissolution Profile Comparison for Gastric pH-Dependent Drug-Drug Interaction Prediction.* Poster Presentation at American College of Clinical Pharmacology (ACCP) Annual Meeting. Chicago, IL, Sept. 16, 2019.

Presentations

- Sharan, S. *Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits for Long Acting Intrauterine Product*. Presentation at FDA/DIA Complex Drug-Device Generic Combination Products 2019 Workshop. Silver Spring, MD, Oct. 9, 2018.
- Gobburu, J. *Population Pharmacokinetic and Pharmacodynamic, Dose Toxicity Modeling and Simulation for Narrow Therapeutic Index (NTI) Drugs.* Presentation at 2018 American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 10, 2018.
- Reisfeld, B. *Enhancing the Reliability, Efficiency, and Usability of Bayesian Population PBPK Modeling.* Presentation at 2018 American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 10, 2018.
- Singh, N. *A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery.* Presentation at 2018 American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 10, 2018.
- Zhang, L. and Fang, L. *Introduction to "FDA Town Hall Update: Modeling and Simulation in GDUFA Regulatory Science Program".* Presentation at 2018 American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 10, 2018.
- Zhao, L. *Overview of GDUFA-funded Modeling and Simulation Grants/Contracts.* Presentation at 2018 American Conference on Pharmacometrics (ACoP) 9 Meeting. San Diego, CA, Oct. 10, 2018
- Zhao, L. *Craft the Art of Using Quantitative Methods and Modeling for Drug Development.*

Presentation at 2018 Annual Meeting for Professional Committee of Pharmacometrics . Changsha, China, Nov. 17, 2018.

- Zhao, L. *Review of Quantitative Modelling of Complex Products*. Presentation at Workshop on Quantitative Evaluation of the Quality of Inhalable Products. Beijing, China, Nov. 28, 2018.
- Zhao, L. *Quantitative Analysis of Opioid ADF PK/ PD*. Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 15, 2019.
- Li, M. *Dose-Scale (Emax) Modeling in Pharmacodynamic Bioequivalence Studies - FDA Perspective*. Presentation at 2019 Scientists Advancing Affordable Medicines (SAAM) Conference. Rockville, MD, Apr. 4, 2019.
- Fang, L. *PK and Statistical Considerations for Steady State Bioequivalence Studies - FDA Perspective.* Presentation at Scientists Advancing Affordable Medicines (SAAM) Conference. Rockville, MD, Apr. 4, 2019.
- Wu, F. *Biopharmaceutics and Bioequivalence A day in Life.* Presentation at AAPS Forum. Boston, MA, May. 6, 2019.
- Sharan, S. *Opportunities and Challenges for Modeling and Simulation in Development of Long-Acting Injectable Drug Products*. Presentation at American College of Clinical Pharmacology (ACCP) Annual Meeting. Chicago, IL, Sept. 16, 2019.
- Fang, L. *PK/PD Meta-Analysis of Abuse Deterrent Opioid Drug Products: PSG Development, Research and ANDA Assessment.* Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop: Complex Drug Product Development, College Park, MD, Sep. 26, 2019.
- Sharan, S. *Application of Quantitative Clinical Pharmacology (QCP) in Development of Long Acting Injectable Products.* Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop: Complex Generic Drug Product Development. College Park, MD, Sept. 26, 2019.
- Zhao, L. *General Overview: The Use of Quantitative Methods and Modeling to Facilitate Generic Drug Development and Regulatory Assessment*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop: Complex Generic Drug Product Development. College Park, MD, Sept. 26, 2019.

FY2019 GDUFA Research Report: Topical Dermatological

Summary of FY2019 Activities

A continuing research priority is to expand characterization-based bioequivalence (BE) methods across all topical dermatological products, wherever possible. This is an expansive initiative that involves research to develop efficient BE approaches for topical dermatological, rectal, vaginal, and urethral reference products, with an emphasis on advancing the technology to evaluate formulation similarity for several unique dosage forms in order to support characterization-based BE approaches. Ongoing research in this area has elucidated how the qualitative (Q1) and quantitative (Q2) composition, as well as the physical and structural arrangement of matter in the dosage form (Q3), control the rate and extent to which topical drugs become available at the site of action.

