

CENTER FOR DRUG EVALUATION AND RESEARCH

FY 2020 GDUFA SCIENCE AND RESEARCH REPORT



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Joint Directors' Message

The Generic Drug User Fee Amendments (GDUFA) established a research program that is implemented through extensive intramural and extramural collaborations. This Directors' Message is a joint message from the Director of the Office of Generic Drugs (OGD) and the Director of the Office of Pharmaceutical Quality (OPQ), as both offices within the Center for Drug Evaluation and Research (CDER) are significantly involved in GDUFA-funded research collaborations and projects. We also acknowledge other offices within FDA that are closely involved with our GDUFA Science and Research program, such as CDER's Office of Translational Sciences, FDA's Center for Devices and Radiological Health, National Center for Toxicological Research, and Office of Regulatory Affairs.

The GDUFA Science and Research program supports the development of additional innovative methodologies and more efficient tools to help establish drug equivalence standards and support the development of, and access to, safe, effective, and high-quality generic drug products for the American public.

In Fiscal Year (FY) 2020, FDA awarded 11 new research contracts and 5 new grants (not including supplements to existing projects) for innovative extramural research projects relevant to generic drugs. FDA also utilized its laboratories and computer systems to conduct more than 50 intramural GDUFA Science and Research projects focused on best using our resources to improve generic drug development and regulatory assessment. These research projects follow the [FY 2020 science and research priority initiatives](#), which fall into the following categories:

- Complex active ingredients, formulations, or dosage forms
- Complex routes of delivery
- Complex drug-device combination products
- Tools and methodologies for bioequivalence and therapeutic equivalence evaluation

GDUFA-funded research provides data supporting the assessment and approval of multiple Abbreviated New Drug Applications (ANDAs) for generic drug products. Laboratory research into advanced analytical technologies and in vitro approaches supported the approvals of first generics for certain complex drug products and equally important, multiple generics of some complex drug products.



Complex drug products are a diverse group of drug products including those with complex active ingredients, dosage forms/formulations, routes of delivery, drug-device combinations, and other complexities. These products are often harder to develop, which means that many face less competition, and therefore can be more expensive and less accessible to the patients who need them.

For example, acyclovir topical ointment, 5%, was originally approved as a new drug product in 1982 and had no approved generics for more than three decades. Practically-speaking, it was unfeasible to develop a generic acyclovir topical ointment, 5%, using the traditional approach (i.e., with a comparative clinical endpoint bioequivalence study) because such a study would likely involve thousands of patients and may still have a high risk of not being able to meet clinically and/or statistically meaningful endpoints. However, based on GDUFA-funded research initiatives and exceptional coordination between OGD and OPQ, more efficient methods for establishing bioequivalence were developed, and now as of this past year there are 15 approved (and multiple marketed) generics of this complex drug product, representing the largest number of approved generics for this type of topical product, which led to exceptional market competition and improved patient access to this important anti-viral medication.

In addition, GDUFA-funded research on modeling directly supported FDA decision-making on several regulatory matters, and these models are now included in some ANDA submissions to support a demonstration of bioequivalence. For example, modeling and simulation substantially contributed to the approval of albuterol sulfate inhalation aerosol, 90 mcg. A state-of-the-art, likelihood-based modeling approach improved the credibility of the pharmacodynamic model with high data censoring and provided key evidence to support the assessment of bioequivalence. Approval of generic albuterol inhalers facilitated access to these critical medical products in response to inhaler shortages and increased demand caused by the novel coronavirus pandemic.

Our GDUFA-funded research collaborations have resulted in significant accomplishments related to developing the scientific basis that supports new and revised product-specific guidances (PSGs) and general guidances for industry, and in refining methods for the scientific evaluation of quality and equivalence for generic drug products.

In FY 2020, we issued 258 new and revised PSGs (124 were for complex products), which provided recommendations for developing generic drugs and generating the evidence supporting ANDA approval. These PSGs helped industry streamline and remove certain risks associated with generic drug product development, and helped FDA to expedite the assessment of ANDAs.

Earlier and enhanced communication between FDA and industry under GDUFA II supports the development of generic drugs, including complex generic drug products, and should continue to help reduce overall time to approval for generic drug submissions. The pre-ANDA program features product development, pre-submission and mid-review cycle meetings with the generic drug industry for complex drug products to help clarify regulatory expectations and provide scientific advice early in product development and during application assessment. In FY 2020, FDA facilitated 79 product development and pre-submission [pre-ANDA meetings](#), which allowed FDA to engage with industry during product development.

The FY 2020 GDUFA Science and Research report provides detailed results for 13 areas of focus, including a summary of research activities, research highlights, comprehensive lists of grants and contracts, and outcomes that the GDUFA Science and Research program funded in FY 2020. The outcomes include a list of PSGs issued in FY 2020 that resulted from relevant research, as well as detailed lists of journal articles, posters, and presentations given in FY 2020. Additional information on outcomes from the GDUFA Science and Research program will be shared in the separate FY 2020 GDUFA Science and Research Outcomes Report, which will be posted on our [website](#) once available.

We would like to thank all of our collaborators who contributed greatly to this effort and we look forward to the future scientific achievements that will help further enhance access to safe, effective, and high-quality generic drugs for the American public.



Abuse-Deterrent Opioid Products

Summary of FY2020 Activities

In FY2020, several intramural and extramural research projects focused on enhancing our assessment of abuse-deterrent formulations (ADF) of opioid drug products.

FDA external research interests on ADF have focused on two clinical studies. In one clinical study, the pharmacokinetics (PK) and pharmacodynamics (PD) of a combination type abuse-deterrent (AD) product formulated with both oxycodone hydrochloride (HCl), an opioid agonist, and naloxone HCl, an opioid antagonist, will be evaluated when that product is manipulated and administered via the intranasal route. In vitro data of the manipulated product, PK bioequivalence (BE) data for naloxone and oxycodone, PD data and the subsequent PK/PD relationship will be generated. The outcome of this study can inform product-specific guidance (PSG) recommendations for combination type abuse-deterrent products. Additionally, the oxycodone PK results of intranasally administered oxycodone HCl; naloxone HCl product may be used to verify an in silico model

developed by FDA to predict oxycodone delivery following intranasal administration.

The second clinical study will evaluate the similarity of the PK of hydrocodone using the hydrocodone bitartrate extended-release (ER) reference product with AD properties to the PK of an in-house developed test product without AD features when both products are chewed prior to oral administration. The objective of the study is to generate PK data after administration of the in-house developed test product, which is designed to have similar rate and extent of hydrocodone release to the reference product when administered as an intact tablet but should release hydrocodone at a faster rate when the hydrocodone bitartrate ER tablets are chewed. This in-house developed product is designed to fail the comparative oral PK study after chewing. The results from this study can verify the findings from FDA developed physiologically-based pharmacokinetic (PBPK) modeling and simulation to predict hydrocodone PK when the tablet system is chewed. The data generated from this study will also evaluate the utility of an in vitro chewing method used in combination with PBPK modeling and simulation to predict the PK outcomes of product when it is chewed prior to oral administration.

FDA has continued to explore in silico tools to predict drug release and exposure outcomes when an ADF product is administered intranasally. PBPK modeling of Embeda, an opioid agonist and antagonist combination drug product, has evaluated the effect of particle size distribution (PSD) on the PK exposure of the systemic circulation (plasma concentration) when crushed morphine sulfate; naltrexone HCl capsule microspheres are administered by nasal insufflation. A hybrid computational fluid dynamics (CFD)-PBPK nasal surface model to simultaneously predict mucociliary clearance and systemic absorption while using in vitro dissolution data as a model input has been developed.

FDA's other internal research efforts focused on five major areas: 1) evaluation of the shelf-life stability of abuse-deterrence property of ADF products; 2) development of advanced characterization techniques for evaluating the safety/toxicity of polyethylene oxide when abused via non-intended route of administration; 3) assessment of drug loss during milling operation and of extractability; 4) development of novel in vitro methods to support nasal abuse assessment and 5) evaluation of quality of naloxone products. Work is also underway to understand the safety risk factors associated with non-intended route of use of opioid products, particularly those containing high molecular weight polymeric excipients.

Research Highlight

A research project has been established by FDA laboratories to develop in vitro methods that may be biopredictive of drug delivery following nasal insufflation of milled oxycodone HCl ER tablets. In FY2020, FDA published a study that described a dissolution method for manipulated abuse deterrent formulations using the United States Pharmacopeia (USP) Apparatus 4, where the model drug was metoprolol succinate (Feng et al., 2020). There is also an effort underway to develop a method for measuring regional deposition of nasally insufflated powder produced from milling ADF tablets.

In parallel with in vitro method development, an in silico model was developed that uses CFD to predict regional deposition of nasally insufflated particles and a hybrid CFD-PBPK nasal surface model to simultaneously predict mucociliary clearance and systemic absorption while using in vitro dissolution data as a model input. To provide this model input, dissolution data for milled oxycodone HCl ER tablets with ADF properties were collected using the same method described in Feng et al., 2020. As shown in Figure 1, plasma concentration predictions for finely milled oxycodone HCl immediate-release (IR) tablet and oxycodone HCl ER tablet as well as coarsely milled oxycodone HCl ER tablet demonstrated reasonably good comparisons to data observed in the contract study HHSF223201510138C. To achieve these favorable comparisons for the ER formulations, mucociliary clearance inputs were optimized with the hypothesis that polyethylene oxide alters mucoadhesive properties, where the half-life of particles present in the nasal cavity was slightly increased for the coarsely milled ER formulation but increased approximately five-fold for the finely milled ER formulation. This result suggests that while the dissolution method developed for this study may be biopredictive, another method may be needed to evaluate the effect of formulation differences on mucoadhesion.

- 1 Boyce H., Sun D., Kinjo M., Raofi S., Frost M., Luke M., Kim M-J., Lionberger R., Vince B., et al. *Pharmacokinetic study of physically manipulated oxycodone hydrochloride products following nasal insufflation in recreational opioid users*. American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360; November 6, 2019; San Antonio, TX, USA.

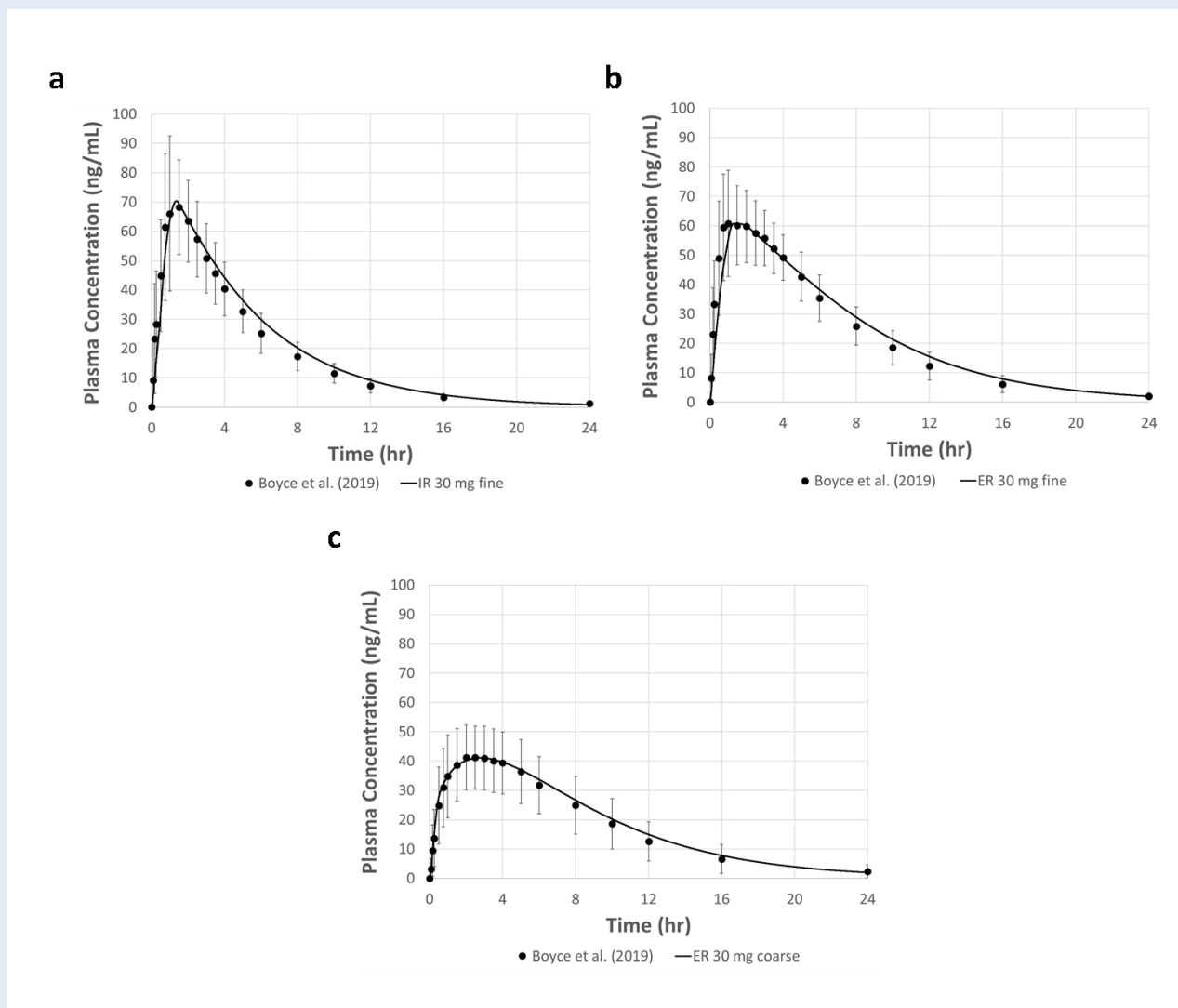


Figure 1: Hybrid CFD-PBPK predictions of systemic PK plasma concentration (lines) as compared with observed mean data \pm standard deviation ($n = 36$ for all formulations) from Boyce et al.¹ after nasal insufflation of a) finely milled powder of oxycodone HCl IR tablet in the 30 mg strength, b) finely milled powder of oxycodone HCl ER tablet in the 30 mg strength, and c) coarsely milled powder of oxycodone HCl ER tablet in the 30 mg strength

Research Projects and Collaborations

Continuing Grants and Contracts

- Grant (3U01FD004275-07S1) *Formulation of Hydrocodone Bitartrate Opioid Tablet* with Vadim J. Gurvich at National Institute for Pharmaceutical Technology and Education (NIPTE)
- Contract (HHSF223201610004I-75F40119F19004) *Pharmacokinetic Study of Opioid Drug Products Following Oral Ingestion of Chewed Products* with Kathleen Doisy at Biopharma Services USA Inc.
- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic/Pharmacodynamic Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Kathleen Doisy at Biopharma Services USA Inc.

Active FDA Research

- *Development and Optimization of In Vitro Methods for Nasal Abuse Assessment ADF Opioids*
- *Development of a Standardized Method and a Predictive Model for Syringeability and Injectability Assessment for Abuse-Deterrent Formulations*
- *Development of an In Vitro Method to Characterize the Swelling Behavior of Excipients Used for Abuse Deterrent Formulations*
- *Effect of Formulation Variables on the Nasal Permeability and Stability of Naloxone Intranasal Formulation*
- *Evaluation of the Emerging Safety Concern Associated with the Abuse of Abuse-deterrent Oral Formulations of Opioids Via Non-Intended Route*
- *Evaluation of Syringeability and Injectability for Injection Abuse*
- *New Analytical Method Based on Field Flow Fractionation for Molecular Weight Determination of Polymers in Opioid Drug Products*
- *Optimization of an In Vitro Method for Regional Deposition Prediction of Nasal Powders*
- *Quantitative Analysis of PKPD Relationship of Abuse Deterrent Opioid Product*

Outcomes

Articles

- Baek, J., Shin, H., Koo, S., Gao, Y., Qu, H., Feng, X., Xu, X., Pinto, J., Katneni, U., Kimchi-Sarfaty, C., and Buehler, P. *Polyethylene Oxide (PEO) Molecular Size Determines the Severity of Atypical Thrombotic Microangiopathy in a Guinea Pig Model of Acute Intravenous Exposure*. *Toxicol Sci.* (2020) **177**(1): 235–247. doi: [10.1093/toxsci/kfaa099](https://doi.org/10.1093/toxsci/kfaa099). PMID: [32579216](https://pubmed.ncbi.nlm.nih.gov/32579216/).
- Boyce, H., Dave, V., Scoggins, M., Gurvich, V., Smith, D., Byrn, S., and Hoag, S. *Physical Barrier Type Abuse-Deterrent Formulations: Mechanistic Understanding of Sintering-Induced Microstructural Changes in Polyethylene Oxide Placebo Tablets*. *AAPS Pharm-SciTech.* (2020) 21(3):86. doi: [10.1208/s12249-019-1594-6](https://doi.org/10.1208/s12249-019-1594-6). PMID: [31997096](https://pubmed.ncbi.nlm.nih.gov/31997096/).
- Feng, X., Zidan, A., Kamal, N., Xu, X., Sun, D., Walenga, R., Boyce, H., Cruz, C., and Ashraf, M. *Assessing Drug Release from Manipulated Abuse Deterrent Formulations*. *AAPS Pharm-SciTech.* (2020) 21(2):40. doi: [10.1208/s12249-019-1595-5](https://doi.org/10.1208/s12249-019-1595-5). PMID: [31897805](https://pubmed.ncbi.nlm.nih.gov/31897805/).

Posters

- Feng, X., Jiang, W., Xu, X., Ashraf, M., and Cruz, C. *Impact of Milling Process on the Evaluation of Abuse-Deterrent Formulations*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 3, 2019.
- Hsu, H., Xu, X., Yang, Y., Balajee, V., Ashraf, M., and Al-Ghabeish, M. *In Vitro Assessments of Nasal Discomfort Caused by Abuse Deterrent Formulations*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 4, 2019.
- Hsu, H., Pavuluri, V., Yang, Y., Abraham, C., Narahariseti, S., Ashraf, M., and Al-Ghabeish, M. *Formulation Challenges Facing Naloxone Intranasal Solution*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 4, 2019.

- Boyce, H., Sun, D., Kinjo, M., Raofi, S., Frost, M., Luke, M. C., Kim, M-J., 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 American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 6, 2019.

Presentations

- Xu, X. *Regulatory Consideration and Research to Evaluate Abuse Deterrence Properties of Opioid Drug Products*. NIPTE Research Conference, Crystal City, VA, Oct. 2–4, 2019.
- Feng, X. *Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-Melt Extrusion, 3rd Annual Extrusion End User Forum*, Rutgers University, Piscataway, NJ, Oct. 31, 2019.
- Al-Ghabeish, M. *Formulation Challenges Facing Naloxone Intranasal Solution*. Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 5, 2019.



Complex Injectables, Formulations, and Nanomaterials

Summary of FY2020 Activities

Drug products that may have nanomaterials present in the dosage form can include, but are not limited to, emulsions, liposomes, and iron colloid formulations. In FY2020, FDA's continued research in this area focused on developing and testing new analytical methods for assessing and comparing structural features of these complex products. For example, an ongoing collaborative project between FDA and the National Institute of Standards and Technology (NIST) continues to develop a nanofluidic slit device to measure the concentration and particle size of liposomal drug particles. In addition, a new grant (U01FD005946) has been awarded to the University of Maryland to explore the use of hyperspectral interferometric scattering microscopy to characterize the size and properties of complex, nano-sized drug products. FDA laboratories also conducted research studies to evaluate the strengths and weaknesses of a wide range of state-of-art sizing technique, as well as determine their suitability in measuring particle sizes in different complex systems (e.g., colloid drug products).

Although the inclusion of nanomaterials in a drug product may promote drug performance compared to other products, the added formulation complexity may produce significant challenges in manufacturing and characterizations. FDA previously completed a contract (HHSF223201610093C) to evaluate the effect of manufacturing crucial process parameters on the critical quality

attributes of amphotericin B liposome. The study showed that changing the formulation steps and/or manufacturing temperature played an important role in the incorporation of the amphiphilic amphotericin B active ingredient into the liposome, as was demonstrated by a UV-Vis spectra peak shift and reduced product toxicity.² In FY2020, a new contract (75F40120C00055) was initiated to expand the knowledge gained from these previous findings. This new contract will evaluate the differences in drug product toxicity when altering the manufacturing process of liposomal amphotericin B and will identify physicochemical test(s) that can serve as surrogate(s) for toxicity.

FDA's laboratory studies continued to focus on developing new analytical techniques or procedures to better characterize and understand the properties of complex products containing nanomaterials. For example, cryogenic transmission electron microscopy (cryo-TEM) images of propofol emulsions suggested the presence of multiple complex structures including oil globules and liposomes, underscoring the need for advanced characterization to facilitate the understanding of product performance. In addition, a new in vitro drug release testing method is currently being developed to assist with the evaluation of complex liposome and emulsion formulations.

In FY2020, FDA awarded a contract (75F40119C10139) for evaluating target site bioequivalence of drug products that incorporate nanomaterials (e.g., liposomal drug products) through in silico systems-based multiscale modeling. The model intends to capture various biological and physicochemical events that affect the transport and residence of nanoparticles and the active ingredient cargo. The outcome of this contract would provide a link between certain nanoparticle attributes and target site bioavailability.

2 Rivnay, Benjamin, et al. "Critical process parameters in manufacturing of liposomal formulations of amphotericin B." *International Journal of Pharmaceutics* 565 (2019): 447–457.

Research Highlight

Propofol injectable emulsion is a complex injectable drug product. While egg lecithin, an inactive ingredient, can stabilize the emulsion by forming a monolayer at the oil-water interface, it may give rise to additional formation of lipid vesicles if an excess amount of lecithin exists in the formulation. Given the limitations of commonly used particle sizing techniques (dynamic light scattering and laser diffraction) in differentiating emulsion oil droplets and lipid vesicles, FDA has developed a high resolution cryo-TEM method and utilized this method to characterize the particle size and morphology of four therapeutically equivalent propofol products. The results reveal that all four products contain a mixture of oil droplets, lipid vesicles, and oil droplet-lipid vesicle aggregates (Figure 1). Although the particle size and amount of lipid vesicles as well as oil droplet-lipid vesicle aggregates are different in the four products tested, the amount of propofol active ingredient in the lipid vesicle fraction was found to be nearly negligible compared to the amount of propofol in the oil emulsion phase. The findings from this internal research gave insight into whether the observed differences in lipid structural composition and vesicle size affect the performance of the propofol drug products. The outcomes of this project provided valuable support to FDA's regulatory activities, such as product-specific guidance and abbreviated new drug application reviews.

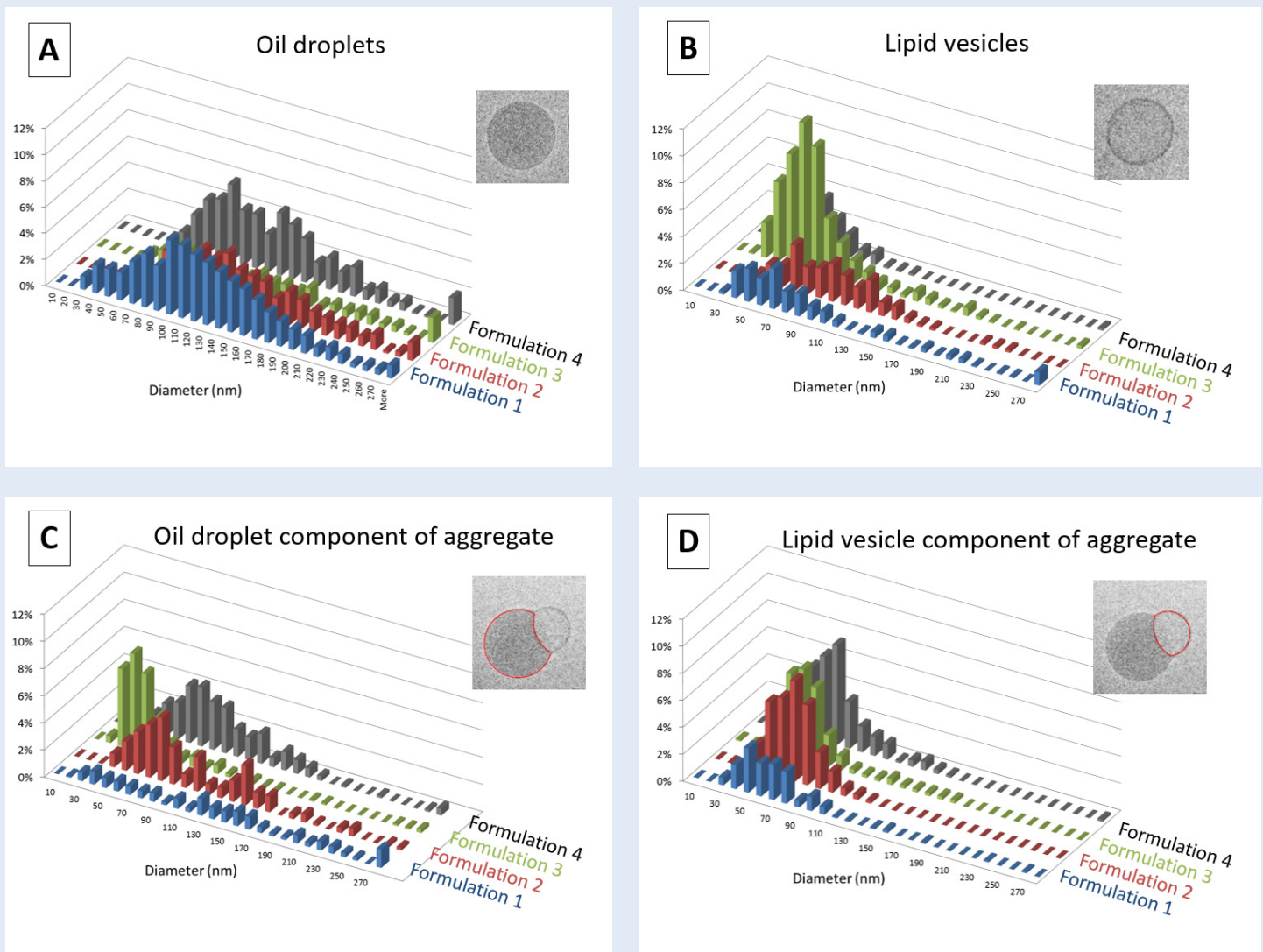


Figure 1: Particle size distribution comparison of oil droplets (A), lipid vesicles (B), and aggregates structures (C & D) in four tested propofol formulations characterized by cryo-TEM (Wu et al., International Journal of Pharmaceutics, 577 (2020) 118998).