During FY2019, research has been actively underway at the University of Mississippi (Grant 1U01FD005233) and the University of South Australia (Grant 1U01FD005226) to characterize Q3 properties of metronidazole, lidocaine, and prilocaine cream and gel products, and has successfully correlated these Q3 results with product performance (based upon cutaneous PK evaluations). Researchers have developed a substantial body of evidence that consistently demonstrates how products that have similar components, compositions, and physical/structural properties exhibit a comparable rate and extent of cutaneous bioavailability. Corresponding in vitro permeation test (IVPT) studies with these products were performed at the University of Maryland (Baltimore) (Grant 1U01FD004947). In parallel, in vivo dermal microdialysis (dMD) studies were performed at Long Island University (Brooklyn) (Grant 1U01FD005862) using the same metronidazole cream and gel products and in vivo dermal open flow microperfusion (dOFM) studies were performed at Joanneum Research (Austria) (Grant 1U01FD005861) using the lidocaine and prilocaine cream and gel products. Collectively, the results of the research with different drugs and drug products, using Q1, Q2, and Q3 characterization techniques, in vitro methodologies (e.g., IVPT), and in vivo techniques (e.g., dMD and dOFM), all performed in parallel by independent research groups, consistently demonstrated that products which are Q1, Q2, and Q3 similar, when compared to a reference product deliver topical drugs at a comparable rate and extent as the reference product.

New research initiatives included grants awarded to the University of Mississippi (Grant 1U01FD006507) and the University of South Australia (Grant 1U01FD006496) to understand the mechanisms by which topical dosage forms modulate drug delivery throughout their metamorphosis (spreading, drying, etc.) on the skin. These research projects focused on understanding how the thermodynamic activity of the drug in the dosage form influences its topical bioavailability, and sought to characterize whether the thermodynamic activity of the drug in the dosage form at different points during its metamorphosis may be a key determinant of whether similar formulations deliver drug to the skin at a comparable rate and to a comparable extent. Another new research initiative during FY2019 was to develop novel technologies to evaluate cutaneous pharmacokinetics non-invasively, using Raman spectroscopy and imaging techniques through a grant awarded to the University of Bath (Grant 1U01FD006533). These new research projects have successfully developed the tools, techniques, model systems, and study designs to conduct the spectroscopic or thermodynamic measurements and to perform well-controlled studies.

Research Highlight

An in vivo dOFM study was conducted in human subjects to characterize the dose-response relationship and the influence of potentially confounding factors such as local "cross-talk" between probes in adjacent treatment sites, or redistribution of the drug via clearance into the systemic circulation and recirculation into the skin. Six healthy subjects were enrolled in this pilot, single center, open label study. The Reference product EMLA® (lidocaine; prilocaine) Topical Cream, 2.5;2.5 % (Actavis Laboratories UT INC, US) was administered at three different doses (5, 10 or 15 mg/cm²) on three of the four test sites on each thigh. On the fourth site, 10 mg/cm² of Oraqix®(lidocaine; prilocaine) Dental Gel, 2.5;2.5 % (Dentsply DETRY GmbH, Germany) was administered, to evaluate the discrimination sensitivity of the test method at the target dose. All products were left on the test sites for 24 hours. The remaining (non-dosed) test site on one thigh, and the non-dosed test site on the arm were intended to monitor for potential "cross-talk" and/or redistribution between test sites. After dose application, blood samples were drawn at pre-specified times to monitor for any appearance of lidocaine or prilocaine in the systemic circulation.

The dose-dependent response of the PK profiles for both drugs when the cream dose was increased or decreased relative to the 10 mg/cm² dose level indicated that the system was sensitive and discriminating to an increase or decrease in the topical bioavailability of lidocaine and prilocaine, and that a 10 mg/cm² dose of the Reference cream may be suitable for a pivotal BE study. At the same dose (10 mg/cm²) the gel delivered substantially less lidocaine and prilocaine than the Reference cream, suggesting that the gel may serve as a good negative control for BE. The absence of probe contamination from systemic redistribution, and the lack of any substantial "cross-talk" between adjacent test sites indicate that individual probes can monitor the local rate and extent of lidocaine and prilocaine specifically without interference from different treatments at other sites.