Research Projects and Collaborations

New Grants and Contracts

- Grant (U01FD005946) *Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics* with Taylor Woehl at the University of Maryland, College Park
- Contract (75F40120C00055) *Evaluation of Critical Process Parameters for the Preparation of Amphotericin B That Influence Toxicity* with Benjamin Rivnay at Landrau Scientific Innovation, LLC.

Continuing Grants and Contracts

- Interagency Agreement (IAA, 75F40119S30028) *Nanofluidic Slit Devices for Measuring Nano-Particle Drug Concentration to Improve Complex Drug Regulation* with Samuel Stavis at the NIST Center for Nanoscale Science and Technology
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie L.S. Au at the Institute of Quantitative Systems Pharmacology

Completed Grants and Contracts

- Grant (1U01FD005266) *Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate* with Sarah L. Michel at the University of Maryland
- Interagency Agreement (IAA-224-17-3008S) *Nanoparticle Tracking in Nanofluidic Slits* with Samuel Stavis at the NIST Center for Nanoscale Science and Technology

Active FDA Research

- *Application of Cryo-Electron Microscopy (cryo-EM) for Morphological Characterization of Drug Products Containing Nanomaterials*
- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Bupivacaine Multivesicle Liposomes*
- *Improving In Vitro Drug Release Testing of Complex Drug Products Containing Nanomaterials*

- *In Vitro Performance Characterizations of Sucroferic Oxyhydroxide to Establish Bioequivalence Methods*
- *In Vivo Biodistribution Evaluation of Liposome Drug Products*
- *In Vivo Biodistribution and In Vitro Characterization of Iron Colloid Drug Products*
- *In Vivo Gel or Depot Formation*
- *Manufacturing and Physicochemical Characterization of Multivesicular Liposomes*
- *Physicochemical Characterization of Protein-Particle Nanotechnology Drug Products*

Outcomes

Product-Specific Guidances (PSGs)

There were nine new and two revised PSGs published in FY2020 related to Complex Injectables, Formulations and Nanomaterials. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance on Amino Acids; Calcium Chloride; Dextrose; Magnesium Sulfate; Potassium Chloride; Sodium Acetate; Sodium Glycerophosphate; Soybean Oil Intravenous Emulsion.* (Mar. 2, 2020) [Link to Posting.](#)
- *Revised Draft Guidance on Amphotericin B Injection Injectable, Liposomal.* (Aug. 28, 2020) [Link to Posting.](#)
- *New Draft Guidance on Aprepitant Intravenous Emulsion.* (June 3, 2020) [Link to Posting.](#)
- *Revised Draft Guidance on Azacitidine Intravenous, Subcutaneous Powder.* (Nov. 21, 2019) [Link to Posting.](#)
- *New Draft Guidance on Clevidipine Intravenous Emulsion.* (Mar. 2, 2020) [Link to Posting.](#)
- *New Draft Guidance on Fish Oil Triglycerides Intravenous Emulsion.* (June 3, 2020) [Link to Posting.](#)

Articles

- Dong, Y., Hengst, L., Hunt, R., Patel, D., Vo, A., Choi, S., Ashraf, M., Cruz, C., and Xu, X. *Understanding Drug Distribution and Release in Ophthalmic Emulsions through Quantitative Evaluation of Formulation-Associated Variables*. *Journal of Controlled Release*. (2019) 313:96–105. doi: [10.1016/j.jconrel.2019.09.010](https://doi.org/10.1016/j.jconrel.2019.09.010). PMID: [31536731](https://pubmed.ncbi.nlm.nih.gov/31536731/).
- Van Haute, D., Jiang, W. and 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](https://doi.org/10.1016/j.ijpharm.2019.118603). PMID: [31401296](https://pubmed.ncbi.nlm.nih.gov/31401296/).
- 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](https://doi.org/10.1016/j.ijpharm.2019.118576). PMID: [31362094](https://pubmed.ncbi.nlm.nih.gov/31362094/).
- Dong, Y., Hengst, L., Hunt, R., Feng, X., Kozak, D., Choi, S., Ashraf, M., and Xu, X. *Evaluating Drug Distribution and Release in Ophthalmic Emulsions: Impact of Release Conditions*. *Journal of Controlled Release*. (2020) 327:360–370. doi: [10.1016/j.jconrel.2020.08.020](https://doi.org/10.1016/j.jconrel.2020.08.020). PMID: [32822741](https://pubmed.ncbi.nlm.nih.gov/32822741/).
- Liu, H., Rivnay B., Avery K., Myung J.H., Kozak, D., Landrau, N., Nivorozhkin, A., Ashraf, M., and Yoon, S. *Optimization of the Manufacturing Process of a Complex Amphotericin B Liposomal Formulation Using Quality by Design Approach*. *International Journal of Pharmaceutics*. (2020) Jul 30;585: doi: [10.1016/j.ijpharm.2020.119473](https://doi.org/10.1016/j.ijpharm.2020.119473). PMID: [32473373](https://pubmed.ncbi.nlm.nih.gov/32473373/).
- Siriwardane, D., Wang, C., Jiang, W. and Mudalige, T. *Quantification of Phospholipid Degradation Products in Liposomal Pharmaceutical Formulations by Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS)*. (2020) *International Journal of Pharmaceutics*. (2020) 578: doi: [10.1016/j.ijpharm.2020.119077](https://doi.org/10.1016/j.ijpharm.2020.119077). PMID: [31988036](https://pubmed.ncbi.nlm.nih.gov/31988036/).

- Skoczen, S., Snapp, K., Crist, R., Kozak, D., Jiang, X., Liu, H., and Stern, S. *Distinguishing Pharmacokinetics of Marketed Nanomedicine Formulations Using a Stable Isotope Tracer Assay*. ACS Pharmacology & Translational Science. (2020) doi: [10.1021/acsptsci.0c00011](https://doi.org/10.1021/acsptsci.0c00011). PMID: [32566919](https://pubmed.ncbi.nlm.nih.gov/32566919/).
- Suh, M., Patil, S., Kozak, D., Pang, E., Choi, S., Jiang, X., Rodriguez, J., Keire, D., and Chen, K. *An NMR Protocol for In Vitro Paclitaxel Release from an Albumin-Bound Nanoparticle Formulation*. AAPS PharmSciTech. (2020) 21(5):136. doi: [10.1208/s12249-020-01669-1](https://doi.org/10.1208/s12249-020-01669-1). PMID: [32419122](https://pubmed.ncbi.nlm.nih.gov/32419122/).
- Wu, Y., Manna, S., Petrochenko, P., Koo, B., Chen, L., Xu, X., Choi, S., Kozak, D., and Zheng, J. *Coexistence of Oil Droplets and Lipid Vesicles in Propofol Drug Products*. International Journal of Pharmaceutics. (2020) 577: doi: [10.1016/j.ijpharm.2019.118998](https://doi.org/10.1016/j.ijpharm.2019.118998). PMID: [31935473](https://pubmed.ncbi.nlm.nih.gov/31935473/).

Posters

- Dong, Y., Hengst, L., Hunt, R., Patel, D., Vo, A., Choi, S., Ashraf, M., Cruz, C., and Xu, X. *Understanding Drug Distribution and Release in Ophthalmic Emulsions*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 3–6, 2019.
- Feng, W., Wu, Y., Chen, L., Qu, H., Patel, D., Xu, X., Manna, S., Choi, S., and Zheng, J. *Effect of Manufacturing Process on Particle Morphology in Propofol Emulsions*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. Washington, DC, Nov. 4, 2019.
- Bae, J., Patel, M., Manna, S., Smith, W., Vo, A., Wang, Y., Choi, S., Kozak, D., Zheng, J., and Xu, X. *Impact of Manufacturing Process on Critical Quality Attributes of Multivesicular Liposomes*. Poster Presentation at Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, Jun. 29, 2020.

- Patel, M., Manna, S., Vo, A., Xu, X., Conti, D., Choi, S., Kozak, D., and Zheng, J. *Scanning Electron Microscope (SEM) Coupled with Energy Dispersive X-Ray Spectroscopy (EDS) — A Potential Analytical Tool for Physico-Chemical Characterization of API in Complex Drug Formulations*. Poster Presentation at Microscopy & Microanalysis (M&M) 2020 Annual Meeting. Virtual Meeting, Aug. 2, 2020.
- Patel, M., Bae, J., Manna, S., Smith, W., Vo, A., Wang, Y., Choi, S., Kozak, D., Xu, X. and Zheng J. *Confocal Laser Scanning Microscopy to Study the Effect of Manufacturing Process on the Critical Quality Attributes of Multivesicular Liposomes*. Poster Presentation at Microscopy & Microanalysis (M&M) 2020 Annual Meeting. Virtual Meeting, Aug. 3–7, 2020.
- Alam, K., Sharan, S., Fang, L., Jiang, W., Kim, K-J., Zhao, L., Zhang, L., and Lionberger, R. *Assessing Whether Partial AUCs are Needed to Demonstrate Bioequivalence for Liposomal Doxorubicin*. Poster Presentation at 2020 American College of Clinical Pharmacy (ACCP) Annual Meeting. Virtual Meeting, Sept. 21–23, 2020.

Presentations

- Tyner, K. *Regulatory Research Supporting the Development of Drug Products Containing Nanomaterials A US-FDA Perspective*. Presentation at The National Institute for Pharmaceutical Technology and Education (NIPTE) Annual Meeting. Washington, DC, Oct. 3, 2019.
- Yilmaz, H. *Scanning Electron Cryomicroscopy (Cryo-SEM)-Raman Spectroscopy for Analysis of Complex Drug Products*. Presentation at FACSS The Great Scientific Exchange (SciX) 2019, Palm Springs, CA, Oct. 14, 2019.
- Tyner, K. *Interplay of Voluntary Consensus Standards and Regulations: Opportunities and Lessons Learned: A US-FDA Perspective*. Presentation at American National Standards Institute (ANSI) Nanotechnology Standards Panel. Washington, DC, Oct. 16, 2019.
- Liao, K., Copeland, C., Myung, J., Kozak, D., and Stavis, S. *Liposomal Doxorubicin Under Microconfinement and Microscopy*. Presentation at American Association of Pharmaceutical Scientists (AAPS) PharmSci 360 2019. San Antonio, TX, Nov. 5, 2019.

- Kozak, D. *Formulation Assessments: General Q1/Q2 Inquiries to Supporting Complex Excipient Sameness*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.
- Xu, X. *Developing and Validating Commonly Employed Particle Sizing Methods to Support Bioequivalence and Product Quality*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.

Complex Mixtures and Peptide Products

Summary of FY2020 Activities

In FY2020, research efforts continued in the development of advanced analytics for the evaluation and characterization of complex active pharmaceutical ingredients (APIs) including complex mixtures (e.g., conjugated estrogens (CEs)), oligonucleotides, peptides and polymers of synthetic, semi-synthetic, and natural origins. Characterization of these complex APIs using advanced analytical methods is essential for supporting pharmaceutical equivalence, linking product attributes to quality, safety, and clinical performance, thereby facilitating the generic drug development, assessment, and approval processes.

Collaborative internal research projects focused on the development of new analytical methods for the characterization of complex APIs. Many of these methods utilized ultra-high-performance liquid chromatography (UHPLC) coupled with high resolution accurate mass (HRAM) mass spectrometry (MS). As highlighted below, FDA laboratories modified a previously developed UHPLC-HRAM-MS method to assess both steroidal and non-steroidal components in PREMARIN (CEs) oral tablets to the PREMARIN vaginal cream drug product, thereby providing industry with an analytical method recommendation for a better understanding of the key structural characteristics of APIs in these different dosage forms (Figure 1). FDA also initiated research to address the analytical challenges with characterizing oligonucleotide APIs. These complex macromolecular therapeutics present unique scientific and regulatory challenges because the efficacy and safety are highly dependent on a specific sequence structure and potential impurities or related substances of these products. To address these challenges, FDA is developing a UHPLC-HRAM-MS-based multi-attribute method for the characterization and impurity profiling of synthetic oligonucleotides. In addition, the lab developed an UHPLC-HRAM-MS/MS method to characterize the impurity profile of the peptide drug product, teriparatide (Figure 2).

Research Highlight

PREMARIN (Conjugated Estrogens, CEs), initially approved in the 1940s as an oral tablet (NDA 004782), is used to treat menopause symptoms. Formulations now include an injectable solution and vaginal cream. All products contain a mixture of CEs obtained from pregnant mares' urine. Due to the complex nature of the API, no generic version of PREMARIN is currently available. To facilitate characterization and methods to support active ingredient sameness, FDA laboratories have developed an UHPLC-MS method to assess both steroidal and non-steroidal components in tablets, which supported the development and recommendations in the product-specific guidance for this product. Since the manufacturing processes of different dosage forms vary, additional research was conducted to develop a modified analytical method to characterize the components in the vaginal cream product. The method was applied to the analysis of different lots of products collected over a 2-year period to characterize lot-to-lot variability and to classify CE products by formulations and expiration years (Figure 1). The use of advanced analytical methods and statistical analysis can help establish standards to demonstrate API sameness of CEs and is a critical step toward the development of a product-specific guidance and ultimately a clearer pathway for the development and approval of generics.

Similar methods can be used for the analysis and comparison of other drugs with complex active ingredient mixtures. For example, FDA laboratories developed an UHPLC-MS/MS method to characterize the impurity profile of teriparatide. Degradation and process impurities were identified in synthetic teriparatide samples (as indicated in Figure 2) and marketed products of the recombinant origin (FORTEO). All samples contained the same degradation impurities, but different production methods gave rise to unique sets of process impurities, some above the reporting threshold of 0.1% (Figure 2).

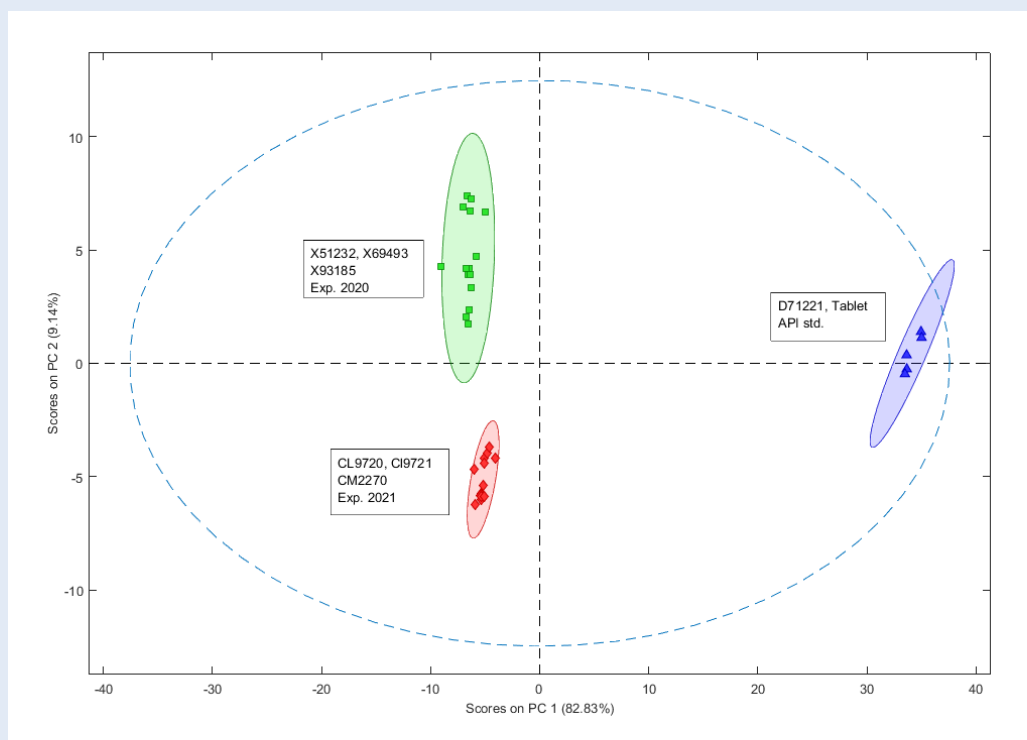


Figure 1: Principal Components Analysis (PCA) model of CE vaginal cream lots with expiration dates of 2020 and 2021 and CE tablet.

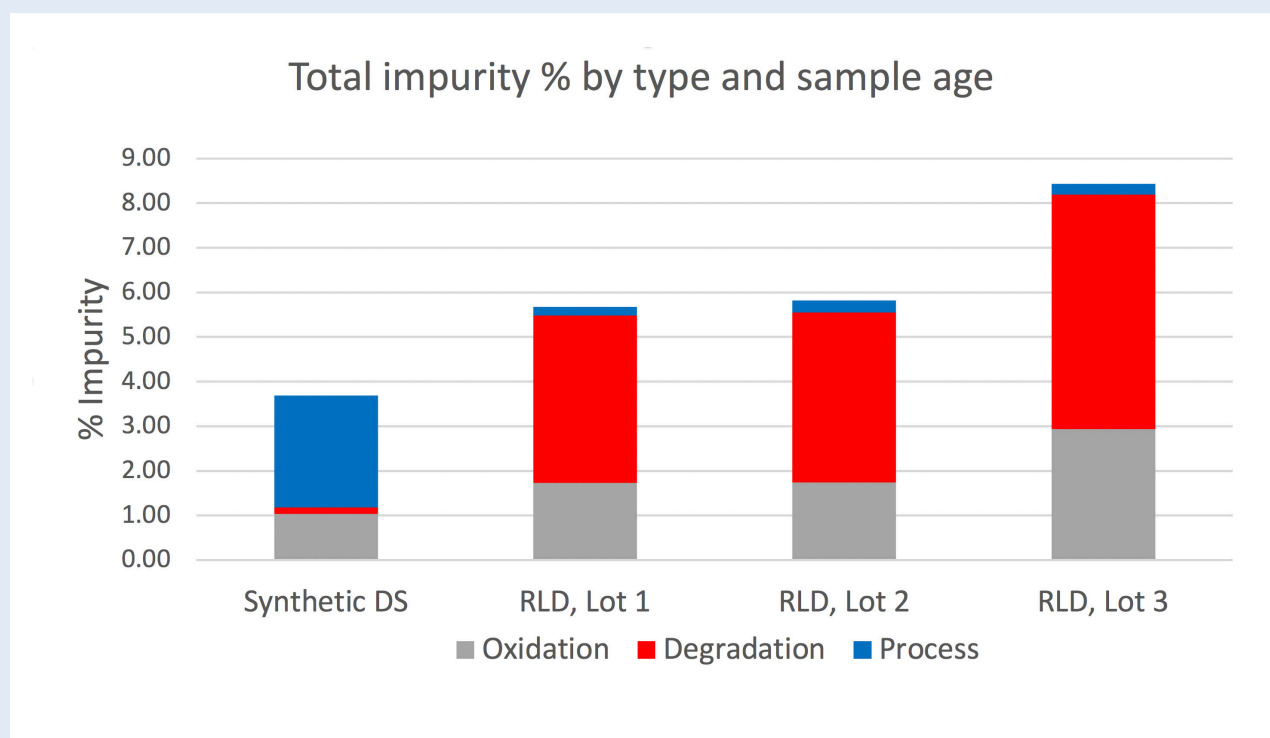
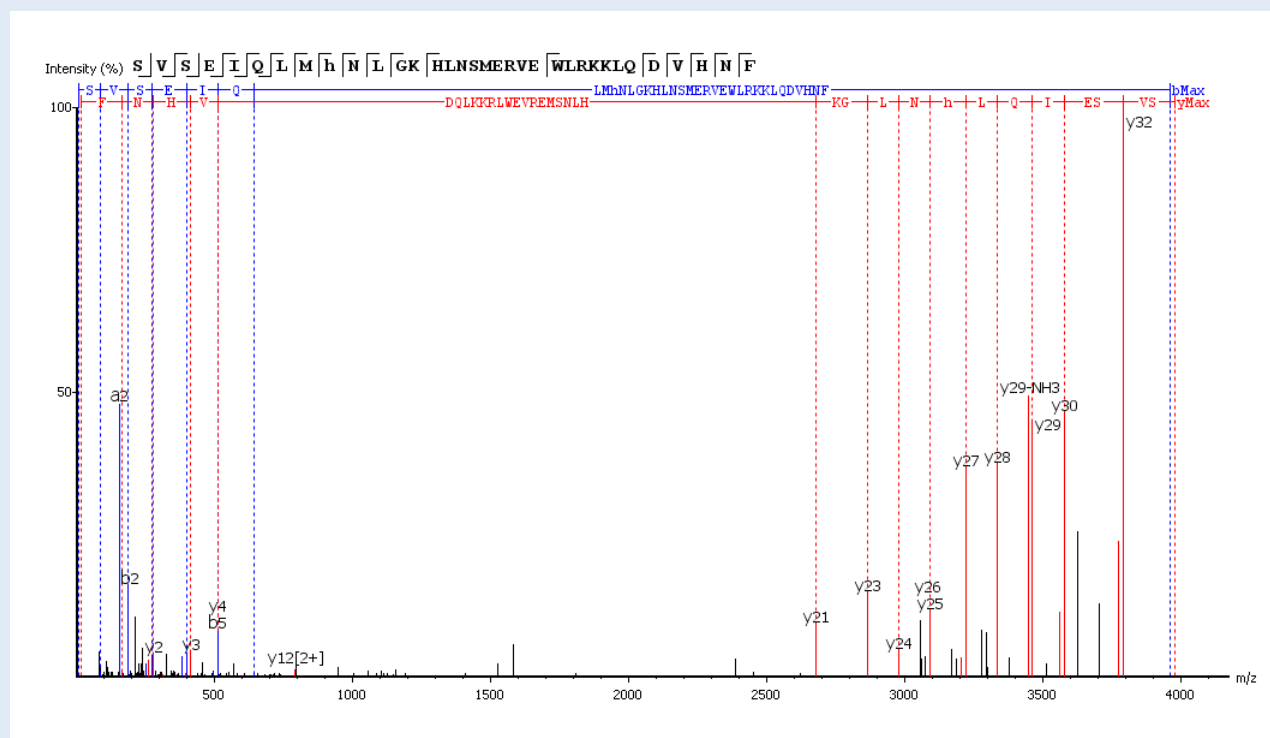


Figure 2: A. An MS/MS spectrum of a process impurity in Bachem synthetic teriparatide. The detected b and y ions identify it as the 9th position histidine deletion. **B.** The total impurity % in synthetic and FORTEO (RLD) recombinant teriparatide, broken down by oxidation, degradation, and process impurity content. Sample age of RLD increases left to right, as indicated.

Collaboration with external partners, via Generic Drug User Fee Amendments (GDUFA)-funded contracts and grants, also investigated advanced analytical tools for the characterization and evaluation of complex APIs. A project with the National Institute for Pharmaceutical Technology and Education (NIPTE) used solid-state nuclear magnetic resonance (SSNMR) spectroscopy to identify, quantify, and compare the relative amounts of three monomer groups in the amorphous block-copolymer drug VELTASSA (patiomer). SSNMR proved to be a sensitive analytical technique for characterizing and quantifying the copolymer structure and may be used to support API sameness of this and other complex API products. FDA also collaborated with EpiVax, Inc. and the National Cancer Institute (NCI) to evaluate *in silico* and *in vitro* tools for assessing the potential immune response of a generic peptide to the approved reference listed drug product. These research efforts provide FDA and the generic industry with insights and recommendations on the use of non-clinical methods to evaluate both the innate and adaptive immune responses, thereby facilitating generic peptide drug development.