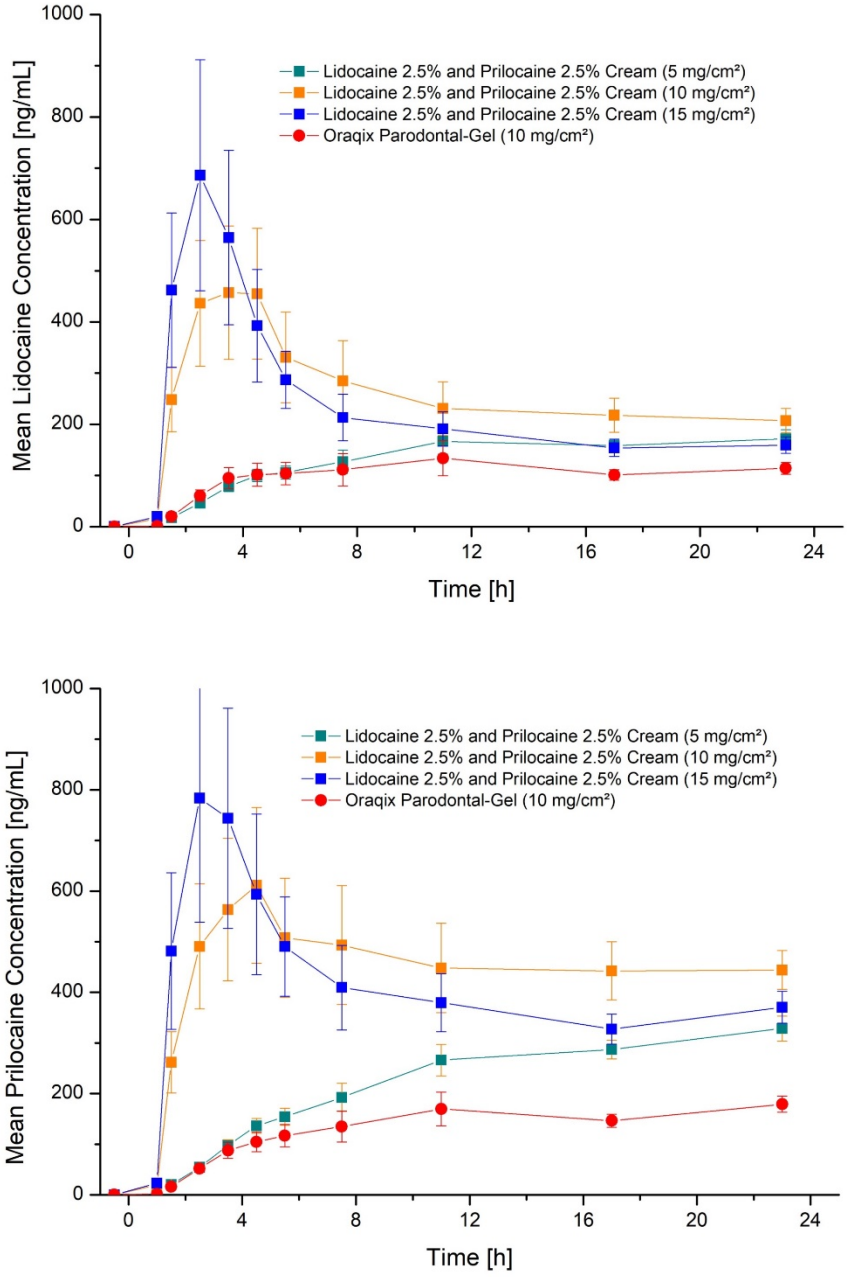

Figure 1: Mean lidocaine concentration-time profiles (± SE) for three different doses of lidocaine 2.5% and prilocaine 2.5% cream, USP and for Oraqix periodontal "parodontal-gel". The cutaneous PK profiles for lidocaine and prilocaine were comparable between the six subjects and showed relatively low inter- and intra-subject variability. The Reference cream showed a dose-response relationship with a peak around 3-5 hours following dose application, which corresponds well with the peak blood levels for these drugs from this drug product. Dermal interstitial fluid (perfusate) and blood samples from non-dosed sites showed no detectable levels of lidocaine or prilocaine, indicating no significant "cross-talk" between adjacent test sites, and no detectable systemic redistribution. At a product dose of 10 mg/cm², the PK profiles for the Test gel were well

differentiated from those for the Reference cream, suggesting that the gel may represent a reasonable negative control for BE with respect to the Reference product.