Research Projects and Collaborations

New Grants and Contracts

- Contract (75F40120C00157) *Establish Predictive in Silico, In Vitro and Animal Studies to Evaluate Immunogenicity Risk of Formulation or Impurity Differences in Generic Products* with Anne S. De Groot at EpicVax/CUBRC

Continuing Grants and Contracts

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

Completed Grants and Contracts

- Grant (5U01FD004275) *Solid State NMR Analysis (NIPTE)* with Vadim J. 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 and EpiVax, Inc.
- Contract (HHSF223201610114C) *Mass Spectrometry Profiling of Pentosan Polysulfate in Urine* with John Cort at Battelle Memorial Institute

Active FDA Research

- *Analytical Characterization of Recombinant and Synthetic Peptide Product Impurities*
- *Characterization of Conjugated Estrogens*
- *Characterization of Synthetic Oligonucleotides to Support Generic Drug Equivalence*
- *Evaluation of Humanized Mouse Model for Peptide Immunogenicity*
- *Method Evaluation on In Vitro Bioequivalence Study of Sucroferic Oxyhydroxide*

Outcomes

Product-Specific Guidances (PSGs)

There were five new and three revised PSGs published in FY2020 related to complex mixtures and peptide products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance on Liraglutide Subcutaneous Solution. (Mar. 2, 2020)*
[Link to Posting.](#)
- *New Draft Guidance on Semaglutide Subcutaneous Solution. (Mar. 2, 2020)*
[Link to Posting.](#)

Articles

- Jarrells, T., Zhang, D., Li, S., and Munson, E. *Quantification of Monomer Units in Insoluble Polymeric Active Pharmaceutical Ingredients Using Solid-State NMR Spectroscopy I: Patiromer*. AAPS PharmSciTech. (2020) 21(3):116. doi: [10.1208/s12249-020-01654-8](https://doi.org/10.1208/s12249-020-01654-8). PMID: [32296974](https://pubmed.ncbi.nlm.nih.gov/32296974/).

Posters

- Liu, H., Suh, M., Kozak, D., and Pang, E. *Evaluation of Quantitative Capsule Rupture Test Methods and Data Variability in Generic Omega-3 Capsule Applications*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.

- Li, S., Zhang, D., Kozak, D., and Jiang, X. *Review of Advanced Analytical Methods in Complex Polymeric Drug Substance Characterization*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Weisz, D., Geerlof-Vidavsky, I., Zeng, K., Jiang, X., and Pang, E. *Quantitative Comparison of Peptide Impurities in Teriparatide from Biological and Synthetic Origin Using LC-MS/MS*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Sung, J., San Emeterio, C., Hosain, S., Knapton, A., Pang, E., and Howard, K. *A Non-Clinical Animal Model to Predict Therapeutic Peptide and Biological Drug Product Immunogenicity*. Poster Presentation at 2019 American College of Toxicology. Phoenix, AZ, Nov. 17, 2019.
- Weisz, D., Geerlof-Vidavsky, I., Zeng, K., and Rogstad, S. *Quantitative Comparison of Peptide Impurities in Teriparatide from Recombinant and Synthetic Origin Using UHPLC-MS/MS*. CASSS Mass Spec 2020, Sept. 14–17, 2020.

Presentations

- Zhang, D. *Considerations in Developing Generic Peptide and Oligonucleotide Drug Products*. Presentation at United States Pharmacopeia (USP) 2019 Workshop. Rockville, MD, Nov. 4, 2019.
- Yang, K., Rogstad, S., Rodriguez, J., and Keire, D. *Characterization and Quality Control of Synthetic Oligonucleotide Therapeutics by Mass Spectrometry: The Current and the Future*. Presentation at 68th ASMS Conference on Mass Spectrometry Reboot. Virtual, June 11, 2020.
- Zhang, D. *Considerations for Abbreviated New Drug Application of Generic Peptide Drug Products*. Presentation at TIDES US 2020 Workshop #3: FDA Draft Guidance on ANDA Filings for Peptides. Virtual Meeting, Sept. 15, 2020.
- Pang, E. *Non-Clinical Evaluation of Comparative Immunogenicity Risk of Complex Peptide Products*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.



Data Analytics

Summary of FY2020 Activities

The FDA is dedicated to building data analytics capacities to support the missions of the Office of Generic Drugs (OGD). The efforts include developing big data analytics toolsets, quantitative methods for bioequivalence (BE) assessment, data management tools, and data analysis methods for generic drug post-marketing surveillance.

For the development of big data analytics toolsets, the Office of Research and Standards (ORS) under the OGD is developing a BE assessment tool to enhance the efficiency of BE assessment. Specifically, the tool was developed to streamline labor-intensive work during the BE assessment (e.g., BE statistical analyses). With several mouse-clicks, the tool will generate a BE assessment report that assessors can utilize to finalize the review. In addition, a broad agency announcement (BAA) contract (#75F40119C10106) was funded to develop a data analytics tool to facilitate the guidance development. Furthermore, FDA has kept working on the abbreviated new drug application (ANDA) workload prediction, such as forecasting ANDA submission based on machine learning (ML) methodologies. Also, the ML-based heterogeneous treatment effect analysis has been investigated aiming to prompt business intelligence in the agency.

Quantitative methods have been applied to address complex BE assessment issues, such as equivalence assessment of complex particle size distribution using earth mover's distance (EMD) algorithm. In the assessment for a pharmacodynamics (PD) BE data and model, a likelihood-based modeling was utilized during the internal analysis to predict the true value for the censored data (out of detection limit). This modeling approach improved the credibility of the PD model and provided the model-informed evidence to support BE assessment. Regarding the data management efforts, ORS developed and maintains a knowledge base regarding complexity of approved drug products to support research on complex generic drug development.

For generic drug post-marketing surveillance, FDA continued efforts to compare the therapeutic performance of generic narrow therapeutic index (NTI) drugs and their brand counterparts, such as warfarin and levothyroxine (see *FY2020 GDUFA Science and Research Report: Patient Substitution of Generic Drugs*). In addition, the FDA-funded studies published on generic substitution for Medicare or Medicaid patients treated with escitalopram or tacrolimus, using competing risk survival analyses. Furthermore, the FDA is exploring the utilization of the Sentinel tool to conduct post-marketing studies to compare generic drug products with the reference listed drug (RLD). Several internal investigations on post-marketing switching patterns have been initiated (see *FY2020 GDUFA Science and Research Report: Patient Substitution of Generic Drugs*).

Research Highlight

To identify measures that might accelerate the development of generic drug products, FDA researchers investigated factors that might predict the likelihood that an abbreviated new drug application (ANDA), relying on a given reference (approved) drug product, would be submitted to the FDA. The investigators evaluated data related to ANDAs to learn whether a drug's characteristics, or factors related to its regulatory history or market sales, were predictive of an ANDA submission. For example, if the period of market exclusivity resulted in annual revenues greater than \$250 million dollars for up to a 4-year period after the approval date, per the RLD, an ANDA submission for the given product was nearly four times more likely to be submitted than a product generating sales of less than \$10 million. The data also suggested a strong positive association between the availability of a product-specific guidance (PSG) before an ANDA submission and an increased likelihood of ANDA submission. More information on this research is available on FDA's website (see Wittayanukorn, S., 2020 and the Regulatory Science Impact Story 'A CDER Study of Factors that May Predict the Likelihood of Generic Drug Marketing Applications' accessible at <https://www.fda.gov/drugs/regulatory-science-action/cder-study-factors-may-predict-likelihood-generic-drug-marketing-applications>).

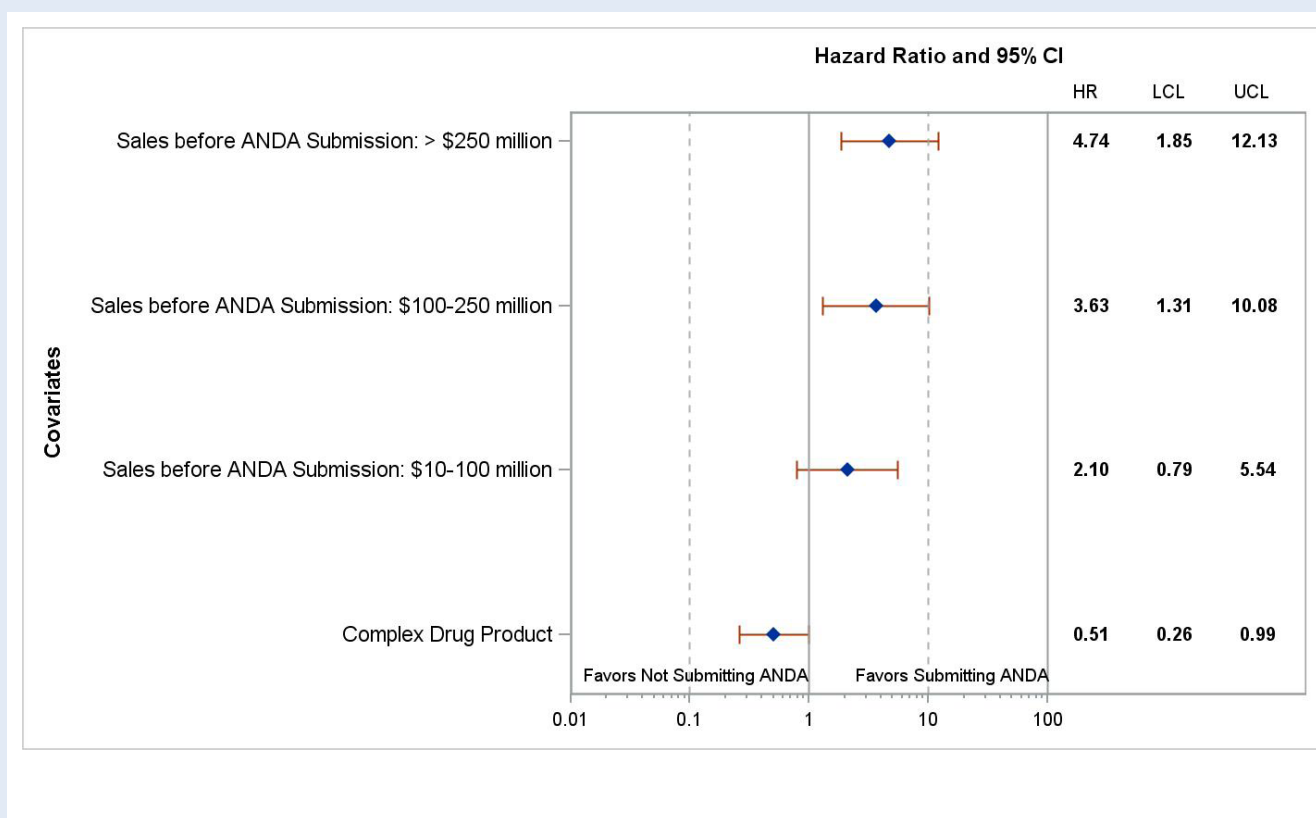


Figure: It was found that new chemical entity drugs with higher sales were more likely to have Abbreviated New Drug Applications submitted, while the opposite was observed for more complex drugs. Results are based on Cox proportional hazards analyses. (A higher hazard ratio indicates that the drug was more likely to have an ANDA submission for a generic at any given time after its exclusivity expired.) HR = hazard ratio; CI = 95% confidence interval; LCL = lower 95% confidence limit; HCL = higher 95% confidence limit; ANDA = abbreviated new drug application. (Modified from Wittayanukorn, S., 2020).

Research

Continuing Grants and Contracts

- Grant (3U01FD005938-03S1) *Characterizing Safety & Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism Among Patients Who Switch Therapy Formulation* with Joseph Ross at Yale University and Nilay Shah at Mayo Clinic
- Contract (75F40119C10106) *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency* with Hualou Liang at Drexel University

Completed Grants and Contract

- Grant (1U01FD005938-01) *Brand Name and Generic Drugs to Treat Hypothyroidism* with Joseph Ross at Yale University and Nilay Shah at Mayo Clinic
- Grant (3U01FD005938-02S1) *Use of Instrumental Variable Approaches to Assess the Safety and Efficacy of Brand-name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross at Yale University and Nilay Shah at Mayo Clinic

Active FDA Research

- *Development and Analysis of a Complex Product Database*
- *Development of PK Data Warehouse for BE Analysis*
- *Machine Learning for Generic Drug Analysis*

Outcomes

Articles

- Desai, R., Gopalakrishnan, C., Dejene, S., Sarpatwari, A., Levin, R., Dutcher, S., Wang, Z., Wittayanukorn, S., Franklin, J., and Gagne, J. *Comparative Outcomes of Treatment Initiation with Brand Vs. Generic Warfarin in Older Patients*. *Clinical Pharmacology & Therapeutics*. (2019) **107**(6): 1334–1342. doi: [10.1002/cpt.1743](https://doi.org/10.1002/cpt.1743). PMID: [31872419](https://pubmed.ncbi.nlm.nih.gov/31872419/).
- Brito, J., Ross, J., Sangaralingham, L., Dutcher, S., Graham, D., Wang, Z., Wu, Y., Yao, X., Smallridge, R., Bernet, V., Shah, N., and Lipska K. *Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels*. *JAMA Network Open*. (2020) **3**(9): e2017645. doi: [10.1001/jamanetworkopen.2020.17645](https://doi.org/10.1001/jamanetworkopen.2020.17645). PMID: [32997127](https://pubmed.ncbi.nlm.nih.gov/32997127/).

- Chen, L., Li, C., Huo, N., Mishuk, A., Hansen, R., Harris, I., Kiptanui, Z., and Qian, J. *Oral Generic Tacrolimus Initiation and Substitution in the Medicaid Population: a New User Cohort Study*. *Current Medical Research and Opinion*. (2020) **36**(9): 1533–1540. doi: [10.1080/03007995.2020.1793750](https://doi.org/10.1080/03007995.2020.1793750). PMID: [32644886](https://pubmed.ncbi.nlm.nih.gov/32644886/).
- Huo, N., Chen, L., Mishuk, A., Li, C., Hansen, R., Harris, I., Kiptanui, Z., Wang, Z., Dutcher, S., and Qian, J. *Generic Levothyroxine Initiation and Substitution among Medicare and Medicaid Populations: a New User Cohort Study*. *Endocrine*. (2020) **68**(2): 336–348. doi: [10.1007/s12020-020-02211-w](https://doi.org/10.1007/s12020-020-02211-w). PMID: [31993992](https://pubmed.ncbi.nlm.nih.gov/31993992/).
- Li, C., Chen, L., Huo, N., Mishuk, A., Hansen, R., Harris, I., Kiptanui, Z., Wang, Z., and Qian, J. *Generic Escitalopram Initiation and Substitution among Medicare Beneficiaries: A New User Cohort Study*. *Plos One*. (2020) **15**(4): e0232226. doi: [10.1371/journal.pone.0232226](https://doi.org/10.1371/journal.pone.0232226). PMID: [32353006](https://pubmed.ncbi.nlm.nih.gov/32353006/).
- Wittayanukorn, S., Rosenberg, M., Schick, A., Hu, M., Wang, Z., Babiskin, A., Lionberger, R., and Zhao, L. *Factors That Have an Impact on Abbreviated New Drug Application (ANDA) Submissions*. *Therapeutic Innovation & Regulatory Science*. (2020). doi: [10.1007/s43441-020-00163-x](https://doi.org/10.1007/s43441-020-00163-x). PMID: [32495310](https://pubmed.ncbi.nlm.nih.gov/32495310/).

Presentations

- Jiang, W. *Complex Drug Product Landscape*. Presentation at Product Quality Research Institute Biopharmaceutical Technical Committee 2020 Webinar Series. Webinar, Apr. 28, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Hu, M. *Quantitative Methods for Determining Equivalence of Particle Size Distributions*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.
- Gong, X. *Alternatives to F2 Testing for Dissolution Similarity — F2 Bootstrapping and Multivariate Statistical Distance (MSD) Method*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.



Drug-Device Combination Products

Summary of FY2020 Activities

The U.S. Food and Drug Administration (FDA) is committed to advancing research that involves drug-device combination products, some of which are considered complex as defined in the Generic Drug User Fee Amendments reauthorization (GDUFA II) commitment letter.³ As stated in the GDUFA Science and Research Priority Initiatives for FY2020,⁴ evaluating the impact of differences in the user interface between complex generic drug-device combination products and their reference listed drugs (RLD) on therapeutic equivalence has been identified as one of the key FDA initiatives. FDA laboratories and external collaborators supported this research initiative.

Two contracts were awarded in FY2019 and are currently ongoing into FY2020. More specifically, these two contracts focus on understanding the impact of generic substitutions for different complex drug-device combination products across various patient populations and caregivers and how generic substitution affects patient perception of such products. The first research project under Contract# HHS-F223201810113C was awarded to Research Triangle Institute (RTI) International (NC, US) to examine behavioral implications of generic drug-device combination product substitutions, to assess how the design and functionality of generic drug-device combination products affect perceptions of product quality, efficacy, and device usability, and to explore participants' views on how generic drug-device combination products compare to the branded counterparts. A comprehensive literature review was completed and showed that there was sparse research on patient use and perception of generic drug-device combination products. RTI has collected data from several focus groups and are continuing to accrue participants to complete a few remaining planned focus groups. Results from preliminary assessments are currently being evaluated.

The second research project under Contract# HHSF223201710072C awarded to the Imperial College of Science Technology & Medicine (London, UK) is evaluating how a patient's perception of a dry powder inhaler's (DPI's) airflow resistance affects compliance and use (or non-

3 GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018–2022, Link: <https://www.fda.gov/media/101052/download>.

4 U.S. Food and Drug Administration (FDA). GDUFA Regulatory Science Priority Initiatives for Fiscal Year, Link: <https://www.fda.gov/media/132370/download>.

use) of various DPI products. The study protocol has received approval from the local Institutional Review Board (IRB) and several expert panel discussions have been conducted to identify the scenarios and preliminary questions to be discussed at the first focus group meeting with asthma and chronic obstructive pulmonary disease (COPD) patients. The outcomes of these contracts are expected to provide significant insights to improve FDA's understanding of the patient's use and perception towards substitution of generic drug-device combination products for their RLDs.

Another GDUFA Science and Research Priority initiative for complex drug-device combination products in FY2020 includes the development of criteria for device performance comparisons that would support a bioequivalence (BE) demonstration by in vitro methods and may eliminate the need for in vivo comparative clinical endpoint BE studies. Under this research initiative, studies involving inhalation products, transdermal, or topical delivery systems (collectively referred to as TDS) have been conducted. The first research project (Grant# U01FD004943) was conducted by the University of Florida (FL, US) to investigate how changes in device design parameters along with formulation factors influence in vitro product performance for suspension-based metered dose inhaler (MDI) products. Details of this study and significant outcomes related to the influence of device (actuator) design changes are described below in the Research Highlight. The second external research project is a continuing project with TDS products, wherein the goal has been to develop in vitro tools that may have the potential to be predictive of in vivo heat effects on 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, and lidocaine. During FY2020, studies with TDS products containing oxybutynin and rivastigmine are ongoing. Data from the research studies supported the recommendations related to the assessment of heat effects on generic TDS products.⁵ CDER laboratories evaluated the critical formulation parameters that may affect the adhesion properties of TDS. Root causes of product failure due to drug crystallization and improper adhesion to patients' skin were determined. Several in vitro tools were developed to predict the deterioration in TDS performance due to drug crystallization. The outcomes from these studies provided new insights related to product design and in vitro tools that can enhance the development of complex generic drug-device combination products, inform guidance development (new and revisions) and contribute to the FDA's abbreviated new drug application (ANDA) reviews for such products.

5 Draft Guidance for Industry, *Transdermal and Topical Delivery Systems — Product Development and Quality Considerations* (November 2019), Link: <https://www.fda.gov/media/132674/download>.

Research Highlight

Metered dose inhalers (MDIs) are complex drug-device combination products widely utilized to treat an assortment of pulmonary disorders.^{6,7} The purpose of this highlighted research study was to investigate the influence of formulation parameters and device (actuator) design on in vitro aerodynamic product performance for mometasone furoate (MF) suspension-based MDIs. The study incorporated three suspension-based MF MDI formulations (F1, F2, F3) manufactured with differences in active pharmaceutical ingredient (API) particle size (D50, drug volumetric median particle size distribution), oleic acid (OA, surfactant) content, and ethanol (EtOH, cosolvent) content in hydrofluoroalkane (HFA-227) propellant and four actuator designs differing in orifice diameter (OD), jet length (JL), and sump depth (SD) (Table 1). Regarding the actuator variants tested, OD had the strongest effect on the MF particles exiting the United States Pharmacopeia (USP) induction port or mouth-throat (M-T) model (i.e., smaller OD led to increased fine particle dose (FPD) values) via measurement of aerodynamic particle size distribution (APSD), which was formulation independent.⁸ This finding is demonstrated in Figure 1 by an increased MF deposition on lower stages of the Next Generation Impactor (NGI) for actuators C and D with smaller ODs as compared to actuators A and B. The change in OD from 0.48 to 0.35 mm caused FPD less than 8 μm (FPD<8 μm) to increase between 14 to 44%. The same change in OD caused FPD<5 μm and FPD<2 μm to change from between 15 to 42% and 15 to 52%, respectively. A more pronounced effect was seen for F2, which contained a smaller API D50 compared to F1 and F3 suggesting control of OD may be more critical for formulation with finer APIs (lower API D50).⁹ When assessing the spray characteristics of the aerosol, JL was shown to have a significant effect on spray pattern area as well as plume geometry angle and width, while SD had significant effects on spray pattern ovality and plume geometry angle.¹⁰ An increase in JL from 0.4 to 0.6 mm led to significant (ANOVA, analysis of variance) decreases in spray pattern area (10–15%), plume geometry angle (5–10%) and width (2–11%) for all three suspension-based MF MDI formulations studied (Figure 2). The outcomes of this study demonstrated the importance of actuator design and its interaction with formulation factors on in vitro product performance for suspension-based MDIs, which have improved the scientific understanding of such products and contributed in the FDA's ANDA reviews for suspension-based MDIs.

6 Stein, Stephen W., et al. "Advances in metered dose inhaler technology: Hardware development." *AAPS PharmSciTech* 15.2 (2014): 326–338.

7 Newman, Stephen P. "Principles of metered-dose inhaler design." *Respiratory care* 50.9 (2005): 1177–1190.

8 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 In Vitro Aerosolization Performance. *Respiratory Drug Delivery* 2020. Volume 3, 2020: 497–502.

9 Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. The Effects of Mometasone Furoate Formulation Factors and Actuator Design on Metered Dose Inhaler (MDI) Performance. Poster Presentation at *American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360*. San Antonio, TX, Nov. 4, 2019.

10 Dhapare S., Bielski E., Conti D., Oguntimein O., Sheth P., Hallinger M., Svensson M., Sandell D., Bulitta J., Hochhaus G. Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers. *Respiratory Drug Delivery* 2020. Volume 3, 2020: 503–508.

Table 1: MF MDI Formulation Factors and Device (Actuator) Variants Included in the Study.

MF Formulation Factors*				Device (Actuator) Variants			
Formulation	API D50 (µm)	EtOH (% w/w)	OA (% w/w)	Actuator	Orifice Diameter (mm)	Jet Length (mm)	Sump Depth (mm)
F1	1.69	0.53	0.004	A	0.48	0.6	1.2
F2	1.10	2.15	0.015	B	0.48	0.4	1.5
F3	1.69	1.35	0.010	C	0.35	0.6	1.5
**D50 = the median diameter (the particle diameter at 50% in the cumulative distribution).				D	0.35	0.4	1.2

(*) Actual results, not targets.

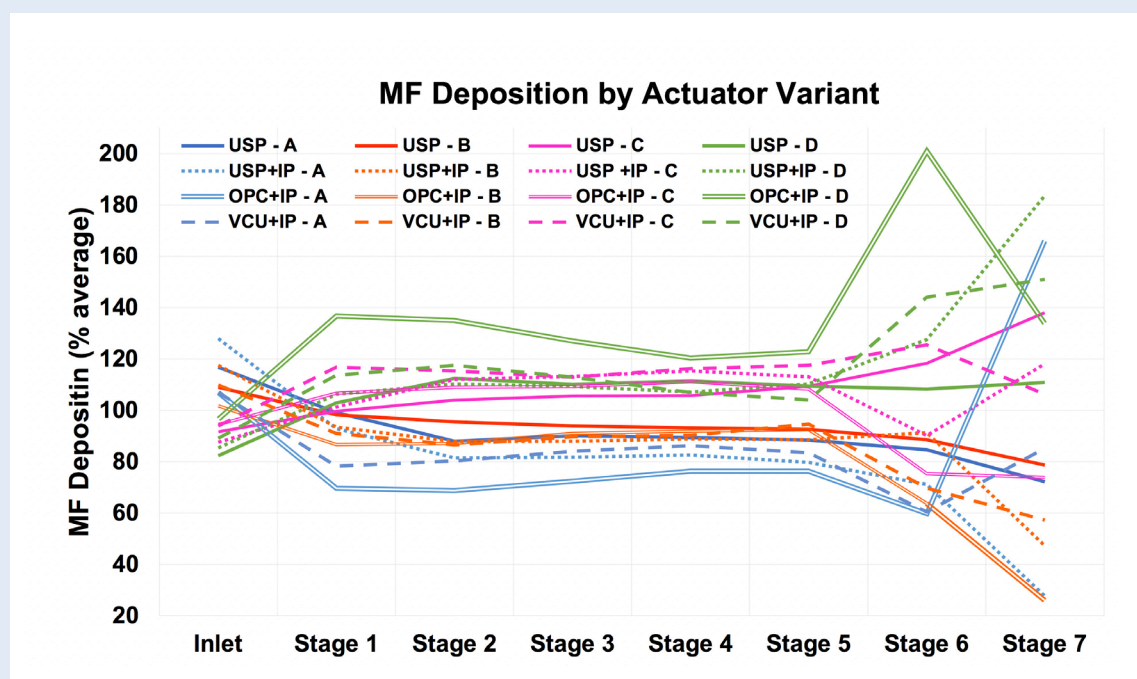


Figure 1: MF deposition (% average) on NGI stages by actuator variant (A, B, C, D) and APSD testing condition from all formulations. The % average for each APSD testing condition (e.g., USP+IP) = (mean MF deposition of each NGI stage by actuator) / (mean MF deposition of that NGI stage for all actuators) x 100%. USP: APSD testing using USP induction port and compendial method as described in USP <601>¹¹; USP+IP / OPC+IP / VCU+IP: APSD testing using of IP with USP induction port or M-T model. OPC: Oropharyngeal Consortium medium-sized M-T model; VCU: Virginia Commonwealth University medium-sized M-T model, USP: United States Pharmacopeia, IP: inhalation profile based on the mathematical formula proposed by Byron et al.¹² and shape parameters by Longest et al.¹³

11 United States Pharmacopeia and National Formulary. In <601> *Inhalation and Nasal Drug Products, Aerosols, Sprays, and Powders — Performance Quality Tests*. Rockville, MD: United States Pharmacopeia Convention USP43-NF38; 2018, 6819.

12 Byron P.R., Wei X., Delvadia R.R., Longest P.W., Venitz J.: Breath profiles for testing new DPI devices in development. In *Respiratory Drug Delivery*. Serentec Press Raleigh, NC; 2014: 295–302.

13 Longest P.W., Tian G., Walenga R.L., Hindle M.: Comparing MDI and DPI aerosol deposition using in vitro experiments and a new stochastic individual path (SIP) model of the conducting airways. *Pharmaceutical Research* 2012, 29:1670–1688.

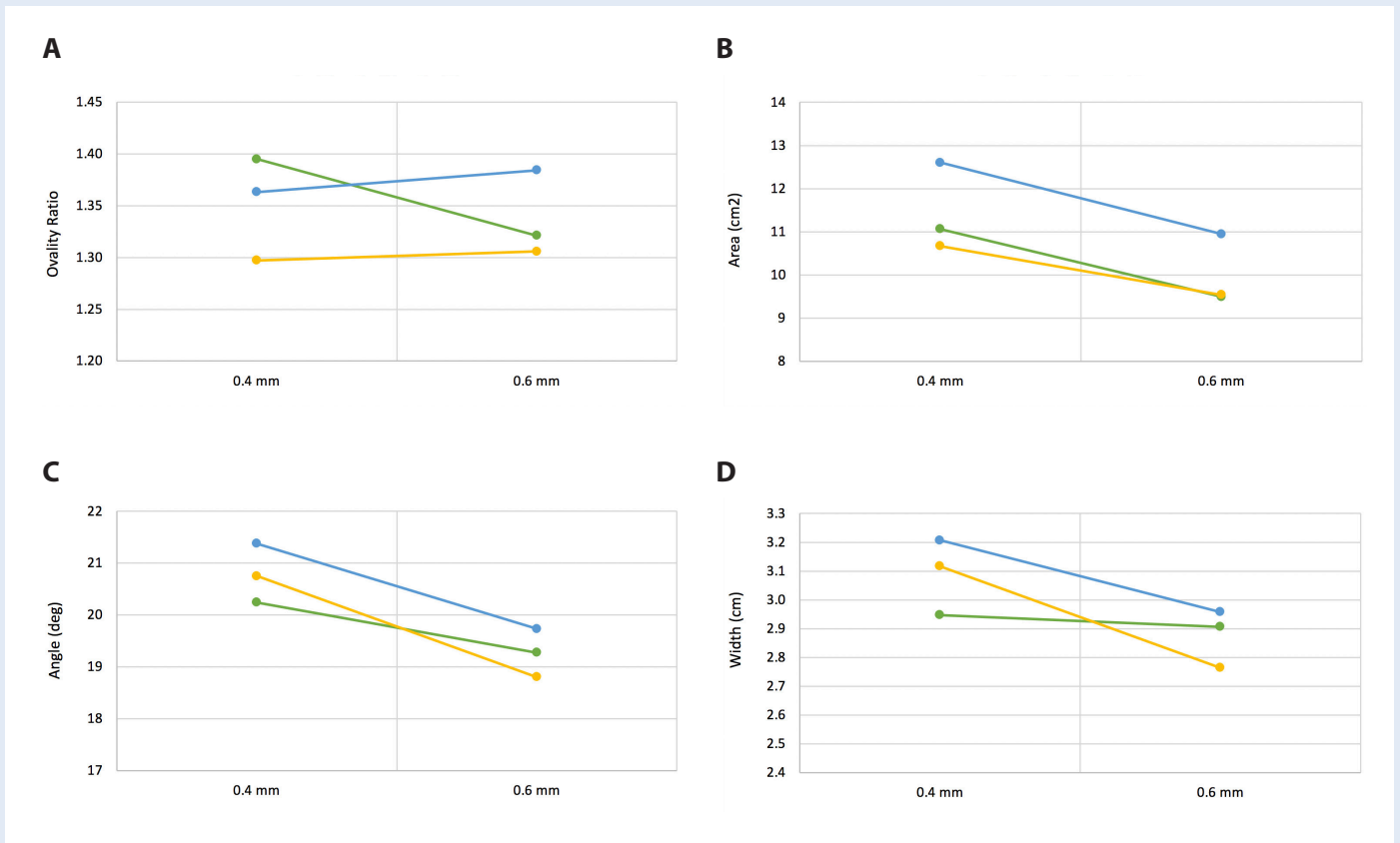


Figure 2: Average change in (A) Ovality, (B) Area, (C), Angle, and (D) Width of the three MF MDI Formulations (F1, F2, F3) by increase in JL from 0.4 to 0.6 mm.

Research Projects and Collaborations

Continuing Grants and Contracts

- 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 University of Sydney
- 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 (HHSF22320180113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Vanessa Boudewyns at RTI International

Completed Grants and Contracts

- Grant (5U01FD004943) *Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance* with Guenther Hochhaus at University of Florida

Active FDA Research

- *Characterization and BE Standards for Nasal Powders*
- *Development of New BE Methods for Transdermal Adhesion*
- *Development of New BE Methods for Transdermal Irritation and Sensitization*
- *Investigating the Impact of Soft Mist Inhaler In Vitro Characteristics on Human Airway Deposition: A Combined In Vitro / In Silico Approach*

Completed 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*

Outcomes

General Guidances

- *Draft Guidance for Industry: Transdermal and Topical Delivery Systems — Product Development and Quality Considerations* (Nov. 2019) [Link to Posting](#).
- *Draft Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Demonstrating Reliability of Emergency—Use Injectors Submitted under a BLA, NDA or ANDA* (Apr. 2020) [Link to Posting](#).

Product-Specific Guidances (PSGs)

There were 8 new and 32 revised PSGs published in FY2020 related to drug-device combination products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance on Albuterol Sulfate Inhalation Aerosol Metered* (Mar. 2020) [Link to Posting](#).
- *Revised Draft Guidance on Albuterol Sulfate Inhalation Powder Metered* (Mar. 2020) [Link to Posting](#).
- *Revised Draft Guidance on Beclomethasone Dipropionate Inhalation Aerosol Metered* (Mar. 2020) [Link to Posting](#).
- *Revised Draft Guidance on Buprenorphine Transdermal Film, Extended Release* (Jun. 2020) [Link to Posting](#).
- *Revised Draft Guidance on Capsaicin Topical Patch* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Clonidine Transdermal Film, Extended Release* (Nov. 2019) [Link to Posting](#).
- *New Draft Guidance on Copper Intrauterine Device* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Diclofenac Epolamine Topical Patch* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Estradiol Transdermal Film, Extended Release (NDA 019081)* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Estradiol Transdermal Film, Extended Release (NDA 203752)* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Estradiol Transdermal Film, Extended Release (NDA 020375; 021674)* (Nov. 2019) [Link to Posting](#).
- *Revised Draft Guidance on Estradiol Transdermal Film, Extended Release (NDA 020538)* (Nov. 2019) [Link to Posting](#).

- *Revised Draft Guidance on Estradiol; Levonorgestrel Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Estradiol; Norethindrone Acetate Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *New Draft Guidance on Estradiol Vaginal Insert, Extended Release (Jun. 2020)* [Link to Posting](#).
- *Revised Draft Guidance on Ethinyl Estradiol; Norelgestromin Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Fentanyl Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *New Draft Guidance on Glycopyrrolate; Indacaterol Maleate Inhalation Powder (Jun. 2020)* [Link to Posting](#).
- *Revised Draft Guidance on Granisetron Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Levalbuterol Tartrate Inhalation Aerosol Metered (Mar. 2020)* [Link to Posting](#).
- *Revised Draft Guidance on Levonorgestrel Intrauterine Device (Jan. 2020)* [Link to Posting](#).
- *Revised Draft Guidance on Lidocaine Topical Patch (NDA 020612) (Nov. 2019)* [Link to Posting](#).
- *New Draft Guidance on Lidocaine Topical Patch (NDA 207962) (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Menthol; Methyl Salicylate Topical Patch (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Methylphenidate Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Nicotine Transdermal Film, Controlled Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Nitroglycerin Transdermal Film, Extended Release (NDA 020144) (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Nitroglycerin Transdermal Film, Extended Release (NDA 020145) (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Oxybutynin Transdermal Film, Extended Release (NDA 021351) (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Oxybutynin Transdermal Film, Extended Release (NDA 202211) (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Rivastigmine Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Rotigotine Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).

- *Revised Draft Guidance on Scopolamine Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Selegiline Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *New Draft Guidance on Semaglutide Subcutaneous Solution (Mar. 2, 2020)* [Link to Posting](#).
- *New Draft Guidance on Sumatriptan Succinate Nasal Powder (Mar. 2020)* [Link to Posting](#).
- *New Draft Guidance on Sumatriptan Succinate Subcutaneous Injectable (Nov. 2019)* [Link to Posting](#).
- *Revised Draft Guidance on Testosterone Transdermal Film, Extended Release (Nov. 2019)* [Link to Posting](#).
- *New Draft Guidance on Umeclidinium Bromide; Vilanterol Trifenatate Inhalation Powder (Mar. 2020)* [Link to Posting](#).

Articles

- Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance*. *Respiratory Drug Delivery*. (2020) 3: 497–502.
- *CDER Statistical Studies Innovate Measures of Adhesion to Assess Generic Products*, In: *Regulatory Science in Action, Regulatory Science Impact Story*. Available at <https://www.fda.gov/drugs/regulatory-science-action/cder-statistical-studies-innovate-measures-adhesion-assess-generic-products>. Content current as of 06/25/2020.
- Dhapare, S., Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers*. *Respiratory Drug Delivery*. (2020) 3: 503–507.
- LaCount, T., Zhang, Q., Hao, J., Ghosh, P., Raney, S., Talattof, A., Kasting, G., and Li, K. *Modeling Temperature-Dependent Dermal Absorption and Clearance for Transdermal and Topical Drug Applications*. *The AAPS Journal*. (2020) 22(3): 70. doi: [10.1208/s12248-020-00451-2](https://doi.org/10.1208/s12248-020-00451-2). PMID: [332390069](https://pubmed.ncbi.nlm.nih.gov/332390069/).
- La Count, T., Zhang, Q., Murawsky, M., Hao, J., Ghosh, P., Dave, K., Raney, S., Talattof, A., Kasting, G., and Li, K. *Evaluation of Heat*

Effects on Transdermal Nicotine Delivery In Vitro and In Silico Using Heat-Enhanced Transport Model Analysis. The AAPS Journal. (2020) 22(4): 82. doi: [10.1208/s12248-020-00457-w](https://doi.org/10.1208/s12248-020-00457-w). PMID: [32488395](https://pubmed.ncbi.nlm.nih.gov/32488395/).

- Mohamed, L., Kamal, N., Elfakhri, K., Willett, D., Wokovich, A., Strasinger, C., Cruz, C., Raney, S., Ashraf, M., and Zidan, A. *Drug Recrystallization in Drug-in-Adhesive Transdermal Delivery System: A Case Study of Deteriorating the Mechanical and Rheological Characteristics of Testosterone TDS.* International Journal of Pharmaceutics. (2020) 578: 119-132. doi: [10.1016/j.ijpharm.2020.119132](https://doi.org/10.1016/j.ijpharm.2020.119132). PMID: [32057892](https://pubmed.ncbi.nlm.nih.gov/32057892/).
- Newman B. and Witzmann, K. *Addressing the Regulatory and Scientific Challenges with Generic Orally Inhaled Drug Products.* Pharmaceutical Medicine. (2020) 34(2): 93–102. doi: [10.1007/s40290-020-00327-y](https://doi.org/10.1007/s40290-020-00327-y). PMID: [32112304](https://pubmed.ncbi.nlm.nih.gov/32112304/).
- Sandell, D., Svensson, M., Conti, D., Sheth, P., Oguntimein, O., Bielski, E., Bulitta, J.B., and Hochhaus, G. *Coating Stages of Next Generation Impactor (NGI) When Testing Metered Dose Inhalers (MDIs) — A Comparative Study on US Commercial MDI Products.* Respiratory Drug Delivery. (2020) 2: 463–468.
- Thomas, S., Shin, S-H., Hammell, D., Hassan, H., and Stinchcomb, A. *Effect of Controlled Heat Application on Topical Diclofenac Formulations Evaluated by In Vitro Permeation Tests (IVPT) Using Porcine and Human Skin.* Pharmaceutical Research. (2020) 37(3): 49. doi: [10.1007/s11095-019-2741-1](https://doi.org/10.1007/s11095-019-2741-1). PMID: [32034502](https://pubmed.ncbi.nlm.nih.gov/32034502/).
- Zhang, Q., Murawsky, M., LaCount, T., Hao, J., Ghosh, P., Raney, S., Kasting, G., and Li, K. *Evaluation of Heat Effects on Fentanyl Transdermal Delivery Systems Using In Vitro Permeation Test (IVPT) Strategy.* Journal of Pharmaceutical Sciences. (2020) 109(10): 3095–3104. doi: [10.1016/j.xphs.2020.07.013](https://doi.org/10.1016/j.xphs.2020.07.013). PMID: [32702372](https://pubmed.ncbi.nlm.nih.gov/32702372/).

Posters

- Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *The Effects of Mometasone Furoate Formulation Factors and Actuator Design on Metered Dose Inhaler (MDI) Performance.* Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 4, 2019.

- Thomas, S., Hammell, D., Hassan, H., and Stinchcomb, A. *A Pharmacokinetic Study of Two Oxybutynin Transdermal Formulations with Transient Heat Exposure*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 5, 2019.
- Bielski, E., Conti D., Oguntimein O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance*. Poster Presentation at Digital Respiratory Drug Delivery (RDD) 2020 Conference. Virtual Meeting, Apr. 26, 2020.
- Dhapare, S., Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers*. Poster Presentation at Digital Respiratory Drug Delivery (RDD) 2020 Conference. Virtual Meeting, Apr. 26, 2020.
- Mohamed, L., Kamal, N., Elfakhri, K., Willett, D., Wokovich, A., Strasinger, C., Raney, S., Ashraf, M., and Zidan, A., *More Than Just Pretty Snowflakes: Impact of Drug Crystals on the In Vitro Performance of TDS*. Poster Presentation at 2020 Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, Jun. 29–Jul. 2, 2020.

Presentations

- Willett, D., Yilmaz, H., Wokovich, A., Zidan, A., Rodriguez, J., and Keire, D. *Raman Mapping and Multivariate Image Analysis for Characterization of Transdermal Delivery Systems*. Presentation at Federation of Analytical Chemistry and Spectroscopy Societies (FACSS) SciX 2019. Palm Springs, CA, Oct. 19, 2019.
- Zidan, A. *Risk Assessment of Drug Recrystallization in Transdermal Delivery System*. Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360, San Antonio, TX, Nov. 5, 2019.
- Newman, B., Dhapare, S., Walenga, R., and Feng, K. *Addressing the Challenges with Orally Inhaled and Nasal Drug Products (OINDPs) Through the Pre-ANDA Meeting Process*. Presentation at Generic + Biosimilar Medicines Conference (GBMC) 2019. Bethesda, MD, Nov. 6, 2019.

- Luke, M. C. *Bioequivalence of Transdermal Systems*. Presentation at American Association of Pharmaceutical Scientists (AAPS) and The European Federation for Pharmaceutical Sciences (EUFEPS), FDA Co-Sponsored Global Bioequivalence Harmonization Initiative (GBHI): 4th International Workshop. Bethesda, MD, Dec. 12, 2019.
- Willett, D. and Yang, Y., *In Vitro Characterizations of Topical and Transdermal Drug Products from the Product Quality Assessment Perspective*. Podium Presentation at USP Workshop. Rockville, MD, Dec. 19, 2019.
- Willett, D., Yilmaz, H., Xi, W., Zidan, A., Yang, Y., and Rodriguez, J. *High Resolution Spectroscopic Imaging for Complex Pharmaceutical Dosage Forms*. Presentation at Nanotechnology Reviewer Network Meeting, Silver Spring, MD. Feb. 20, 2020.
- Willett, D., Yilmaz, H., Xi, W., Zidan, A., Yang, Y., and Rodriguez, J. *High Resolution Spectroscopic Imaging for Complex Pharmaceutical Dosage Forms*. Presentation at International Foundation Process Analytical Chemistry (IFPAC) Annual Meeting 2020, Bethesda, MD, Feb. 24, 2020.
- Bielski, E. *The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance*. Presentation at Digital Respiratory Drug Delivery 2020. Virtual Meeting, Apr. 26, 2020.
- Dhapare, S. *The Effects of Formulation Factors and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers*. Presentation at Digital Respiratory Drug Delivery 2020. Virtual Meeting, Apr. 26, 2020.
- Luke, M. C. *Drug-Device Combination Products Breakout Session*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Witzmann, K. *GDUFA Regulatory Science and Research on Generic Drug-Device Combination Products*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.

Inhalation and Nasal Products

Summary of FY2020 Activities

GDUFA research in FY2020 supported the posting of the first product-specific guidances (PSGs) for Beclomethasone Dipropionate, a solution-based metered dose inhaler (MDI) product. In lieu of the recommended comparative clinical endpoint (CCEP) bioequivalence (BE) study, these PSGs provided an option for conducting in vitro, in vivo, and/or in silico studies as an alternative approach for establishing BE in the context of the weight-of-evidence approach.^{14,15} Studies in this area included development of dissolution methods (Grants# 1U01FD004953, 1U01FD004950, and 1U01FD004941),^{16,17} testing of more predictive aerodynamic particle size distribution (APSD) using anatomical mouth-throat (MT) models (Grant# 1U01FD005231),^{18,19} and quantitative methods and modeling approaches for assessing the impact of product- and patient-related factors on regional drug deposition in the lung (Grants# 1U01FD004570, 1U01FD005837, and 1U01FD005214). Specifically, to better understand when alternative BE approaches to CCEP BE studies may be possible for more complex orally inhaled products, such as suspension-based MDIs and dry powder inhalers (DPIs), the Agency has continued research into identifying which factors can most significantly

- 14 DA draft PSG for Beclomethasone Dipropionate Inhalation Aerosol Metered (Reference Listed Drug: N207921). Posted May 2019. Available at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.
- 15 FDA draft PSG for Beclomethasone Dipropionate Inhalation Aerosol Metered (Reference Listed Drug: N020911). Posted January 2016, Revised March 2020. Available at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.
- 16 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.
- 17 Price, R., Shur J., Ganley W., Farias G., Fotaki N., Conti D., Delvadia R., Absar M., Saluja B., Lee S. Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products. *The AAPS Journal*. 2020, 22:47.
- 18 Wei X., Hindle M., Kaviratna A., Huynh BK., Delvadia RR., Sandell D., Byron P.R. 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):358–371.
- 19 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.

impact how aerosolized drug will distribute regionally and be absorbed once deposited in the lung. One example is the research conducted at the University of Florida (Grant# U01FD004943), where studies evaluating how changes in MDI formulation and device factors impact the delivered dose, aerodynamic particle size distribution (APSD), and spray characteristics of different mometasone furoate (MF) formulations. This study found that decreasing the active pharmaceutical ingredient (API) particle size led to increases in Next Generation Impactor (NGI) lower stage deposition and fine particle dose (FPD) without impacting the delivered dose performance (Figure 1).²⁰

The Agency has also continued its efforts on the development and extension of in vitro methods or other alternative approaches (e.g., pharmacokinetic) to be used for establishing BE with orally inhaled and nasal drug products. In a research study conducted at the University of Florida (Contract# 75F40119C10154) for orally inhaled products, different MT models are being screened against a range of different study parameters (e.g., coating type, insertional angle, and inhalation profile), to evaluate their effects on the aerosol droplet size distribution from MDI products before and after passing through a MT model. This study aimed to identify critical method parameters to consider when optimizing more predictive APSD testing with MT models in order to improve correlation with in vivo data. For nasal products, a research project conducted at the University of Florida (Contract# HHSF223201310220C) was completed that aimed to evaluate whether pharmacokinetic (PK) studies were sensitive to changes in the PSD of an API, such as mometasone furoate. Approximately 44 healthy subjects participated in a single-dose, two-way, crossover PK study with doses of charcoal to block mometasone furoate from gastrointestinal absorption, where two mometasone furoate suspension nasal formulations with different API PSDs were intranasally administered by trained clinical study personnel. Analysis of the study results are currently ongoing. Within the Agency, internal research studies established laser diffraction as a discriminatory particle sizing technique for a nasal powder drug product, providing support for the newly posted PSG for sumatriptan succinate nasal powder that recommends laser diffraction as part of the in vitro BE studies.²¹

20 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 In Vitro Aerosolization Performance. *Respiratory Drug Delivery*. 2020, 3:497–502.

21 FDA draft PSG for Sumatriptan Succinate Nasal Powder. Posted March 2020. Available at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

MF Formulation Factors*			
Formulation	API D50 (μm)**	EtOH (% w/w)	Oleic Acid (% w/w)
F1	1.69	0.53	0.004
F2	1.10	2.15	0.015
F3	1.69	1.35	0.010

MF Deposition by Formulation

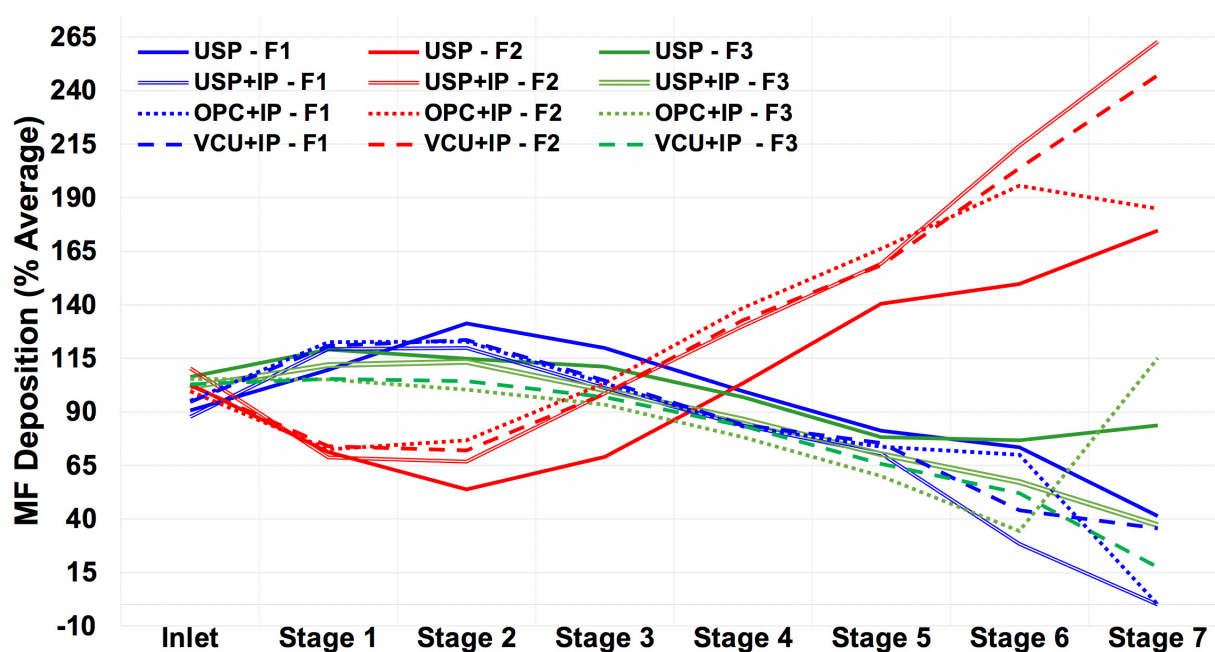


Figure 1: (Upper Panel) Mometasone Furoate (MF) MDI formulation design variants. *Actual results, not target values. **D50 = median volumetric particle size. (Bottom Panel) MF deposition (% average) on NGI stages by formulation and APSD testing. The % average at a particular APSD testing condition is calculated as the mean MF deposition of each NGI stage by formulation / mean MF deposition of that NGI stage for all formulations \times 100%. APSD testing was done with the USP induction port using either compendial methods or with inhalation profiles (IP). The IP was based on the mathematical formula proposed by Byron et al.²² and shape parameters by Longest et al.²³ MT models (medium-sized OPC (Oropharyngeal Consortium), medium-sized VCU (Virginia Commonwealth University)) were used with IPs in all cases for APSD testing.