Research Projects and Collaborations

New Grants

- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Grant (1U01FD006700) *Elucidating Sensorial and Functional Characteristics of Topical Formulations* with Yousuf Mohammed at University of Queensland
- Grant (1U01FD006721) *Bioequivalence Considerations of Topical Rectal and Vaginal Suppositories* with Jie Shen at University of Rhode Island

Continuing Grants and Contract

- Grant (1U01FD004947) *Bioequivalence of Topical Drug Products: In Vitro - In Vivo Correlations* with Audra L. Stinchcomb at University of Maryland
- Grant (1U01FD005233) *Topical Products and Critical Quality Attributes* with Sathyanarayana N. Murthy at University of Mississippi
- Grant (1U01FD005226) *Characterization of Critical Quality Attributes for Semisolid Topical Drug Products* with Michael Roberts at University of South Australia.
- Grant (1U01FD005861) *Development of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM* with Frank Sinner at Joanneum Research
- Grant (1U01FD005862) *Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products* with Grazia Stagni at Long Island University
- Grant (1U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques (U01)* with Richard Guy at University of Bath
- Grant (1U01FD006521) *Characterize Skin Physiology Parameters Utilized in Dermal Physiologically-Based Pharmacokinetic Model Development Across Different Skin Disease States (U01)* with Sebastian Polak at Simcyp, Ltd.
- Grant (1U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations(U01)* with Michael Roberts and Yousuf Mohammed at University of South Australia
- Grant (1U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations (U01)* with Sathyanarayana N. Murthy at University of Mississippi
- Grant (1U01FD006522) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems (U01)* with Michael Roberts at University of Queensland
- Grant (1U01FD006526) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems (U01)* with Jessica Spires at Simulations Plus, Inc.
- Contract (HHSF223201610125C) *Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations* with Shanna Geigle at QPS, LLC

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Completed Grants

- Grant (1U01FD005232) *Physiologically Based Biopharmaceutics and Pharmacokinetics of Drug Products for Dermal Absorption in Humans* with Michael Roberts at University of South Australia

Active FDA Research

- *Development of a Novel Bio-Relevant In Vitro Skin Permeation Test (IVPT) for Hydrophobic Drugs Using in-Line Flow Through Diffusion Cells (FTC*) *CFD Analysis of Spreadability of Topical Formulations*
- *Snowflakes in Transdermal Systems: Influence of Drug Crystallization on Drug Permeation and Quality of TDS*

Outcomes

General Guidances

- Draft guidance for industry *Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs.* Oct. 9, 2018. Link to Posting.
- Draft guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs.* Oct. 9, 2018. Link to Posting.

Product-Specific Guidances

- *New Draft Guidance for Capsaicin Topical Patch.* FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Diclofenac Epolamine Topical Patch.* FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Lidocaine Topical Patch (NDA 020612).* FDA Guidance Posting. Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Menthol; Methyl Salicylate Topical Patch.* FDA Guidance Posting, Oct. 9, 2018. Link to Posting.
- *Revised Draft Guidance for Clindamycin Phosphate Topical Gel (NDA 050615).* FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Doxepin Hydrochloride Topical Cream*. FDA Guidance Posting. Nov. 28, 2018. Link to Posting.
- *New Draft Guidance for Bexarotene Topical Gel*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *Revised Draft Guidance for Crisaborole Topical Ointment*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Ozenoxacin Topical Cream*. FDA Guidance Posting. Feb. 22, 2019. Link to Posting.
- *New Draft Guidance for Halcinonide Topical Ointment*. FDA Guidance Posting. May 15, 2019. Link to Posting.
- *Revised Draft Guidance for Acyclovir Topical Ointment*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *New Draft Guidance for Glycopyrronium Tosylate Topical Cloth*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.