22 Byron P.R., Wei X., Delvadia R.R., Longest P.W., Venitz J.: Breath profiles for testing new DPI devices in development. In *Respiratory Drug Delivery*. Serentec Press Raleigh, ND; 2014: 95–302.

23 Longest P.W., Tian G., Walenga R.L., Hindle M.: Comparing MDI and DPI aerosol deposition using in vitro experiments and a new stochastic individual path (SIP) model of the conducting airways. *Pharmaceutical Research* 2012, 29: 1670–1688.

Research Highlight

For characterizing the APSD of a DPI product, standardized methods often recommend coating the different stages of a cascade impactor (CI) with an adhesive substance to minimize the chance for particles bouncing and depositing on lower stages, which can impact the results. For APSD testing with MDIs, there is more uncertainty as to whether similar coating of the stages will have a significant impact on the results across different products and formulations. As part of a research study conducted at the University of Florida (Grant# 1U01FD004953), initial studies on MF MDIs found differences in the FPD measured between different laboratories, which was dependent on whether the CI stage coating was performed. To evaluate whether coating produced similar effects on other MDI products, 11 different suspension-based (Symbicort[®], Advair[®] HFA, Flovent[®] HFA, Asmanex[®] HFA, ProAir[®] HFA, Ventolin[®] HFA, Proventil[®] HFA, Bevespi Aerosphere[®]) and solution-based (QVAR RediHaler[®], Alvesco[®], Atrovent[®] HFA) MDI products were tested using an NGI with or without stage coating using a glycerol/Brij-35 solution mixture. Coating of the NGI stages led to a reduction in FPD < 2 microns and had a larger impact on particles less than 4 microns as compared to larger particles (Figure 2). Therefore, the magnitude of the stage coating impact was particle size dependent. Also, suspension-based MDI products (especially those formulated with HFA-227 as a propellant) were more significantly affected by the use of stage coating as compared to MDIs that were solution-based or that were formulated with HFA-134a propellant. These results suggest that the consideration for using NGI stage coating during an APSD study cannot be generalized across all MDIs and may be dependent on the particular formulation being tested.²⁴

24 Dennis S., Svensson M., Conti D., Sheth P., Oguntimein O., Bielski E., Bulitta J., Hochhaus G. Coating Stages of Next Generation Impactor (NGI) When Testing Metered Dose Inhalers (MDIs) — A Comparative Study on US Commercial MDI Products. *Respiratory Drug Delivery*. 2020, 3:463–468.

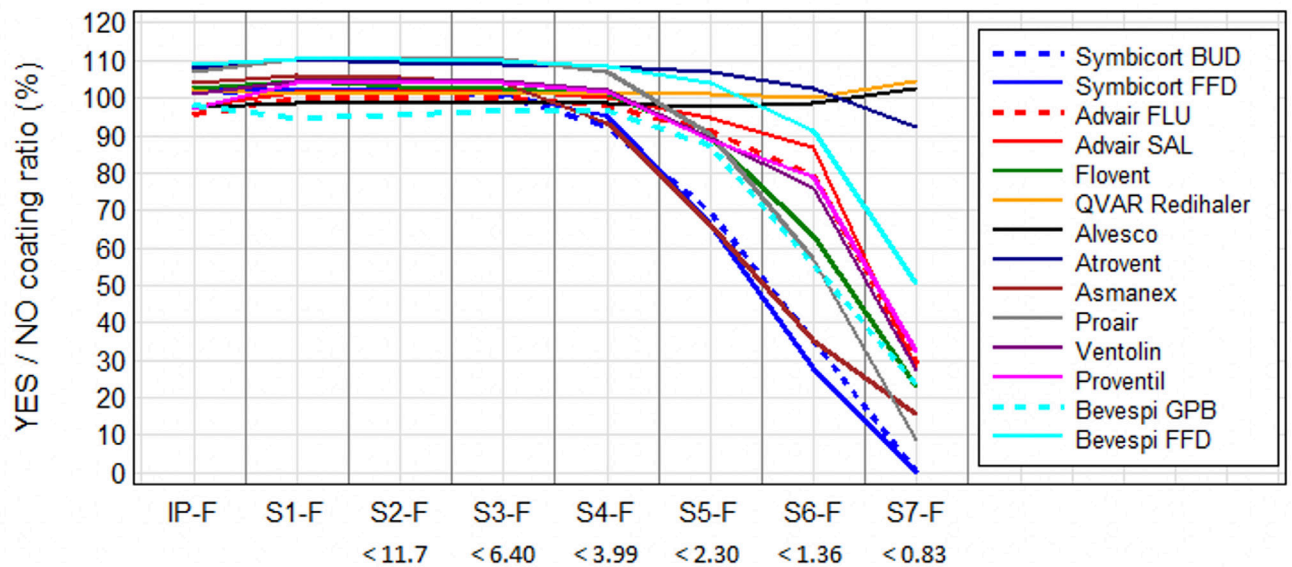
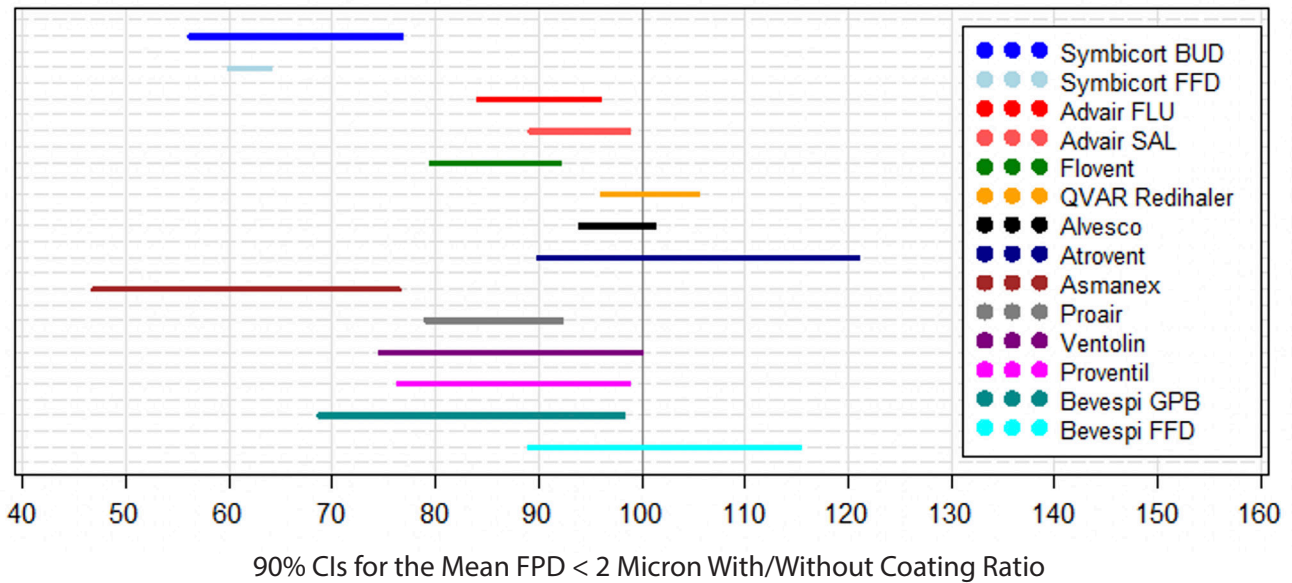


Figure 2: (Upper Panel) 90% Confidence intervals for the ratio of the mean Fine Particle Dose (FPD) less than 2 microns obtained with coating to the mean FPD less than 2 microns obtained without coating. (Lower Panel) The effect of coating (YES/NO coating ratio - %) on an MDI's aerodynamic particle size across the different stages of a Next Generation Impactor (NGI). IP-F (Induction Port Fraction), S1-F (Stage 1 Fraction), S2-F (Stage 2 Fraction), S3-F (Stage 3 Fraction), S4-F (Stage 4 Fraction), S5-F (Stage 5 Fraction), S6-F (Stage 6 Fraction), S7-F (Stage 7 Fraction). Values shown below the stage fraction labels indicate the aerodynamic particle diameter cutoff value for the respective stage when tested using a 30 L/min flow rate. BUD (budesonide), FFD (formoterol fumarate dihydrate), FLU (fluticasone propionate), SAL (salmeterol xinafoate), GPB (glycopyrrolate).

Research Projects and Collaborations

New Grants and Contracts

- Contract (75F40120C00036) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Jag Shur at Nanopharm Ltd.

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 (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) *Development of Computational Models to Predict Delivery of Inhalation Drug Powders: From Deagglomeration in Devices to Deposition in Airways* 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
- Contract (75F40119C10154C) *Systematic evaluation of the ex-throat plume properties of MDI formulations* with Guenther Hochhaus at University of Florida
- Contract (HHSF223201710072C) *Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London
- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Prediction of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffrey Schroeter at Applied Research Associates
- Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches* with Robert Price; Jag Shur at University of Bath

- Contract (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price at University of Bath
- 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 (HHSF223201810169C) *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers* with Hugh D. C. Smyth at University of Texas at Austin

Completed Grants and Contracts

- Grant (5U01FD004943) *Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance* with Guenther Hochhaus at University of Florida
- 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 (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

Active FDA Research

- *Assessment of Variability and Dose Sensitivity of FEV1 in Comparative Clinical Endpoint BE Studies of OIDs*
- *CFD Models of Droplet Formulation from MDI*
- *CFD Models of Soft Mist Inhalers*
- *In Vitro Performance Testing of Soft Mist Inhalers*
- *Optimization of an In Vitro method for Regional Deposition Prediction of Nasal Powders*
- *Orally Inhaled Drug Product (OIDP) Data Collection and Analysis from Drug Product Submissions*
- *Particle Size Characterization in Nasal Spray Suspensions Using MDRS Method*

- *Physiological Mouth-Throat Models for Inhalation Products*
- *Product Quality and Performance Evaluation of Tiotropium Bromide Inhalation Powder Drug Products*
- *The Use of Lung-on-a-Chip to Obtain Physiologically Relevant Parameters for Orally Inhaled Drug Products*

Outcomes

Product-Specific Guidances (PSGs)

There were 9 new and 14 revised PSGs published in FY2020 related to inhalation and nasal products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance on Albuterol Sulfate Inhalation Aerosol, Metered. (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Albuterol Sulfate Inhalation Powder, Metered. (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Beclomethasone Dipropionate Inhalation Aerosol Metered (NDA 020911) (Mar. 2, 2020) [Link to Posting](#).*
- *New Draft Guidance on Glycopyrrolate; Indacaterol Maleate Inhalation Powder. (June 3, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Levalbuterol Tartrate Inhalation Aerosol, Metered. (Mar. 2, 2020) [Link to Posting](#).*
- *New Draft Guidance on Sumatriptan Succinate Nasal Powder. (Mar. 2, 2020) [Link to Posting](#).*
- *New Draft Guidance on Talc Intrapleural Powder. (Aug. 28, 2020) [Link to Posting](#).*
- *New Draft Guidance on Umeclidinium Bromide; Vilanterol Trifenatate Inhalation Powder (Mar. 2, 2020) [Link to Posting](#).*

Articles

- Golshahi, L., Manniello, M., Hosseini, S., Alfaifi, A., Schuman, T., Hindle, M., Longest, W., and Sandell, D. *In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically-Correct Nasal Airway Models*. *Respiratory Drug Delivery*. (2020) 1: 155–164.

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- Elserfy, K., Kourmatzis, A., Chan, H-K., Walenga, R., and Cheng, S. *Effect of an Upstream Grid on the Fluidization of Pharmaceutical Carrier Powders*. *International Journal of Pharmaceutics*. (2020): doi: [10.1016/j.ijpharm.2020.119079](https://doi.org/10.1016/j.ijpharm.2020.119079). PMID: [31988029](https://pubmed.ncbi.nlm.nih.gov/31988029/).
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- Zhao, Y., Raco, J., Kourmatzis, A., Diasinos, S., Chan, H., Yang, R., and Cheng, S. *The Effects of Upper Airway Tissue Motion on Air-flow Dynamics*. *Journal of Biomechanics*. (2020) 99: doi: [10.1016/j.jbiomech.2019.109506](https://doi.org/10.1016/j.jbiomech.2019.109506). PMID: [31780123](https://pubmed.ncbi.nlm.nih.gov/31780123/).

Posters

- Kurumaddali, A., Amini, E., Drescher, S., Chen, M., Bulitta, J., and Hochhaus, G. *A Semi-Physiological Approach for Evaluating the Sensitivity of Pharmacokinetics to Detect Differences in Regional Lung Deposition of Orally-Inhaled Drug Products (OIDPs)*. Poster Presentation at American College of Clinical Pharmacy (ACCP) 2019 Annual Meeting. New York City, NY, Oct. 26, 2019.
- Bielski, E., Conti, D., Oguntimein, O., Sheth, P., Hallinger, M., Svensson, M., Sandell, D., Bulitta, J., and Hochhaus, G. *The Effects of Mometasone Furoate Formulation Factors and Actuator Design on Metered Dose Inhaler (MDI) Performance*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 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., and Hochhaus, G. *Investigation of Pharmacokinetic Sensitivity to Lung Deposition of Locally-Acting Orally Inhaled Drug Products*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Hsu, H., Pavuluri, V., Yang, Y., Abraham, C., Narahariseti, S., Ashraf, M., and Al-Ghabeish, M. *Formulation Challenges Facing Naloxone Intranasal Solution*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Manniello, M., Hosseini, S., Hindle, M., Schuman, T., Longest, W., Sandell, D., and Golshahi, L. *In Vitro Investigation of Regional Nasal Drug Delivery Using Two Glucocorticoid Nasal Spray Products and Twenty Anatomical Nasal Replicas*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 7, 2019.
- Holtgrewe, N., Reed, N., Kaviratna, A., Rodriguez, J., and Guo, C. *Evaluation of the Fast Screening Impactor with Dry Powder Inhalers*. Poster Presentation at Respiratory Drug Delivery (RDD) 2020 Conference. (Virtual). Apr. 26, 2020.

- Kolanjiyil, A., Hosseini, S., Manniello, M., Alfaifi, A., Farkas, D., Golshahi, L., and Longest, W. *Effect of Spray Momentum on Nasal Spray Droplet Transport and Deposition*. Poster Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.
- Sandell, D., Svensson, M., Conti D., Sheth, P., Oguntimein, O., Bielski, E., Bulitta, J., and Hochhaus, G. *Coating Stages of Next Generation Impactor (NGI) When Testing Metered Dose Inhalers (MDIs) — A Comparative Study on US Commercial MDI Products*. Poster Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.

Presentations

- Hochhaus, G. *Preclinical Models for Pulmonary Delivery*. Presentation at American Association of Pharmaceutical Scientists (AAPS) Pharmsci360 2019. San Antonio, TX, Nov. 6, 2019.
- Newman, B., Dhapare, S., Walenga, R., and Feng, K. *Addressing the Challenges with Orally Inhaled and Nasal Drug Products (OINDPs) Through the Pre-ANDA Meeting Process*. Presentation at Generic + Biosimilar Medicines Conference (GBMC) 2019. Bethesda, MD, Nov. 6, 2019.
- Hochhaus, G. *Dissolution Methods for Orally Inhaled Drug Products*. Presentation at United States Pharmacopoeial (USP) 2019 Workshop. Bethesda, MD, Dec. 12, 2019.
- Hochhaus, G. *In Vitro Testing — Predictive of In Vivo Performance of OINDPs*. Presentation at American Association of Pharmaceutical Scientists (AAPS) and The European Federation for Pharmaceutical Sciences (EUFEPS), FDA Co-Sponsored Global Bioequivalence Harmonization Initiative (GBHI): 4th International Workshop. Bethesda, MD, Dec. 13, 2019.
- Bielski, E., *The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance*. Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.

- Dhapare, S., *The Effects of Formulation Factors and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers*. Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.
- Golshahi, L., Manniello, M., Hosseini, S., Alfaifi, A., Schuman, T., Hindle, M., Longest, W., and Sandell, D. *In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically Correct Nasal Airway Models*. Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.
- Hochhaus, G., *Unraveling the Pulmonary Fate of Fluticasone and Friends: Meeting the Physiologic and Pharmacokinetic Challenge*. Presentation at Respiratory Drug Delivery (RDD) 2020 Conference (Virtual). Apr. 26, 2020.
- Luke, M. C. *Drug-Device Combination Products Breakout Session*. Podium Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual. May 4, 2020.
- Witzmann, K. *GDUFA Regulatory Science and Research on Generic Drug-Device Combination Products*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Kakhi, M. *Prediction of Respimat, Inhaler Spray: Co-Flow Air Behavior*. Presentation at 15th Openfoam Workshop. Arlington, VA, Jun. 25, 2020.
- Xu, X. *Developing and Validating Commonly Employed Particle Sizing Methods to Support Bioequivalence and Product Quality*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.

- Bielski, E. *Advancements in In Vitro Studies for Alternative Bioequivalence (BE) Approaches to Comparative Clinical Endpoint BE Studies*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.
- Golshahi, L. *Pathways to Establish Bioequivalence and Facilitate Development of Innovative and Generic Intranasal Drug Delivery Products: In Vitro Anatomically Correct Nasal Models*. Presentation at 3rd Annual Inhalation & Respiratory Drug Delivery (Virtual). Sept. 30, 2020.
- Han, L. *The Potential of Pharmacokinetic Bioequivalence (BE) Studies in Detecting Regional Deposition with Orally Inhaled Drug Products*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.
- Walenga, R. *Bridging the Gap Between Regional Deposition and Systemic Pharmacokinetic Data of OINDPs with Modeling and Simulation*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.



Locally-Acting Physiologically-Based Pharmacokinetic Modeling

Summary of FY2020 Activities

One of the main objectives of this research is to continue to work with external experts to develop and advance mechanistic-based modeling, such as physiologically-based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD), in order to better inform the role that product properties play on local bioavailability. In total, modeling specific to locally-acting product modeling and platform advancements was part of 18 separate external projects (i.e., contracts and grants) in FY2020 — 4 of which were initiated in FY2020 or at the end of FY2019. Among these four projects:

- In the complex injectable area (see *FY2020 GDUFA Science and Research Report: Complex Injectables, Formulations, and Nanomaterials*), one contract (75F40119C10139) was awarded that aims to utilize a model-informed drug development approach (Figure 1) for evaluating target site bioequivalence of drug products that incorporate nanomaterials (e.g., liposomal drug products). The contract intends to develop an in-silico systems-based multiscale model to capture various biological and physicochemical events that affect the transport and residence of nanoparticles (NP) and its cargo active pharmaceutical ingredient (API).

- In the nasal area (see *FY2020 GDUFA Science and Research Report: Inhalation and Nasal Products*), one new contract (75F40119C10079) was awarded for further development of an existing hybrid model that uses CFD and PBPK to predict the influence of device and formulation variables on systemic pharmacokinetics (PK) of nasally inhaled corticosteroid suspension spray products.
- In the ocular delivery area (see *FY2020 Regulatory GDUFA Science and Research Report: Ophthalmic Products*), two new grants (1U01FD006927 and 1U01FD006929) were awarded to support research relevant to ophthalmic drug products that will predict human ocular PK and pharmacodynamics (PD) through interspecies extrapolation by PBPK modeling. The focus is on understanding the current existing knowledge gaps and potential solutions of human model scale-up from animal models.

In addition, two contract studies (under Contract# 75F40119D10024) were kicked off in FY2020 for data generation to support ocular model development. One study is focused on measuring the effect of ophthalmic suspension formulation changes on the ocular PK and PD in rabbits. The second study uses optical coherence tomography to measure tear film and tear film meniscus thickness in rabbits to study the impact of emulsion formulation characteristics such as surface tension, osmolarity and viscosity on tear film breakup time (TBUT) and bioavailability. Both studies use formulations with different desired formulation characteristics, manufactured through FDA internal collaborations. These measurements will ultimately be used to validate rabbit suspension PBPK/PD models and emulsion TBUT models.

Internally, FDA continues to see increased usage of mechanistic-based modeling and simulation in pre-ANDA meeting packages and ANDA submissions for complex locally acting drug products. For pre-ANDA interactions, in FY2020 alone, various modeling topics have been discussed, including aspects of pulmonary regional deposition modeling (such as with CFD), aerosol evaporation modeling, and PBPK modeling for the following routes of administration — dermal, inhalation, ocular, and subcutaneous. In each instance, the purpose of the model has been to eliminate or reduce human in vivo testing in bioequivalence approaches for these products — a purpose in alignment with the goals of this research area. With anticipation, the knowledge gained by applicants from dissemination of the FDA's internal and external research in this area as well as the knowledge gained by the FDA's assessors in managing these efforts will lead to more ANDA approvals with model-integrated evidence in future years.

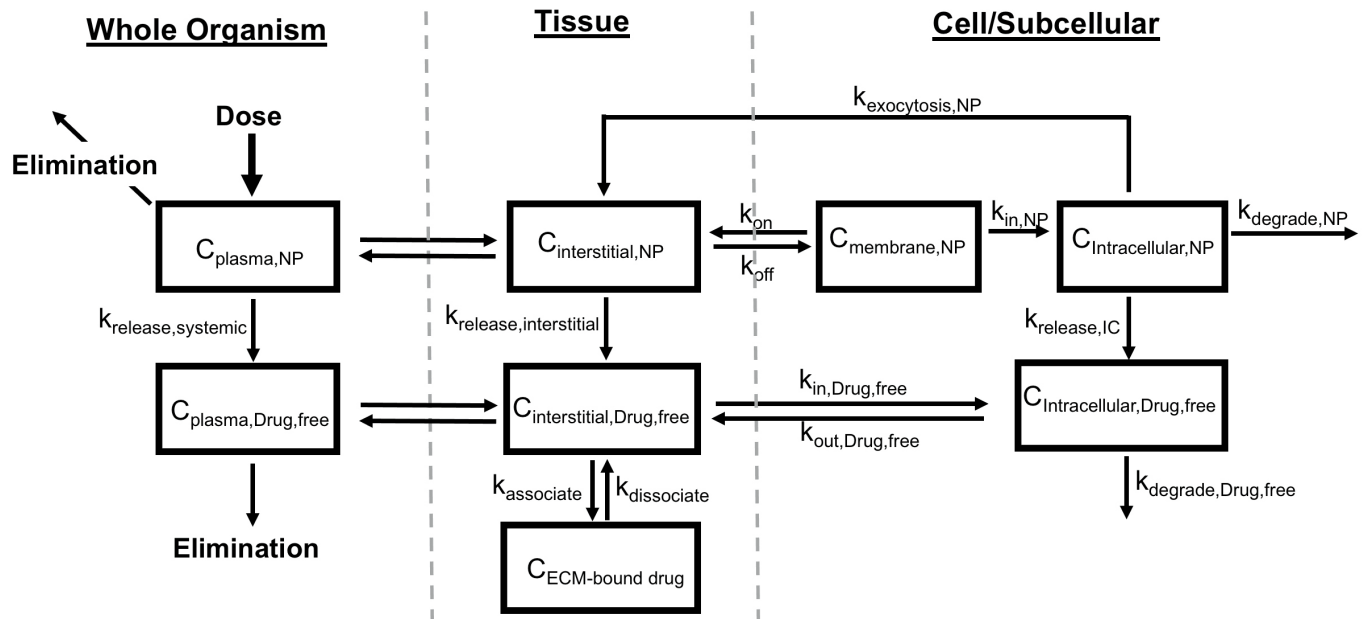


Figure 1: Structure of a multiscale model to depict the scale-specific kinetic processes that determine the target site pharmacokinetics of drug-loaded nanoparticles (NP) and drug cargo. This model covers the subcellular-to-systemic spatiotemporal events. The whole organism scale model accounts for (a) release of free drug from NP, and (b) disposition of NP and free drug, including distribution and elimination. The tissue scale model accounts for (a) bi-directional transvascular convective and diffusive transport of NP and free drug, (b) interstitial transport of NP and free drug in tissues (as a porous matrix), (c) release of free drug from NP in tissue interstitium, and (d) binding of free drug to extracellular matrix components (ECM). The cell/subcellular scale model accounts (a) receptor-mediated uptake of NP into cells, (b) intracellular release of free drug from NP, (c) exocytosis of NP, (d) bi-directional passive diffusion of free drug across cell membrane, and (e) degradation of NP and free drug within the cell. The resulting multiscale model can be used to predict the target site pharmacokinetics of NP/drug as functions of individual scale-specific properties (e.g., leaky vasculature in tumors and kidney, cells with the intended targets), or NP/drug-specific properties (e.g., binding to extracellular or intracellular proteins)

Research Highlight

Several publications resulted from external research projects that focused on modeling of orally inhaled and nasal drug products (OINDP). The overall purpose of these projects is to expand the knowledge base for various types of models (e.g., PBPK and CFD) to facilitate reliable predictions of local drug delivery to the site of action (e.g., lung or nasal tissue). Reliable models that can predict local delivery of OINDPs may be useful for quantifying the impact of differences observed with relevant in vitro and in vivo studies, where these predictions may be useful for streamlining bioequivalence approaches for this class of drug products.

The influence of an upstream grid in a dry powder inhaler was investigated via in vitro experiments by Elserfy, et al. (2020), where the results are to be used to validate a CFD-discrete element method (DEM) hybrid model as part of Grant# 1U01FD006525. For another study supported by the same grant, Zhao, et al. (2020) measured air-flow velocity in a realistic in vitro deformable mouth-throat model using particle image velocimetry, where the results will be useful for validating the same CFD-DEM model. A new hygroscopic growth model was developed and validated using experimental data collected by O'Shaughnessy, et al. (2020) for Grant# 1U01FD005837. For the same grant, Rajaraman, et al. (2020) subsequently used the newly developed hygroscopic growth model as part of a CFD model that was used to investigate the influence of hygroscopic growth on regional deposition of droplets from a solution-based metered dose inhaler in a realistic lung model (Figure 2). Due to difficulties with accurate sectioning of the nasal vestibule from the nasal cavity in realistic in vitro and in silico nasal models, Hosseini, et al. (2020) developed a novel method for determining the relevant cut plane, where the study was conducted as part of Contract# HHSF223201810144C.

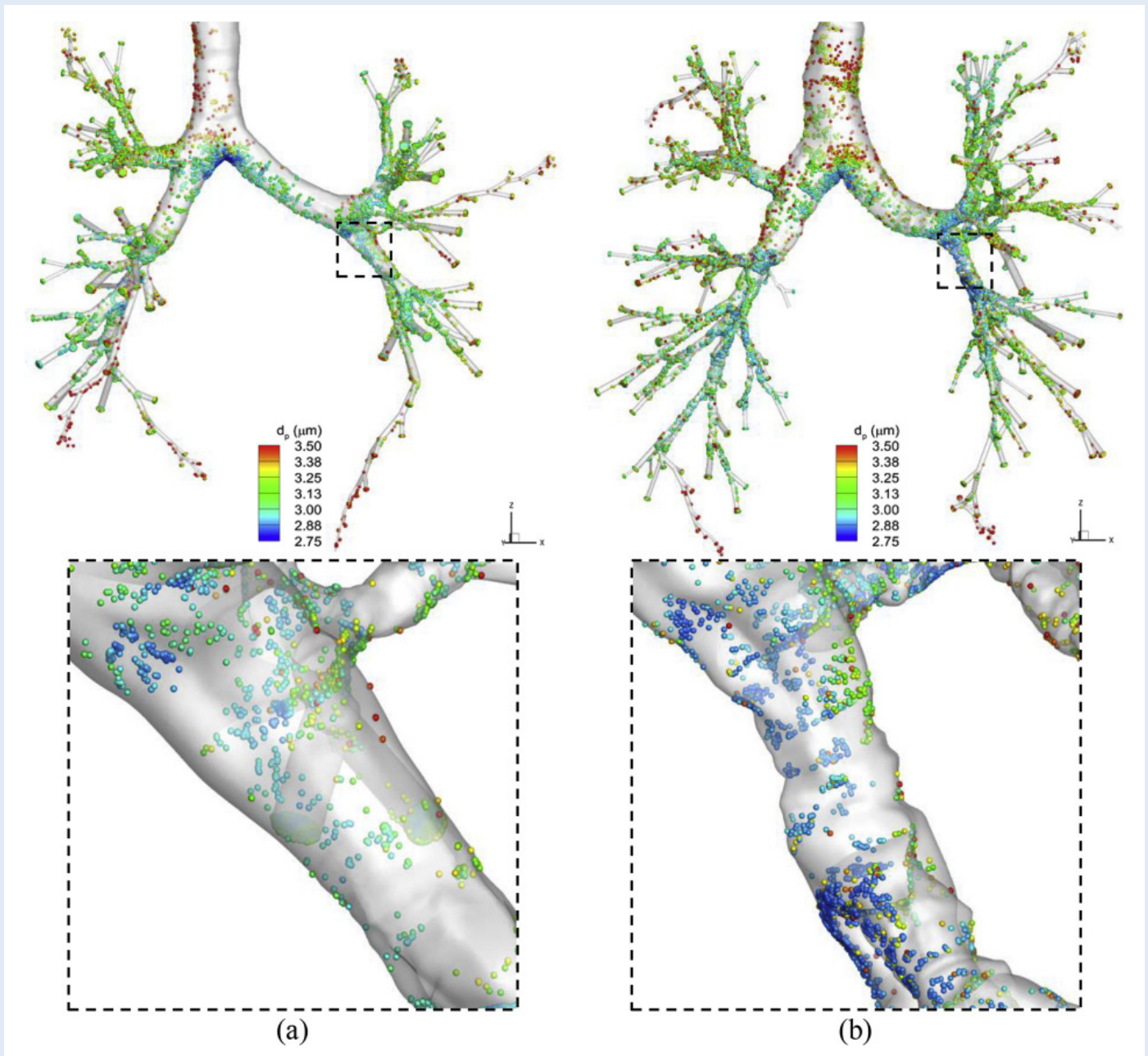


Figure 2: Regional deposition predictions of particles with an initial diameter (d_p) of $2\ \mu\text{m}$ after 1.25 s of inhalation in an asthmatic patient model representing (a) Cluster 3 and (b) Cluster 4 as defined in a previous study by Choi, et al.²⁵ The insets with the dotted lines show a close-up of the lower left lobe where the Cluster 3 subject does not show constriction while the Cluster 4 subject does. The figure is reproduced with permission from Elsevier.²⁶

- 25 Choi J., LeBlanc L.J., Choi S., Haghighi B., Hoffman E.A., O'Shaughnessy P., Wenzel S.E., Castro M., Fain S., Jarjour N., Schiebler M.L. *Differences in particle deposition between members of imaging-based asthma clusters.* Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2019 Aug 1;32(4):213–23.
- 26 Rajaraman P.K., Choi J., Hoffman E.A., O'Shaughnessy P.T., Choi S., Delvadia R., Babiskin A., Walenga R., Lin C.L. *Transport and deposition of hygroscopic particles in asthmatic subjects with and without airway narrowing.* Journal of Aerosol Science. 2020 Apr 28:105581.

Research Projects and Collaborations

New Grants and Contracts

- Grant (1U01FD006927) *Development and Validation of a PBPK/PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human* with Jessica Spires at Simulations Plus, Inc.
- Grant (1U01FD006929) *Computational Biology (Cobi) Tools as a Framework for Physiologically-Based Pharmacokinetic/Pharmacodynamic Model Extrapolation from Rabbit to Human for Ophthalmic Drug Products* with Carrie German at CFD Research Corporation
- Contract (75F40120C00150) *Robust in vitro/in silico Model to Accelerate Generic Drug Product Development for the Oral Cavity Route of Administration* with Giovanni M. Pauletti at St. Louis College of Pharmacy, Missouri

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 (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael N. Neely at Children's Hospital of Los Angeles
- 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 University of Sydney
- Grant (1U01FD006537) *Nasal Mucociliary Clearance Affecting Local Drug-absorption in Subject-specific Geometries* with Clement Kleinstreuer at North Carolina State University Raleigh

- 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 (1U01FD006526) *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations* with Jessica Spires at Simulations Plus, Inc.
- 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
- Contract (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation
- 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)
- 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 (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 Drugs* 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

Completed Grants and Contracts

- 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 (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.
- Grant (1U01FD005442) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Catherine Mary Turner Sherwin at University of Utah
- Contract (HHSF223201810255P) *Simulation Plus Ophthalmic Ointment Implementation* with Jessica Spires at Simulations Plus, Inc.

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *CFD Models of Droplet Formulation from MDI*
- *CFD Models of Soft Mist Inhalers*
- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*
- *Dissolution Testing of Nasally Insufflated OxyContin Using an In Vitro Method*

- *Impact of Soft Mist Inhaler In Vitro Characteristics on Human Airway Deposition: A Combined In Vitro-In Silico Approach*
- *Internally Implement PBPK Model Development for Locally-Acting Nasal Drug Products*
- *In Vivo Biodistribution Evaluation of Ophthalmic Suspension Drug Products*
- *Laser Diffraction of Soft Mist Inhalers*
- *Manufacture of Ophthalmic Suspension Test Formulations with Meaningful Variations in Viscosity and Particle Size*
- *Ocular PBPK Model Development and Verification*
- *Optimization of an In Vitro Method for Regional Deposition Prediction of Nasal Powders*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*
- *Utilize PBPK Model to Understand the Effect of Particle Size of Injectable Suspensions on Their Systemic Exposure*

Outcomes

Product-Specific Guidances (PSGs)

PSG listed below was directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance for Beclomethasone Dipropionate Inhalation Aerosol, Metered (Mar. 2, 2020)* [Link to Posting](#).

Articles

- Bois, F., Hsieh, N-H., Gao, W., Chiu, W., and Reisfeld, B. *Well-tempered MCMC Simulations for Population Pharmacokinetic Models*. J Pharmacokinet Pharmacodyn. 2020 Jul 31. doi: [10.1007/s10928-020-09705-0](https://doi.org/10.1007/s10928-020-09705-0). Online ahead of print. PMID: [32737765](https://pubmed.ncbi.nlm.nih.gov/32737765/).
- Elserfy, K., Kourmatzis, A., Chan, H-K., Walenga, R., and Cheng, S. *Effect of an Upstream Grid on the Fluidization of Pharmaceutical Carrier Powders*. International Journal of Pharmaceutics. (2020); doi: [10.1016/j.ijpharm.2020.119079](https://doi.org/10.1016/j.ijpharm.2020.119079). PMID: [31988029](https://pubmed.ncbi.nlm.nih.gov/31988029/).

- Golshahi, L., Manniello, M., Hosseini, S., Alfaifi, A., Schuman, T., Hindle, M., Longest, W., and Sandell, D. *In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically-Correct Nasal Airway Models*. *Respiratory Drug Delivery*. (2020) 1: 155–164.
- Hosseini, S., Schuman, T., Walenga, R., Wilkins Jr., J., Babiskin, A., and Golshahi, L. *Use of Anatomically-Accurate 3-dimensional Nasal Airway Models of Adult Human Subjects in a Novel Methodology to Identify and Evaluate the Internal Nasal Valve*. *Computers in Biology and Medicine*. (2020): doi: [10.1016/j.compbimed.2020.103896](https://doi.org/10.1016/j.compbimed.2020.103896). PMID: [32768043](https://pubmed.ncbi.nlm.nih.gov/32768043/).
- Kohno, M., Andhariya, J., Wan, B., Bao, Q., Rothstein, S., Hezel, M., Wang, Y., and Burgess, D. *The Effect of PLGA Molecular Weight Differences on Risperidone Release from Microspheres*. *International Journal of Pharmaceutics*. (2020) 582: doi: [10.1016/j.ijpharm.2020.119339](https://doi.org/10.1016/j.ijpharm.2020.119339). PMID: [32305366](https://pubmed.ncbi.nlm.nih.gov/32305366/).
- Kolanjiyil, A., Manniello, M., Alfaifi, A., Farkas, D., Hosseini, S., Hindle, M., Golshahi, L., and Longest, W. *Effect of Spray Momentum on Nasal Spray Droplet Transport and Deposition*. *Respiratory Drug Delivery*. (2020) 3: 691–696.
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- Liu, X., Yousef, S., Anissimov, Y., Van der Hoek, J., Tsakalozou, E., Ni, Z., Grice, J., and Roberts, M. *Diffusion Modelling of Percutaneous Absorption Kinetics. Predicting Urinary Excretion from In Vitro Skin Permeation Tests (IVPT) for an Infinite Dose*. *European Journal of Pharmaceutics and Biopharmaceutics*. (2020) 149:30–44. doi: [10.1016/j.ejpb.2020.01.018](https://doi.org/10.1016/j.ejpb.2020.01.018). PMID: [32018051](https://pubmed.ncbi.nlm.nih.gov/32018051/).
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Posters

- Kohno, M., Andhariya, J., Rothstein, S., Wang, Y., Qin, B., and Burgess, D. *The Effect of PLGA Molecular Weight on Drug Release from Microspheres*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Puttrevu, S., Arora, S., Polak, S., and Patel, N. *Evaluation of Methamphetamine and Amphetamine Disposition Discrepancy Upon Selegiline Transdermal Patch Administration in Healthy Volunteers Versus Special Populations Using PBPK Modelling*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.

- Manniello, M., Hosseini, S., Hindle, M., Schuman, T., Longest, W., Sandell, D., and Golshahi, L. *In Vitro Investigation of Regional Nasal Drug Delivery Using Two Glucocorticoid Nasal Spray Products and Twenty Anatomical Nasal Replicas*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 7, 2019.
- Kolanjiyil, A., Hosseini, S., Manniello, M., Alfaifi, A., Farkas, D., Golshahi, L., and Longest, W. *Effect of Spray Momentum on Nasal Spray Droplet Transport and Deposition*. Poster Presentation at Digital Respiratory Drug Delivery (RDD) 2020 Conference, Virtual Meeting, Apr. 26, 2020.
- Arora S., Patel N., Polak S., Jamei M., Tsakalozou E., Ghosh P., Alam K., Liu X., Namjoshi S., Grice J., Mohammed Y., and Roberts M. *Simulating the Effect of Propylene Glycol on Acyclovir (Zovirax® Cream, 5%) Permeation Across the Skin Using a Physiologically Based Pharmacokinetic (PBPK) Model of In Vitro Flow-through Skin Permeation*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, Jun. 29–Jul. 2, 2020.
- Van Osdol, W., Dong, J., and Spires, J. *Simulating the Dermal Permeation of Clobetasol-17 Propionate from a Topical Formulation*. Poster presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, Jun. 29–Jul. 2, 2020.

Presentations

- Zhao, L. *Regulatory Challenges and Opportunities for Model-Based Approaches for Patient Pharmacokinetic (PK) Studies with Sparse Sampling Design*. Presentation at American Conference on Pharmacometrics (ACoP10) Conference. Orlando, FL, Oct. 22, 2019.
- Arora, S. *Formulation Drug Product Quality Attributes Additions in Dermal PBPK Model*. Presentation at 10th Annual Simcyp Virtual Seminar. Webinar, Oct. 24, 2019.
- Clarke, J. *Formulation Drug Product Quality Attributes Additions in Dermal PBPK Model*. Presentation at 10th Annual Simcyp Virtual Seminar. Webinar, Oct. 24, 2019.

- Puttrevu, S. *PBPK Modeling of Transdermal Selegiline Disposition Discrepancy in Special Populations*. Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci360. San Antonio, TX, Nov. 4, 2019.
- Wu, F. *Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs*. Presentation at AAPS 2019 Pharmsci360. San Antonio, TX, Nov. 4, 2019.
- Ghosh, P., Luke, M. C., Tsakalozou, E., and Simamora, P. *Bioequivalence of Generic Topical Dermatological Drug Products*. Presentation at Association for Accessible Medicines (AAM): Generic + Biosimilar Medicines Conference (GBMC) 2019. Bethesda, MD, Nov. 6, 2019.
- Kozak, D., Cai, B., and Babiskin, A. *Complex Generic Drug Products (CGDPs) with Complex Formulations Including Nanotechnology Products*. Presentation at Association for Accessible Medicines (AAM): Generic + Biosimilar Medicines Conference (GBMC) 2019. Bethesda, MD, Nov. 6, 2019.
- Newman, B., Dhapare, S., Walenga, R., and Feng, K. *Addressing the Challenges with Orally Inhaled and Nasal Drug Products (OINDPs) Through the Pre-ANDA Meeting Process*. Presentation at Association for Accessible Medicines (AAM): Generic + Biosimilar Medicines Conference (GBMC) 2019. Bethesda, MD, Nov. 6, 2019.
- Clarke, J. and Roberts, M. *Predicting Dermal Absorption in Diseased or Damaged Skin Using PBPK Modelling*. Presentation at Certara Simcyp Workshop. Webinar, Dec. 13, 2019.
- Roberts, M. *Mathematical Modeling of Skin Absorption and Transport*. Presentation at American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Free Webinar. Feb. 7, 2020.
- Golshahi, L., Manniello, M., Hosseini, S., Alfaifi, A., Schuman, T., Hindle, M., Longest, W., and Sandell, D. *In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically-Correct Nasal Airway Models*. Presentation at Respiratory Drug Delivery. Webinar, Apr. 26, 2020.

- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Walenga, R. *Role of Computational Fluid Dynamics and Physiologically-Based Pharmacokinetic Modeling in Development of Orally Inhaled and Nasal Drug Products*. Presentation at University of Texas-El Paso Student Seminar. El Paso, TX, May 11, 2020.
- Kakhi, M. *Prediction of Respimat® Inhaler Spray: Co-Flow Air Behavior*. Presentation at 15th Openfoam Workshop. Arlington, VA, Jun. 25, 2020.
- Arora, S., Patel, N., Polak, S., Jamei, M., Tsakalozou, E., Ghosh, P., Alam, K., Liu, X., Namjoshi, S., Grice, J., Mohammed, Y., and Roberts, M. *Simulating the Effect of Propylene Glycol on Acyclovir (Zovirax® Cream, 5%) Permeation Across the Skin Using a Physiologically Based Pharmacokinetic (PBPK) Model of In Vitro Flow-Through Skin Permeation*. Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, Jun. 29, 2020.
- Arora, S. *Modeling Dermal Drug Absorption from Complex Semisolid Formulations: Insights from Multi-Phase, Multi-Layer MechDermA Model*. Presentation at the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) and FDA Co-Sponsored Topical Drug Development: Evolution of Science and Regulatory Policy II Workshop. Virtual Meeting, Jul. 23, 2020.
- Hamadeh, A. *A Workflow for Mechanistic Dermal Model Optimization and In vitro-In vivo Inference*. Presentation at the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) and FDA Co-Sponsored Topical Drug Development: Evolution of Science and Regulatory Policy II Workshop. Virtual Meeting, Jul. 23, 2020.
- Spires, J. *Computational Modeling of Absorption from Complex Topical Formulations*. Presentation at the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) and FDA Co-Sponsored Topical Drug Development: Evolution of Science and Regulatory Policy II Workshop. Virtual Meeting, Jul. 23, 2020.

- Golshahi, L. *Pathways to Establish Bioequivalence and Facilitate Development of Innovative and Generic Intranasal Drug Delivery Products: In Vitro Anatomically correct Nasal Models*. Presentation at 3rd Annual Inhalation & Respiratory Drug Delivery. Webinar, Sept. 30, 2020.
- Tsakalozou, E. *Physiologically-based Pharmacokinetic Modeling to Guide Study Design and Product Development for Generic Dermatological Products*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.
- Walenga, R. *Bridging the Gap Between Regional Deposition and Systemic Pharmacokinetic Data of OINDPs with Modeling and Simulation*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.



Long-Acting Injectable and Implant Products

Summary of FY2020 Activities

In FY2020, research efforts for long-acting injectables and implants focused on four aspects: 1) evaluation of new analytical methods for characterizing complex polymeric excipients and complex formulations; 2) development of novel in vitro drug release testing (IVRT) methods and in vitro-in vivo correlations (IVIVCs); 3) investigation of the impact of variation in raw materials on drug release characteristics and drug polymer interactions; and 4) development of new modeling tools to facilitate formulation development and bioequivalence (BE) study design. Significant progress has been made in each aspect as briefly discussed below.

To further improve the characterization of poly (lactide-co-glycolide) (PLGA) polymers and PLGA microparticles, two novel analytical tools, namely 3D laser scanning microscopy and focused ion beam scanning electron microscopy (FIB-SEM) have been evaluated. In addition to PLGA microparticles, the FIB-SEM is also used to characterize polydimethylsiloxane levonorgestrel intrauterine systems (LNG-IUSs) pre- and post-IVRT. The image data are analyzed to obtain information about the morphology, porosity, and drug distribution within the polymer matrix and the impact on drug release kinetics.

In the area of IVRT and IVIVC for long-acting injectables and implants, efforts continued on developing IVRT methods for LNG-IUSs and determining IVIVCs of PLGA microparticles and suspensions of drug substance particles. The effect of variable burst release on IVIVC of PLGA microspheres containing risperidone or leuprolide acetate was reported for the first time. It was observed that IVIVCs developed using formulations with less variation in burst release had better predictability and vice-versa (see *Research Highlight* below for more information).

The impact of variations in raw materials on drug release characteristics and drug polymer interactions was investigated in three external projects (Contract# HHSF223201810115C, HHSF223201810187C, and 75F40119C10157), which focused on two model drug products including leuprolide acetate PLGA microspheres and octreotide PLGA microspheres. In general, the study results indicate that physicochemical properties (e.g., drug loading, particle size, and porosity) and in vitro release characteristics of microspheres are sensitive to the source of the polymers. Differences in the manufacturing processes or process controls during synthesis of PLGAs from different sources can alter PLGA properties (such as molecular weight and crystallinity).

In the area of developing modeling and simulation tools for long acting injectable products, efforts have been made to develop model-informed and model-integrated approaches to aid development of long-acting injectables. As described in more detail in the *FY2020 GDUFA Science and Research Report: Quantitative Clinical Pharmacology*, the long-term goal of these modeling projects is to facilitate development of alternative in vivo BE study design to the currently recommended in vivo multi-dose steady state study in patients.

Research Highlight

A revised draft product-specific guidance (PSG) was posted recommending an in vitro and in vivo combination approach for establishing BE of generic LNG-IUS referencing MIRENA (Levonorgestrel Intrauterine Device, NDA 021225). Although the recommended approach reduces the duration of an in vivo BE study from 5 years to 12 months, conducting an in vitro drug release testing for 5-plus years can still be burdensome. Accordingly, efforts have been made on developing both real time and accelerated in vitro drug release testing methods for LNG-IUSs. In FY2020, study results of the research grant (1U01FD005443) on *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Dr. Diane Burgess at University of Connecticut have led to two significant publications.^{27,28}

The publication titled “Drug Release Testing of Long Acting Intrauterine Systems” is the first report describing in vitro drug release methods and drug release mechanism of levonorgestrel intrauterine systems (LNG-IUSs). Results of accelerated release testing under various conditions indicate that the drug release rate is correlated with swelling of the polydimethylsiloxane (PDMS) membrane and experimental temperatures as shown in the figure below.

27 Bao, Q., Zou, Y., Wang, Y., Kozak, D., Choi, S., and Burgess, D. J. *Drug Release Testing of Long-Acting Intrauterine Systems*. *Journal of Controlled Release*. (2019) 316:349–358. doi: 10.1016/j.jconrel.2019.11.015. PMID:31733294.

28 Bao, Q., Zou, Y., Wang, Y., Choi, S., and Burgess, D. J. *Impact of Product Design Parameters on In Vitro Release from Intrauterine Systems*. *International Journal of Pharmaceutics*. (2020): doi: 10.1016/j.ijpharm.2020.119135. PMID:32057890.

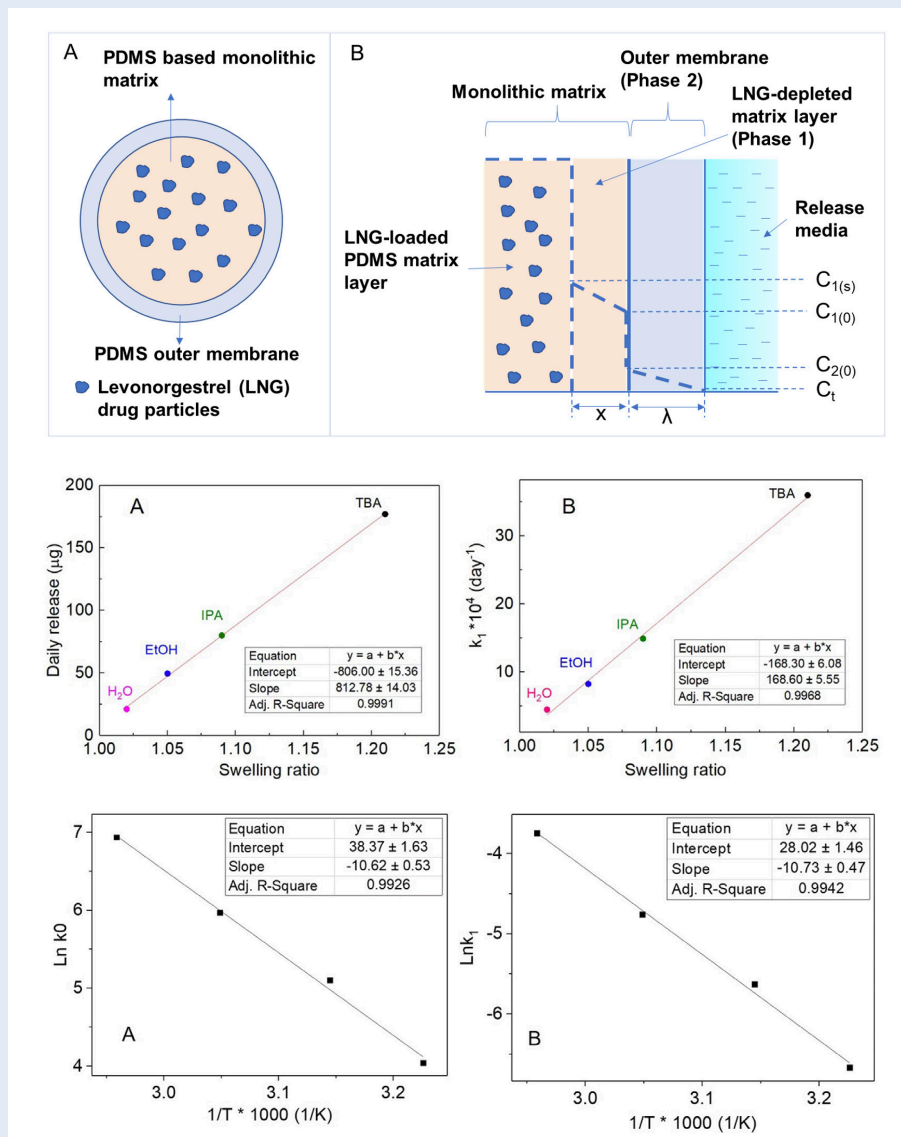


Figure: Description of LNG-IUS structure and concentration profile in LNG-IUS (Panel 1 on the top); Linear regression of the in vitro release rate of LNG-IUS versus the swelling ratio of PDMS in different solvents (Ethanol (EtOH), Isopropanol (IPA); tert-Butanol (TBA)) (Panel 2 in the middle); Arrhenius plot for in vitro release rate of LNG-IUS obtained at different temperatures in TBA aqueous media (Panel 3 at the bottom).