- *New Draft Guidance for Hydrogen Peroxide Topical Solution*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Metronidazole Topical Gel, 0.75%* (*NDA 019737)*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Metronidazole Topical Cream (NDA 020531).* FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Metronidazole Topical Cream (NDA 020743).* FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Metronidazole Topical Lotion*. FDA Guidance Posting. Sept. 16, 2019. Link to Posting.
- *Revised Draft Guidance for Metronidazole Topical Gel, 1% (NDA 021789).* FDA Guidance Posting. Sept. 16, 2019. Link to Posting.

Article

- Sun, W., Grosser, S., Kim, C., Raney, SG. *Statistical Considerations and Impact of the FDA Draft Guidance for Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs,* J. Biopharm. Stat., Sept. 8, 2019, 2019. doi 10.1080/10543406.2019.1657440, PMID: 31495266
- Willett, D. R., Yilmaz, H. Wokovich, A. M., Rodriguez, J. D. *Low-Frequency Raman Mapping and Multivariate Image Analysis for Complex Drug Products,* American Pharma. Rev., 2019, **22**, 48-51. Retrieved from https://www.americanpharmaceuticalreview.com/

Posters

- *Rangappa, S., Ajjarapu, S., Ghosh, P., Rantou, E., Raney, S., Repka, M., and Murthy, S. Evaluation of Bioavailability of Lidocaine and Prilocaine from Topical Drug Products Using an In Vitro Permeation Test (IVPT). Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.*
- Rangappa, S., Ajjarapu, S., Varadarajan, A., Prado, R., Ghosh, P., Raney, S., Kundu, S., Repka, M., and Murthy, S. *Comparative Assessment of the Physical and Structural Similarity of Topical Drug Products Containing Lidocaine and Prilocaine*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Shukla, S., Thomas, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *Assessment of Local and Systemic Bioavailability of Lidocaine from Two Lidocaine Topical Delivery Systems Using Pharmacokinetic and Skin (Tape) Stripping Analyses*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Tiffner, K., Birngruber, T., Schwagerle, G., Bodenlenz, M., Augustin, T., Raml, R., Kanfer, I., Raney, S., and Sinner, F. *Evaluation of Dermal Open Flow Microperfusion (DOFM) As a General Methodology to Assess the Bioequivalence of Hydrophobic, Protein-Bound Topical Drug Products*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.
- Tiffner, K., Kanfer, I., Augustin, T., Raml, R., Raney, S., and Sinner, F. *In Vitro Release Test (IVRT) Comparisons of Six Acyclovir Cream, 5% Products to Evaluate the Impact of Compositional Differences on Product Performance*. Poster Presentation at AAPS Pharmsc. 360. Washington, DC, Nov. 5, 2018.
- Tiffner, K., Rantou, E., Bodenlenz, M., Augustin, T., Reisnegger, P., Raml, R., Raney, S., and Sinner, F. *Reference-Scaled Average Bio-Equivalence (SABE): A Promising Statistical Approach to Analyze Cutaneous Pharmacokinetic Results for Topically Applied Drug Products*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 5, 2018.