The second publication titled “Impact of Product Design Parameters on In Vitro Release from Intrauterine Systems” is the first literature describing investigations of product design parameters including the source and dimensions of the outer membrane, the particle size of drug substance, the dimensions of the drug reservoir, as well as the configuration of the entire device. The results indicate that the thickness of the outer membrane is critical to the drug release and can be used to tune the drug release rate. Other parameters, including surface area of the drug reservoir and particle size of drug substance, also play role on drug release rate.

The findings reported in these two publications help lay the groundwork for potentially utilizing accelerated drug release testing for establishing equivalence between generic and brand name LNG-IUSs.

Research Projects and Collaborations

New Grants and Contracts

- Contract (75F40120C00021) *Impact of Polymer Attributes on the Performance of in Situ Forming Implants Improve Scientific Approaches to Evaluate Generic Drugs* with Diane Burgess at University of Connecticut
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded Poly(Lactide-Co-Glycolide)-Based, Long-Acting Implants* with Dr. Nate Lynd and Dr. Feng Zhang at University of Texas at Austin

Continuing Grants and Contracts

- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane Burgess at University of Connecticut
- 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
- Contract (75F40119C10018) *Development of Model-Informed Bioequivalence Evaluation Strategies for Long-acting Injectable Products* with Mats Karlsson at Uppsala University
- Contract (HHSF223201810115C) *Impact of Polymer Source Variations on Parenteral Microsphere Drug Product Performance* with Diane 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 (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(Lactide-Co-Glycolide)-Based, Long-Acting Implants* with Nathaniel Lynd at University of Texas at Austin

- Contract (75F40120C00136) *Assessing Long-Acting Injectable Formulations Using In Vivo Imaging* with Xiuling Lu at University of Connecticut

Completed Grants and Contracts

- Grant (1U01FD005442) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Catherine Mary Turner Sherwin 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
- Contract (HHSF223201710135C) *In-Vitro in-Vivo Correlation of the Long-Acting Injectable Suspensions Improve Scientific Approaches to Evaluate Generic Drugs* with Diane Burgess at University of Connecticut

Active FDA Research

- *Bupivacaine Multivesicular Liposomes: Investigation of Impact of Variation in Formulation and Manufacturing Parameters and Development of Novel In Vitro Drug Release Testing Method*
- *Characterization and In Vitro Drug Release Testing of Long-Acting Injectable Suspensions*
- *Long-Acting Intrauterine Systems: Advanced Characterization and Development of Fit-for-Purpose Drug Release Testing Method*

Outcomes

Product-Specific Guidances (PSGs)

There were three new and one revised PSGs published in FY2020 related to long-acting injectable and implant products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance on Copper Intrauterine Intrauterine Device. (Nov. 21, 2019) [Link to Posting](#).*
- *New Draft Guidance on Granisetron Subcutaneous Injection, Extended Release. (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Levonorgestrel Intrauterine Intrauterine Device. (Jan. 22, 2020) [Link to Posting](#).*

Articles

- Andhariya, J., Jog, R., Shen, J., Choi, S., Wang, Y., Zou, Y., and Burgess, D. *In Vitro-In Vivo Correlation of Parenteral PLGA Microspheres: Effect of Variable Burst Release*. Journal of Controlled Release. (2019) 314:25–37. doi: [10.1016/j.jconrel.2019.10.014](https://doi.org/10.1016/j.jconrel.2019.10.014). PMID: [31654687](https://pubmed.ncbi.nlm.nih.gov/31654687/).
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Posters

- Bao, Q., Zou, Y., Wang, Y., Choi, S., Kozak, D., and Burgess, D. *Source Variation of Outer Membranes on Drug Release from Intrauterine Systems*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.
- Wan, B., Andhariya, J., Wang, Y., Choi, S., Zou, Y., and Burgess, D. *Effect of Polymer Source Variation on In Vitro Drug Release of Leuprolide Acetate Microspheres*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.
- Kohno, M., Andhariya, J., Rothstein, S., Wang, Y., Qin, B., and Burgess, D. *The Effect of PLGA Molecular Weight on Drug Release from Microspheres*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Beig, A., Ackermann, R., Jiang, X., Wang, Y., and Schwendeman, S. *Preparation of Long-Acting Release Microspheres for Octreotide LAR Using Formulation Techniques to Control the Release Kinetics*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 5, 2019.
- Bae, J., Patel, M., Manna, S., Smith, W., Vo, A., Wang, Y., Choi, S., Kozak, D., Zheng, J., and Xu, X. *Impact of Manufacturing Process on Critical Quality Attributes of Multivesicular Liposomes*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
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- Garner, J, Hadar, J., Skidmore, S., Jessmon, F., Park, H., Park, K., Wang, Y., Qin, B., and Jhon, Y. *Effect of Solvent Isomeric Structures on the Dissolution of PLGAs with Different Lactide:Glycolide (L:G) Ratios*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
- Garner, J., Hadar, J., Skidmore, S., Jessmon, F., Park, H., Park, K., Wang, Y., Qin, B., and Jhon, Y. *Use of Optical-Laser-Scanning (OLS) Microscope to Assay Microparticle Morphological Changes*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
- Schutzman, R., Shi, N., and Schwendeman, S. *In Vitro Characterization of Initial Burst Release in Leuprolide-Loaded Poly(Lactic-Co-Glycolic Acid) Microspheres*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
- Smith, W., Bae, J., Vo, A., Wang, Y., Qin, B., Kozak, D., and Xu, X. *Influence of Polymeric Excipients on the Precision of Particle Size Distribution Measurements of Suspensions Using Laser Diffraction*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
- Wan, B., Andhariya, J., Bao, Q., Wang, Y., Choi, S., Zou, Y., and Burgess D. *Effect of Polymer Source Variation on In Vitro Drug Release and Degradation of Peptide Loaded Microspheres*. Poster Presentation at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Meeting, June 29–July 2, 2020.
- Liang, J., Wang, Y., Qin, B., Zhou, J., Schwendeman, S., and Zheng, J. *Micro-Imaging and Microanalysis of PLGA Complex Drug Products by Scanning Electron Microscopy (SEM)*. Poster Presentation at M&M 2020 Annual Meeting. Virtual Meeting, Aug. 6, 2020.

Presentations

- Jiang, W. *Bioequivalence Assessment for Long-Acting Injectables (LAIs) — FDA Regulatory Perspectives*. Presentation at American Association of Pharmaceutical Scientists (AAPS) and The European Federation for Pharmaceutical Sciences (EUFEPS), FDA Co-Sponsored Global Bioequivalence Harmonization Initiative (GBHI): 4th International Workshop. Bethesda, MD, Dec. 12, 2019.
- Burgess, D. *Development of IIVCs for Complex Parenteral Products*. Presentation at 3rd Long-Acting Injectables & Implantables Conference. La Jolla, CA, Feb. 6, 2020.
- Lukacova, V. *What Does It Take to Develop a PBPK Model That Mimics In Vivo Behavior of LAIs*. Presentation at 3rd Long-Acting Injectables & Implantables Conference. La Jolla, CA, Feb. 6, 2020.
- Schwendeman, S. *A Cage Implant to Study Drug Release from Microspheres In Vivo*. Presentation at 3rd Long-Acting Injectables & Implantables Conference. La Jolla, CA, Feb. 6, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Burgess, D. *In Vitro Release Testing and In Vitro In Vivo Correlation of PLGA based drugs: Challenges to Solutions*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Garner, J. *Poly(lactide-co-glycolide) Semi-Solvent Separation: A Tale of Many Polymers in One*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Lionberger, R. *Generics for Long-Acting Injectables: Building a Pathway to Success*. Presentation at 2020 Controlled Release Society Annual Meeting. Virtual Meeting, July 1, 2020.

- Park, K. *PLGA Polymers: The Very Familiar Strangers in Drug Delivery*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Qin, B. *Bioequivalence of Long Acting Injectable (LAI) Suspensions: Current Perspective and Future Directions*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Schwendeman, S. *A Cage Model to Understand the Impact of Raw Materials on Formulation Performance In Vitro and In Vivo*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Wang, Y. *Bioequivalence of Polymeric Long Acting Drugs*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 1–2, 2020.
- Zhao, L. *Leveraging Modeling and Simulation to Make Regulatory Impacts for Long-Acting Generic Drug Approvals*. Presentation at Equivalence of Complex Long Acting Drugs Workshop at 2020 Controlled Release Society Virtual Annual Meeting. Virtual Workshop, July 2, 2020.
- Fang, L. *Model-informed Drug Development for Long-acting Injectable Products*. Presentation at 2020 American College of Clinical Pharmacy (ACCP) Annual Meeting. Virtual Meeting, Sep 21–23, 2020.
- Zhao, L. *Generating Model-Integrated Evidence for Developing & Approving Complex Generic LAI Products*. Presentation at 2020 American College of Clinical Pharmacy (ACCP) Annual Meeting. Virtual Meeting, Sept. 21, 2020.
- Sharan, S. *Model-Informed and Model-Integrated Approaches in BE Assessment of Long Acting Injectable Products*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.



Ophthalmic Products

Summary of FY2020 Activities

In FY2020, research efforts continued to address challenges in the development and selection of appropriate criteria to facilitate the approval of bioequivalent complex generic ophthalmic drug products (e.g., emulsions, ointments, and suspensions). This research area includes three main focus areas: 1) development and testing of new innovative approaches to characterize formulation properties (e.g., drug diffusion and partitioning); 2) identification and characterization of critical physicochemical properties of complex ophthalmic products (particularly those resulting from manufacturing process changes), both in vitro and in animals; and 3) advancement of in silico modeling to better understand how differences in formulation properties impact the ocular pharmacokinetics and/or pharmacodynamics.

Internally, significant progress was made in the development of novel approaches for characterization of ophthalmic ointments, emulsions, and suspensions. For example, FDA researchers developed a new biphasic diffusion method to study the drug diffusion and partitioning in emulsions (see *Research Highlights* below for more details). The new method provides useful information on both the rate and extent of drug distribution, while capturing the changes in the formulation, process, and release environment. Overall, this internal research has allowed for a better understanding of the drug partitioning phenomenon in conditions relevant to those in emulsion drug products and biologically relevant environments. In addition, a new method was also developed internally to evaluate the impact of formulation and manufacturing process variations on quality and release in ophthalmic suspensions.

In addition to FDA's internal efforts, external research projects focused on evaluating critical physicochemical properties of complex ophthalmic products and determining their impact on product performance in vitro and in animals. One project, in collaboration with Absorption Systems, Inc. (Contract# 75F40119F19001), measured the tear film thickness and menisci of a rabbit ocular surface after instillation of cyclosporine ophthalmic emulsion using Optical Coherence Tomography (OCT). Key sources of variability and/or error in OCT were identified and experimental procedures were validated. Another project, in collaboration with the University of Connecticut and Virginia Commonwealth University (Contract# HHSF223201810114C), aimed at investigating in vitro-in vivo correlation of ophthalmic ointments in rabbits. Tobramycin (TOB) and dexamethasone (DEX) ophthalmic ointment was selected as the model drug product. The research team successfully developed and validated a sensitive, rapid, and specific ultra-high-performance liquid chromatography-tandem mass spectrometry method that can simultaneously quantify both TOB and DEX in rabbit ocular matrices including tears, aqueous humor, and cornea. In addition, the research team conducted studies to understand the impact of membranes on in vitro drug release testing of DEX.

As described in more detail in the *FY2020 GDUFA Science and Research Report: Locally-Acting Physiologically-Based Pharmacokinetic Modeling*, advances have been made in ocular physiologically-based pharmacokinetic (PBPK) and pharmacodynamic (PD) in silico models to predict the effect of formulation properties on ocular PK in rabbits and PBPK/PD model scale-up from preclinical species to human. Results of the aforementioned contract with Absorption Systems will be used to validate the developed PK/PD models. In addition, two new external grants were awarded to Simulations Plus, Inc. (Grant# 1U01FD006927) and CFD Research Corporation (Grant# 1U01FD006929) to develop and validate PBPK/PD modeling strategy for ophthalmic drug products to support translation from preclinical species to human and to use Computational Biology (Cobi) tools as a framework for PBPK/PD model extrapolation to human from rabbit for ophthalmic drug products, respectively.

Research Highlights

Ophthalmic emulsions contain multiple components, including oil phase, aqueous phase, and micelles. As a result, ophthalmic emulsions exhibit complex drug transfer and equilibrium phenomena. The aim of this research is to develop a new analytical method to investigate the process of drug transfer and the mechanism of drug release from emulsions. With the new method (Figure 1), the diffusion rate constants for both the oil-to-aqueous and aqueous-to-oil were determined. Specifically, three formulation variables and five release environment factors were studied. The changes in diffusion rate constants by both formulation and release environment changes provided valuable insight into the drug distribution and transfer in ophthalmic emulsions. For example, surfactant such as polysorbate 80 played a significant role in drug transfer and distribution: it promoted the formation of micelles in the aqueous phase and hence the solubilization of drug in the aqueous phase. This led to an increase in both the rate and extent of drug transfer towards the aqueous phase. Additionally, oil globule size exhibited an effect on drug transfer and drug distribution. Specifically, a decrease in oil globule size resulted in an increase in oil/water interfacial area, which significantly enhanced the rate of drug transfer towards aqueous phase. Subsequently, the increase in oil/water surface area reduced the amount of surfactant that can form micelles (Figure 2), and therefore resulted in reduced micellar solubilization and reduced drug transfer towards the aqueous phase. Detailed analysis of these examples and others were published in two articles: Dong, Y. et al. *Journal of Controlled Release* (2019), and Dong, Y. et al. *Journal of Controlled Release* (2020).

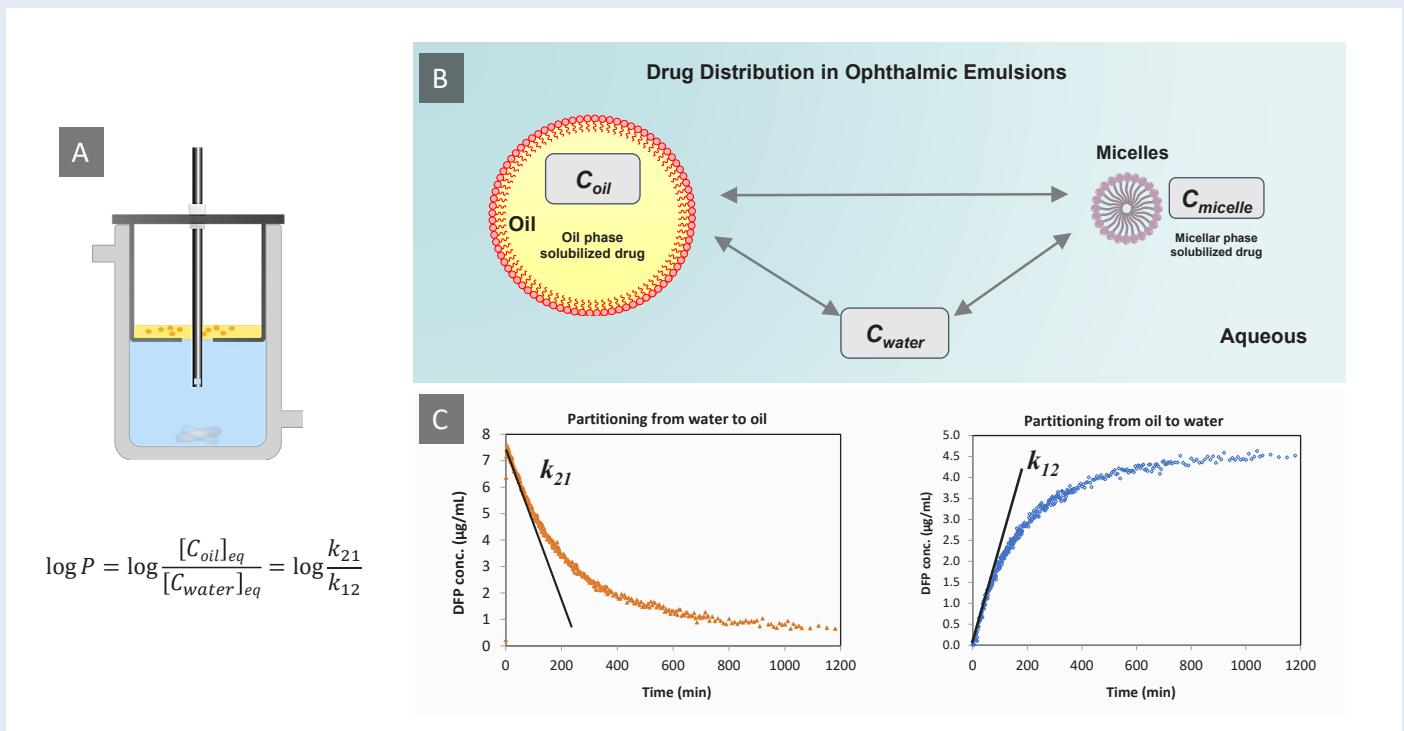


Figure 1: A) The experimental setup for evaluating the effects of formulation variables, including the fiber optic dissolution workstation and 25 mL mini vessels; B) The phase composition and complex drug diffusion in the microenvironment of an emulsion formulation; C) Profiles of biphasic drug diffusion detected by in-situ UV fiber optic probes using difluprednate as model drug, where the black solid line indicates the initial slope.

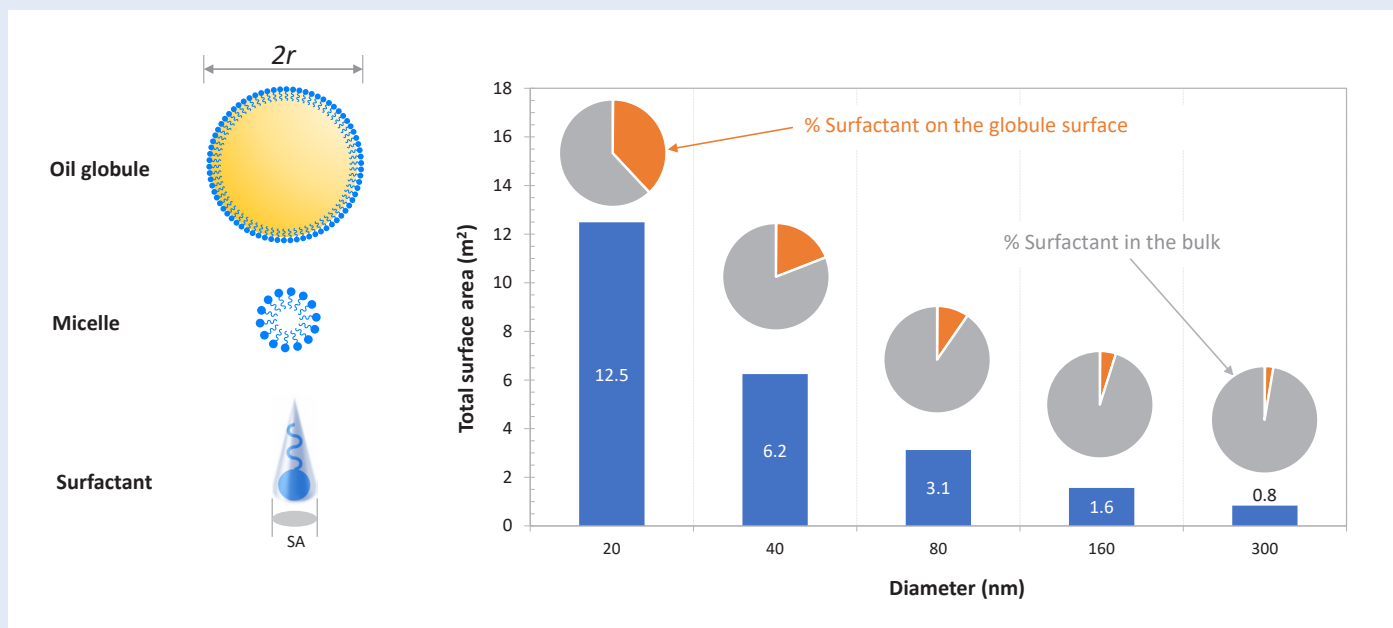


Figure 2: Schematic showing the structure of oil globule (with surfactant), micelle, and individual surfactant shape; and the estimation of total globule surface area and relative distribution of surfactant with varying globule sizes. From Dong, Y. et al. *Journal of Controlled Release* (2019). 313, pp 96-105.

Research Projects and Collaborations

New Grants and Contracts

- Grant (1U01FD006929) *Computational Biology (Cobi) Tools as a Framework for Physiologically-Based Pharmacokinetic/ Pharmacodynamic Model Extrapolation from Rabbit to Human for Ophthalmic Drug Products* with Carrie German at CFD Research Corporation
- Grant (1U01FD006927) *Development and Validation of a PBPK/ PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human* with Jessica Spires at Simulations Plus, Inc.
- Contract (75F40119F19002) *PK/PD of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Absorption Systems, Inc.

Continuing Grants and Contracts

- Contract (75F40119D10024-75F40119F19001) *Tear Film Thickness and Menisci Measurements on Rabbit Ocular Surface After Instillation of Cyclosporine Ophthalmic Emulsion* with Glenwood Gum at Absorption Systems, Inc.

Completed Grants and Contracts

- Contract (HHSF223201810255P) *Simulation Plus Ophthalmic Ointment Implementation* with Jessica Spires at Simulations Plus, Inc.

Active FDA Research

- *Ophthalmic Antimicrobial Kill Rate Study*
- *Physicochemical Characterization of Topical Ophthalmic Suspension Products*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

Outcomes

Product-Specific Guidances (PSGs)

There were six new and one revised PSGs published in FY2020 related to ophthalmic products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Besifloxacin Hydrochloride Ophthalmic Suspension, Drops.* (Mar. 2, 2020) [Link to Posting](#).
- *New Draft Guidance for Fluorometholone Ophthalmic Suspension, Drops.* (June 3, 2020) [Link to Posting](#).
- *New Draft Guidance for Latanoprost Ophthalmic Emulsion.* (June 3, 2020) [Link to Posting](#).
- *Revised Draft Guidance for Loteprednol Etabonate; Tobramycin Ophthalmic Suspension, Drops.* (Aug. 28, 2020) [Link to Posting](#).
- *New Draft Guidance for Timolol Maleate Ophthalmic Solution, Gel Forming/Drops.* (Nov. 21, 2019) [Link to Posting](#).

Articles

- Matter, B., Ghaffari, A., Bourne, D., Wang, Y., Choi, S., and Kompella, U. *Dexamethasone Degradation in Aqueous Medium and Implications for Correction of In Vitro Release from Sustained Release Delivery Systems.* AAPS PharmSciTech. (2019) 20(8):320. doi: [10.1208/s12249-019-1508-7](https://doi.org/10.1208/s12249-019-1508-7). PMID: [31646399](https://pubmed.ncbi.nlm.nih.gov/31646399/).
- Dong, Y., Hengst, L., Hunt, R., Feng, X., Kozak, D., Choi, S., Ashraf, M., and Xu, X. *Evaluating Drug Distribution and Release in Ophthalmic Emulsions: Impact of Release Conditions.* Journal of Controlled Release. (2020) 327:360–370. doi: [10.1016/j.jconrel.2020.08.020](https://doi.org/10.1016/j.jconrel.2020.08.020). PMID: [32822741](https://pubmed.ncbi.nlm.nih.gov/32822741/).
- LeMerdy, M., Tan, M., Babiskin, A., and Zhao, L. *Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development.* AAPS Journal. (2020) 22(2):26. doi: [10.1208/s12248-019-0408-9](https://doi.org/10.1208/s12248-019-0408-9). PMID: [31907674](https://pubmed.ncbi.nlm.nih.gov/31907674/).
- Vo, A., Feng, X., Patel, D., Mohammad, A., Kozak, D., Choi, S., Ashraf, M., and Xu, X. *Factors Affecting the Particle Size Distribution and Rheology of Brinzolamide Ophthalmic Suspensions.* International Journal of Pharmaceutics. (2020) 586: doi: [10.1016/j.ijpharm.2020.119495](https://doi.org/10.1016/j.ijpharm.2020.119495). PMID: [32553495](https://pubmed.ncbi.nlm.nih.gov/32553495/).
- Vo, A., Feng, X., Patel, D., Mohammad, A., Patel, M., Zheng, J., Kozak, D., Choi, S., Ashraf, M., and Xu, X. *In Vitro Physicochemical Characterization and Dissolution of Brinzolamide Ophthalmic Suspensions with Similar Composition.* International Journal of Pharmaceutics. (2020) 588: doi: [10.1016/j.ijpharm.2020.119761](https://doi.org/10.1016/j.ijpharm.2020.119761). PMID: [32795488](https://pubmed.ncbi.nlm.nih.gov/32795488/).