- Ajjarapu, S., Rangappa, S., Raney, S., Repka, M., and Murthy, S. *Method Development and Optimization of an In Vitro Permeation Test (IVPT) to Compare the Rate and Extent of Drug Permeation from Topical Drug Products*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Kuzma, B., Senemar, S., DePinto, R., and Stagni, G. *LC/MS/MS Method for the Quantification of Metronidazole in Skin Dialysate*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Kuzma, B., Senemar, S., Ramezanli, T., Ghosh, P., Raney, S., and Stagni, G. *Evaluation of Local Bioavailability of Metronidazole from Topical Formulations Using Dermal Microdialysis: Preliminary Studies in Yucatan Mini-Pig*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Shukla, S., Thomas, S., Yu, M., Shin, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *Assessment of Bioavailabilty of Diclofenac from Two Topical Drug Products Using Pharmacokinetic and Skin (Tape) Stripping Analyses*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Zhang, Q., Ghosh, P., Raney, S., Hammell, D., Hassan, H., and Stinchcomb, A. *Assessment of Bioavailability of Rivastigmine from Two Rivastigmine Transdermal Delivery Systems with and Without Exposure to Heat Using In Vitro Permeation Test (IVPT)*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 6, 2018.
- Kuzma, B., Senemar, S., and Stagni, G. *Effect of Formulation Wipe-Off Time on Topical Bioavailability of Metronidazole Using Dermal Microdialysis*. Poster Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Tsakalozou, E., Zi, Z., Babiskin, A., and Zhao, L. *Advancements in the Dermal Physiologically-Based Pharmacokinetic (PBPK) Modeling Under the Generic Drug User Fee Amendments (GDUFA) Program.* Poster Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT) Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.
- Dabbaghi, M., Mohammed, Y., Namjoshi, S., K, T., Rantou, E., Ramezanli, T., Raney, S., Roberts, M., and Grice, J. *Deciphering the Effects of Microstructure on Lidocaine-Prilocaine Topical Product Performance*. Poster Presentation at Controlled Release Society Annual Meeting. Valencia, Spain, July 21, 2019.
- Kuzma, B., Senemar, S., and Stagni, G. *Estimation of In Vivo Skin Permeation (Flux) and Cumulative Amount Input of Metronidazole Formulations in Mini-Pigs' Dermis*. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Namjoshi, S., Mohammed, Y., Telaprolu, K., Dabbaghi, M., Jung, N., Windbergs, M., Grice, J., Ramezanli, T., Raney, S., and Roberts, M. *Topical Semisolid Product Bioequivalence-A Case for Product Quality and Performance Assessment As Evaluation Tools*. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Senemar, S., Kuzma, B., Ramezanli, T., Ghosh, P., Raney, S., and G, S. *Evaluating the Bioequivalence of Topical Dermatological Drug Products Containing Metronidazole Using Dermal Microdialysis: Preliminary Studies in Rabbits*. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Shukla, S., Thomas, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *Impact of Operator Variability on the Reproducibility of Tape Stripping Results*. Poster Presentation at Gordon

Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.

- *Vitry, P., Tabosa, A., Belsey, N., Tsikritsis, D., Woodman, T., Bunge, A., Delgado-Charro, M., and Guy, R. Evaluating Topical Drug Bioavailability in the Skin Using Raman Spectroscopy. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.*
- Zhang, Q., Ghosh, P., Rantou, E., Raney, S., Hammell, D., and Stinchcomb, A. *Evaluation of Metronidazole Bioavailability from Dermal Products Using an In Vitro Permeation Test (IVPT) Across Human Skin*. Poster Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Kelchen, M., Ghosh, P., Ramezanli, T., and Raney, S. *Strategic Analysis of the Roadmap for Implementing Characterization-Based Bioequivalence Approaches in Product-Specific Guidances for Generic Topical Dermatological Drug Products*. Poster Presentation at Innovations in Dermatological Sciences. Somerset, NJ, Sept. 9, 2019.
- Kuzma, B., Senemar, S., and Stagni, G. *Estimation of In Vivo Skin Permeation (Flux) and Cumulative Amount Input of Metronidazole Formulations in Mini-Pigs' Dermis*. Poster Presentation at Innovations in Dermatological Sciences. Somerset, NJ, Sept. 9, 2019.
- Tiffner, K., T, B., Schwagerle, G., Bodenlenz, M., Augustin, T., Raml, R., Kanfer, I., and Sinner, F. *Dermal Pharmacokinetic Endpoint Studies to Evaluate Bioequivalence of Topically Applied Lidocaine and Prilocaine Drug Products*. Poster Presentation at Skin and Formulation 5th Symposium. Reims, France, Sept. 22, 2019.

Presentations

- Jiang, Xiaohui (Jeff). *Understanding FDA's Rules and Expectations Surrounding Q1/Q2 Determinations*. Presentation at Scientists Advancing Affordable Medicines. Baltimore, MD, Oct. 18, 2018.
- Ghosh, P. *In Vitro Data Analysis Issues: IVPT Analyses and Other Challenges*. Presentation at Scientists Advancing Affordable Medicines. Baltimore, MD, Oct. 18, 2018.
- Ramezanli, T. *CGDP with a Locally-Acting Route of Delivery Including Topical Dermatological Drug Products*. Presentation at AAPS Pharmsci 360 Workshop: Flight Simulator: Learning How to Develop Complex Generic Drug Products. Washington, DC, Nov. 3, 2018.
- Ghosh, P. *Topical Semisolids-Similarities/Differences Between Products Administered Via Different Routes.* Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Ghosh, P. *Use of Imaging Techniques in Dermal Drug Development*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Murthy, S. N. *Effect of Excipients on the In Vitro Permeation of Drugs from Topical Products*. Presentation at AAPS Pharmsci 360. Washington, DC, Nov. 7, 2018.
- Luke, M. *Generic Drugs for Dermatology*. Presentation at FDA Symposium at the 2019 AAD Annual Meeting. White Oak, MD, Mar. 3, 2019.
- Sinner, F. *In-Vivo Skin PK Testing for New and Generic Topical Dermatological Drug Development*. Presentation at European Federation for Pharmaceutical Sciences. Frankfurt, Germany, Mar. 6, 2019.
- Patel, N. *PBPK Modeling of Dermally Applied Drug Products to Support Clinical Development and Regulatory Assessment*. Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 13, 2019.
- Tsakalozou, E. *Physiologically-Based Pharmacokinetic Modeling for the Development of Dermatological Drug Products and Its Regulatory Impact*. Presentation at 2019 Annual Meeting,

American Society for Clinical Pharmacology and Therapeutics (ASCPT) Pre-Conference: PBPK Modeling for the Development and Approval of Locally Acting Products. Washington, DC, Mar. 13, 2019.

- Roberts, M. *PBPK Models of the Skin*. Presentation at 2019 Annual Meeting, American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington, DC, Mar. 13, 2019.
- Rantou, E. *Statistical Issues with Aberrant IVRT/IVPT Data- FDA Perspective*. Presentation at Scientists Advancing Affordable Medicines (SAAM). Rockville, MD, Apr. 4, 2019.
- Ramezanli, T. *Bioequivalence of Topical Products Scientific Consideration*. Presentation at 4th FDA/PQRI Conference on Advancing Product Quality. Rockville, MD, Apr. 9, 2019.
- Ghosh, P. *FDA Initiatives to Stimulate Innovation and Improve Patient Access to Generic Topical & Transdermal Products Part II*. Presentation at Wellman Center for Photomedicine. Massachusetts, MA, Apr. 23, 2019.
- Raney, S. *FDA Initiatives to Stimulate Innovation and Improve Patient Access to Generic Topical & Transdermal Products Part I*. Presentation at Wellman Center for Photomedicine. Massachusetts, MA, Apr. 23, 2019.
- Raney, S. *A Generic Perspective on the Use of In Vitro Assessment Methods*. Presentation at Topical Drug Development – Evolution of Science and Regulatory Policy Workshop sponsored by the University of Maryland Center of Excellence in Regulatory Science. Baltimore, MD, July 30, 2019.
- Kuzma, B. *Estimation of in-Vivo Percutaneous Permeation (Flux) and Cumulative Amount Input of Metronidazole Formulations in Mini-Pigs' Dermis*. Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Shukla, S., Thomas, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *Impact of Operator Variability on the Reproducibility of Tape Stripping Results*. Presentation at Gordon Research Conference on the Barrier Function of Mammalian Skin. Waterville Valley, NH, Aug. 12, 2019.
- Ghosh, P. *Bioequivalence Fundamentals for Generic Topical Dermatological Drug Products*. Presentation at Innovations in Dermatological Sciences. Somerset, NJ, Sept. 9, 2019.
- Ramezanli, T. *How to Structure Efficient Development Programs for Generic Topical Drug Products*. Presentation at Innovations in Dermatological Sciences. Somerset, NJ, Sept. 9, 2019.
- Ghosh, P. *Innovation and Harmonization of Bioequivalence Standards for Generic Topical and Transdermal Products*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop, Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 25, 2019.
- Ramezanli, T. *Best Practices & Efficient Strategies for Generic Topical Product Development*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop, Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 25, 2019.
- Raney, S. *Research Activities, Scientific Advances, & Modernization of Bioequivalence Standards for Generic Topical and Transdermal Products*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop, Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 25, 2019.
- Tsakalozou, E. *Physiologically-Based Pharmacokinetic Modeling and Simulation Approaches: Best Practices for Regulatory Applicators Related to Locally-Acting Generic Drugs*. Presentation at 2019 Small Business and Industry Assistance (SBIA) Workshop, Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019.