- Vooturi, S., Bourne, D., Jyoti Panda, J., Choi, S., Kim, H., Yandrapu, S., and Kompella, U. *Effect of Particle Size and Viscosity of Suspensions on Topical Ocular Bioavailability of Budesonide, a Corticosteroid*. *Journal of Ocular Pharmacology and Therapeutics*. (2020) 36(6):404–409. doi: [10.1089/jop.2019.0150](https://doi.org/10.1089/jop.2019.0150). PMID: [32678687](https://pubmed.ncbi.nlm.nih.gov/32678687/).

Posters

- Vo, A., Feng, X., Kozak, D., Choi, S., and Xu, X. *Pitfalls and Challenges of Analyzing Particle Size Distribution in Ophthalmic Suspensions Using Laser Diffraction*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.
- Vo, A., Feng, X., Patel, D., Patel, M., Kozak, D., Choi, S., Zheng, J., and Xu, X. *Impact of Manufacturing Processes on Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.
- Dong, Y., Hengst, L., Hunt, R., Patel, D., Vo, A., Choi, S., Ashraf, M., Cruz, C., and Xu, X. *Understanding Drug Distribution and Release in Ophthalmic Emulsions*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Smith, W., Vo, A., Bae, J., Wang, Y., Qin, B., Kozak, D., and Xu, X. *Influence of Polymeric Excipients on the Precision of Particle Size Distribution Measurements of Suspensions Using Laser Diffraction*. Poster Presentation at 2020 Controlled Release Society. Virtual Meeting, June 29, 2020.
- Patel, M., Manna, S., Vo, A., Xu, X., Conti, D., Choi, S., Kozak, D., Zheng, J. *Scanning Electron Microscope (SEM) Coupled with Energy Dispersive X-Ray Spectroscopy (EDS)— A Potential Analytical Tool for Physico-Chemical Characterization of API in Complex Drug Formulations*. *Microscopy & Microanalysis (M&M) Annual Meeting*. Virtual Meeting. August 02, 2020.

Presentations

- Zhao, L. *Regulatory Challenges and Opportunities for Model-Based Approaches for Patient Pharmacokinetic (PK) Studies with Sparse Sampling Design*. Presentation at American Conference on Pharmacometrics (ACoP10). Orlando, FL, Oct. 22, 2019.
- Kozak, D. *GDUFA Regulatory Science Research on In Vitro Bioequivalence Methods*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Xu, X. *Look & See: Innovative Research to Address Regulatory Challenges in Complex Ophthalmic Drug Products*. Presentation at 2020 Controlled Release Society Annual Meeting. Virtual Meeting, Jun. 30, 2020.
- Kozak, D. *Formulation Assessments: General Q1/Q2 Inquiries to Supporting Complex Excipient Sameness*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.
- Xu, X. *Developing and Validating Commonly Employed Particle Sizing Methods to Support Bioequivalence and Product Quality*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 29, 2020.



Oral Absorption Models and Bioequivalence

Summary of FY2020 Activities

The extramural and intramural projects in FY2020 cover a spectrum of scientific areas primarily aiming to (1) expand biowaiver for Biopharmaceutical Classification System (BCS) Class III Drugs, (2) enhance physiologically-based pharmacokinetic (PBPK) modeling capabilities, and (3) evaluate bioequivalence (BE) approaches and standards for product-specific guidance (PSG) development and global harmonization.

1. Expand biowaiver for BCS Class III drugs beyond products that are formulated to be Q1/Q2 to the reference listed drug (RLD) (i.e., qualitatively (Q1) the same and quantitatively (Q2) similar to the corresponding RLD product)

To minimize unnecessary in vivo BE studies, PSGs for developing generic versions of orally administered immediate release dosage forms of BCS Class III drugs may recommend waiver of in vivo BE studies, provided that the products are formulated to be Q1/Q2 to the RLD and have acceptable in vitro dissolution data. Otherwise, further justifications are needed as differences in excipients may impact drug absorption. Three extramural projects aim to study the impact of excipients on drug absorption to potentially expand biowaiver beyond Q1/Q2 products. One project (Grant# 1U01FD005978-P2) has screened in vitro interactions of excipients with intestinal drug transporters. The findings have led to a new clinical study (Grant# 3U01FD005978-04S3) to assess the effect of one excipient on the bioavailability of a model drug. (See the *Research Highlight* section for details.) Another ongoing project (Contract# 75F40119C10127) employs an in vitro dissolution-absorption system to evaluate the effect of frequently used excipients on the permeability of BCS Class III drugs.

Additionally, there is an ongoing internal research project that explores the space of formulation differences with BE findings for BCS Class 3 drugs. To this end, as the first step, the formulations and BE study results of the approved generic products containing potential BCS Class 3 drug substances have been investigated. Further evaluation of these products is being undertaken to determine if they meet the solubility and dissolution criteria for a bio-waiver of BCS Class 3 drug products.

2. Enhance PBPK modeling capabilities

For this aim, one project (Grant# 1U01FD005865) focused on predicting supersaturation and precipitation behavior of orally administered drug products. Taking into consideration the in vitro data and relevant in vivo evidence, these efforts resulted in progressive changes implemented in Simcyp software (Versions 18, 19, and 20) to account for formulation factors (e.g., wetting, disintegration, amorphous solid dispersion, excipient-drug complexation), time-variant bile salt concentrations, in vivo precipitation parameters and the associated population variability. These were discussed in publications, presentations, and workshops to share with the pharmaceutical community, forging one crucial step forward in utilizing oral absorption PBPK modeling for predicting the impact of formulation differences on in vivo performance. Another project (Contract# HHSF223201510146C) aimed to develop a prototype wireless device for direct gastrointestinal (GI) fluid sampling to enable generation of in vivo drug dissolution profiles along the GI tract to help verify PBPK models.

3. Assess BE approaches and standards for PSG development and global harmonization

This section includes the following four intramural research projects:

Identification of Critical Factors for Oral Solution Bioequivalence:

By studying eight regulatory agencies' BE study recommendations for oral solution products, potential areas for PSG development and global harmonization regarding biowaiver for oral solution products have been identified.

Physicochemical Characterization of Sucralfate Tablets to Support

In Vitro BE Methods: The study identified key in vitro tests that have facilitated an in vitro approach for BE demonstration of sucralfate tablet.

Dissolution Measurements of Extended Release (ER) Product to

Support the Development of Predictive Models of BE: An in-house dissolution apparatus was developed to study the effect of simulated GI contractions on drug release from ER products, which suggest that modified dissolution testing devices may generate additional metrics for quality assurance and BE assessment.

Improvement of Drug Dissolution Method for Application to Nano-

crystal Drugs: Using USP Apparatus 2 for fenofibrate and celecoxib, preliminary results suggest an approximately 5% difference between filtered and unfiltered samples, possibly due to nanoparticle interference on the assay.

Research Highlight

A study was conducted to enhance our understanding on the impact of excipients on drug absorption as part of an initiative to potentially expand biowaivers to non-Q1/Q2 generic versions of BCS Class III drugs. In FY2020, the focus was on the interaction between excipients and organic anion transporting polypeptide 2B1 (OATP2B1), which is an uptake transporter abundantly expressed in the intestine and transports drugs such as antihistamines, statins, and antihypertensive agents. An in vitro assay method (see Figure 1) was developed which employed a stable OATP2B1-overexpressing cell line (human embryonic kidney (HEK) Flp-In cells) and used the fluorescent molecule 4',5'-dibromofluorescein (DBF) as the probe substrate for OATP2B1 uptake ($K_m=4.7 \mu\text{M}$) along with estrone sulfate (ES) as the positive control for OATP2B1 inhibition. A total of 136 excipients commonly used in oral dosage forms were screened, including dyes, buffering agents, antimicrobial agents, flavoring agents, and surfactants. Considering that the amount of excipients in an oral drug product can outweigh the active ingredient by more than 10-fold, the concentration of excipients at screening was $200 \mu\text{M}$ (10-fold above the standard $20 \mu\text{M}$ used in drug screens). Using an inhibition of OATP2B1 transport by $>50\%$ as the criterion, 24 excipients were identified as OATP2B1 inhibitors, which were chemically and functionally diverse but tended to have higher molecular weight and lipophilicity among the excipients tested. The findings of this study indicated a potential influence of excipients on the bioavailability of drugs that are OATP2B1 substrates. Weighing on the OATP2B1 inhibition potency of sodium lauryl sulfate (inhibition constant, $K_i = 1.98 \mu\text{M}$) and its quantity in oral drug products, Grant# 3U01FD005978-04S3 was awarded in FY2020 to determine how the in vitro findings translate into clinical significance using a tablet product of fexofenadine, an OATP2B1 substrate, as the model drug product.

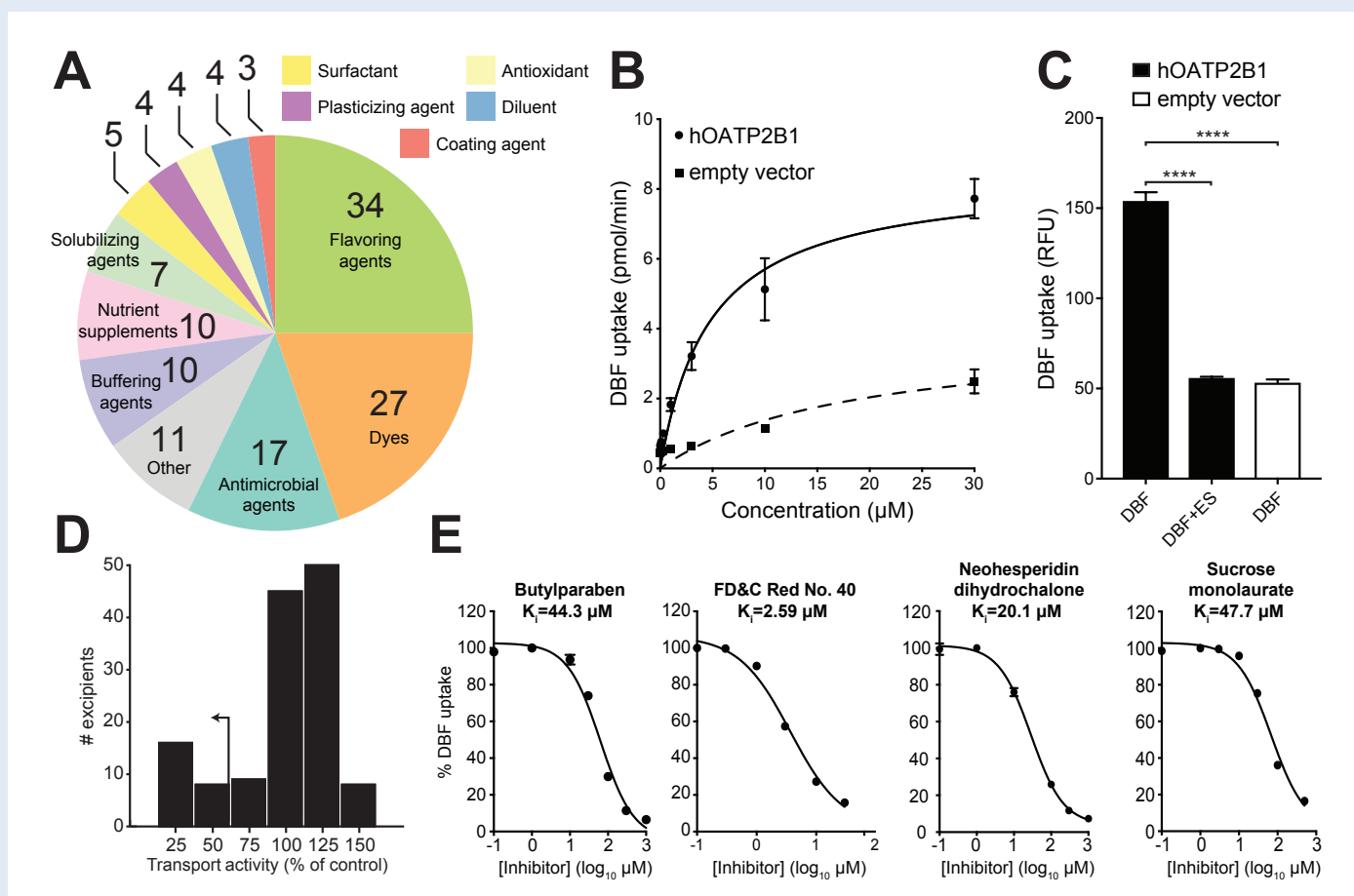


Figure 1. Multiple Oral Excipients Inhibit OATP2B1-mediated Transport. [Permission obtained from the journal Proc Natl Acad Sci (PNAS) and Dr. Giacomini]²⁹ (A) Functional categories of the 136 oral molecular excipients included in the screen. (B) Kinetics of human OATP2B1-mediated DBF uptake. Human OATP2B1-overexpressing (circles) and empty vector-transfected HEK cells (squares) were incubated with DBF from 0.01 μM to 30 μM for 2 min. Data points represent the mean \pm SD of DBF uptake from three or more replicate determinations in three experiments. (C) Human OATP2B1-overexpressing HEK cells (black bars) were incubated in HBSS uptake buffer containing 2 μM DBF for 3 min with or without 200 μM estrone sulfate (ES). Empty vector-transfected HEK cells (white bar) were assayed as above for background DBF uptake determination. Each column represents the mean \pm SD of DBF uptake from eight replicate determinations. **** $P < 0.0001$, ANOVA with Dunnett's correction. (D) Histogram showing the inhibition results of screening 136 excipients against OATP2B1 uptake. The <50% transport activity cutoff is indicated by the arrow. (E) Dose-response curves of excipients against OATP2B1 transport. A representative excipient from each functional category is shown. Values represent the mean \pm SD of DBF uptake from three replicate determinations in a single experiment with the bold line representing the median. Points outside the bars are shown as open circles. P values represent Student's t tests.

29 Zou, L., et al., *Bacterial Metabolism Rescues the Inhibition of Intestinal Drug Absorption by Food and Drug Additives*. Proc Natl Acad Sci U S A. (2020) 117(27):16009; doi: 10.1073/pnas.1920483117. PMID: 32571913.

Research Projects and Collaborations

New Grants and Contracts

- Grant (3U01FD005978-04S3) *The Effect of Excipients on the Oral Absorption of Fexofenadine in Humans* with Kathleen M. Giacomini at University of California, San Francisco
- Contract (75F40120C00150) *Robust in vitro/in silico Model to Accelerate Generic Drug Product Development for the Oral Cavity Route of Administration* with Giovanni Pauletti at St. Louis College of Pharmacy
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive in Vitro Dissolution-Models* with Duxin Sun at University of Michigan

Continuing Grants and Contracts

- Contract (HHSF223201610004I) *A Randomized, Open Label, Two Treatment, Four Period, Single Dose, Fully Replicate, Crossover Bioequivalence (BE) Study of Tacrolimus Capsules* with Artan Markollari at Biopharma Services
- Contract (75F40119C10127) *Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2* with Chris Bode at Absorption Systems
- Contract (HHSF223201810112C) *Research to Better Understand Risk Mitigation in The Evaluation of Relative Bioavailability of Pediatric Generic Products* with Marie-Christine Jones at University of Birmingham

Completed Grants and Contracts

- 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.
- Grant (1U01FD005978-P2) *Effect of Excipient Transporter Interactions on BCS Class Drugs* with Kathleen M Giacomini at University of California, San Francisco

- Contract (HHSF223201510146C) *Wireless Sampling Pill to Measure In Vivo Drug Dissolution in GI Tract and Computational Model to Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients with Duxin Sun at University of Michigan*

Active FDA Research

- *Analysis of the Predictability of Bioequivalence in the Fed State*
- *Baseline Correction in Bioequivalence Studies for Drug Products Containing an Endogenous Compound*
- *Best Practice for Using Physiologically Based Pharmacokinetic (PBPK) Modeling for Orally Absorbed Generic Drug Products*
- *Comparison of Steady State and Single Dose BE Studies for Modified Release (MR) Products*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Dissolution Measurements of ER Product to Support the Development of Predictive Models of BE*
- *Evaluation of the Need for Sprinkle BE Studies for MR products*
- *Identification of Critical Factors for Oral Solution Bioequivalence*
- *Identification of the Critical BE Issues for Gastro-Retentive Delivery Systems*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *In Vitro Method Development to Assess Drug Product Integrity when Sprinkled on Soft Food for Ease of Oral Administration*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *Physicochemical Characterization of Sucralfate Tablets to Support In Vitro BE Methods*
- *Prioritization and Optimization of BE Guidances for MR Products*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based Supports for Bioequivalence Assessment During the COVID-19 Public Health Emergency*

- *Solubility and Multi-media Dissolution Testing on Immediate Release Drug Products of BCS 3 Potentials*
- *Verification of Pharmaceutical Quality of the Tacrolimus Products Prior to In Vivo BE Study*

Outcomes

Product-Specific Guidances (PSGs)

There were 69 new and 59 revised PSGs published in FY2020 related to oral absorption models and bioequivalence. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance on Abiraterone Acetate Oral Tablet (NDA 210308) (June 3, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Albendazole Oral Tablet (June 3, 2020) [Link to Posting](#).*
- *New Draft Guidance on Budesonide Oral Capsule, Extended Release (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Carglumic Acid Oral Tablet (June 3, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Didanosine Oral Capsule, Delayed Release Pellets (Nov. 21, 2019) [Link to Posting](#).*
- *New Draft Guidance on Duloxetine Hydrochloride Oral Capsule, Delayed Release (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Edoxaban Tosylate Oral Tablet (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Ferric Citrate Oral Tablet (June 3, 2020) [Link to Posting](#).*
- *Final Guidance on Hydroxychloroquine Sulfate Oral Tablet (Apr. 13, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Ibrutinib Oral Capsule (Mar. 2, 2020) [Link to Posting](#).*
- *New Draft Guidance on Rifamycin Sodium Oral Tablet, Delayed Release (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Tipiracil Hydrochloride; Trifluridine Oral Tablet (Nov. 21, 2019) [Link to Posting](#).*

Articles

- Arora, S., Pansari, A., Kilford, P., Jamei, M., Gardner, I., and Turner, D. *Biopharmaceutic In Vitro In Vivo Extrapolation (IVIV_E) Informed Physiologically-Based Pharmacokinetic Model of Ritonavir Norvir Tablet Absorption in Humans Under Fasted and Fed State Conditions*. *Mol Pharm.* (2020) 17(7):2329: doi: [10.1021/acs.molpharmaceut.0c00043](https://doi.org/10.1021/acs.molpharmaceut.0c00043). PMID: [32427480](https://pubmed.ncbi.nlm.nih.gov/32427480/).
- Bermejo, M., Hens, B., Dickens, J., Mudie, D., Paixao, P., Tsume, Y., Shedden, K., and Amidon, G. *A Mechanistic Physiologically-Based Biopharmaceutics Modeling (PBBM) Approach to Assess the In Vivo Performance of an Orally Administered Drug Product: From IVIVC to IVIVP*. *Pharmaceutics*. (2020) 12(1): doi: [10.3390/pharmaceutics12010074](https://doi.org/10.3390/pharmaceutics12010074). PMID: [31963448](https://pubmed.ncbi.nlm.nih.gov/31963448/).
- Dong, Z., Li, J., Wu, F., Zhao, P., Lee, S-C., Zhang, L., Seo, P., and Zhang, L. *Application of Physiologically-Based Pharmacokinetic Modeling to Predict Gastric pH-Dependent Drug-Drug Interactions for Weak Base Drugs*. *CPT: pharmacometrics & systems pharmacology*, (2020) 9(8): 456–465. doi: [10.1002/psp4.12541](https://doi.org/10.1002/psp4.12541). PMID: [32633893](https://pubmed.ncbi.nlm.nih.gov/32633893/).
- Gao, Z., Tian, L., and Rodriguez, J. *Nifedipine Release from Extended-Release Solid Oral Formulations Using In Vitro Dissolution Testing Under Simulated Gastrointestinal Compression*. *Journal of Pharmaceutical Sciences*. (2020) 109(7):2173{2179. doi: [10.1016/j.xphs.2020.03.023](https://doi.org/10.1016/j.xphs.2020.03.023). PMID: [32240693](https://pubmed.ncbi.nlm.nih.gov/32240693/).
- Miao, L., Mousa, Y., Zhao, L., Raines, K., Seo, P., and Wu, F. *Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations*. *AAPS J.* (2020) 22(5):107. doi: [10.1208/s12248-020-00493-6](https://doi.org/10.1208/s12248-020-00493-6). PMID: [32779046](https://pubmed.ncbi.nlm.nih.gov/32779046/).
- Pottel, J., Armstrong, D., Zou, L., Fekete, A., Huang, X-P., Torosyan, H., Bednarczyk, D., Whitebread, S., Bhatarai, B., Liang, G., Jin, H., Ghaemi, N., Slocum, S., Lukacs, K., Irwin, J., Berg, E., Giacomini, K., Roth, B., Shoichet, B., and Urban, L. *The Activities of Drug Inactive Ingredients on Biological Target*. *Science*. (2020) **369**(6502): 403–413. doi: [10.1126/science.aaz9906](https://doi.org/10.1126/science.aaz9906). PMID: [32703874](https://pubmed.ncbi.nlm.nih.gov/32703874/).

- Stamatopoulos, K., Pathak, S., Marciani, L., and Turner, D. *Population-Based PBPK Model for the Prediction of Time Variant Bile Salt Disposition within GI Luminal Fluids*. Mol Pharm. (2020) 17(4):1310: doi: [10.1021/acs.molpharmaceut.0c00019](https://doi.org/10.1021/acs.molpharmaceut.0c00019). PMID: [32176503](https://pubmed.ncbi.nlm.nih.gov/32176503/).
- Zou, L., Pottel, J., Khuri, N., Ngo, H., Ni, Z., Tsakalozou, E., Warren, M., Huang, Y., Shoichet, B., and Giacomini, K. *Interactions of Oral Molecular Excipients with Breast Cancer Resistance Protein, BCRP*. Mol Pharm. (2020) 17(3):748: doi: [10.1021/acs.molpharmaceut.9b00658](https://doi.org/10.1021/acs.molpharmaceut.9b00658). PMID: [31990564](https://pubmed.ncbi.nlm.nih.gov/31990564/).
- Zou, L., Spanogiannopoulos, P., Pieper, L., Chien, H-C., Cai, W., Khuri, N., Pottel, J., Vora, B., Ni, Z., Tsakalozou, E., Zhang, W., Shoichet, B., Giacomini, K., and Turnbaugh, P. *Bacterial Metabolism Rescues the Inhibition of Intestinal Drug Absorption by Food and Drug Additives*. Proc Natl Acad Sci U S A. (2020) 117(27):16009: doi: [10.1073/pnas.1920483117](https://doi.org/10.1073/pnas.1920483117). PMID: [32571913](https://pubmed.ncbi.nlm.nih.gov/32571913/).

Posters

- Hakeem, S., Huang, Y-C., Zhang, L., and Jiang, W. *Evaluation of U.S. FDA Approved Generic Oral Solution Products*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 3, 2019.
- Chan, T., Ren, P., Yang, W., Wang, Y., Luke, M. C., Jiang, X., and Zhang, Y. *Excipient Similarity in Generic Formulations Containing Biopharmaceutics Classification System 3 Drugs*. Poster Presentation at AAPS 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Li, M., Gao, Z., Tang, F., Choi, S., Toth, R., and Rodriguez, J. *Assessment of the Impact of Drug Dissolution on Pharmacokinetics of Diltiazem Extended Release Drug Products Using Physiologically Based Pharmacokinetic Analysis*. AAPS 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Miao, L., Wu, F., Moldthan, H., Xu, D., Zhao, L., Raines, K., and Seo, P. *Application of Physiologically-Based Pharmacokinetic Absorption Modeling and Simulations for Biopharmaceutics: Risk Assessment and Control of*

Critical Quality Attributes for Medical Countermeasure Drug Products. Poster Presentation at AAPS 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.

- Gao, Z., Patel, S., Li, M., Tang, F., Harris, B., Toth, R., Choi, S., and Rodriguez, J. *Dissolution Testing of Diltiazem HCl Extended-Release Capsule Products*. Poster Presentation at AAPS 2019 Pharmsci 360. San Antonio, TX, Nov. 5, 2019.
- Li, M., Gao, Z., Tang, F., Choi, S., Toth, R., and Rodriguez, J. *Assessment of the Impact of Drug Dissolution on Pharmacokinetics of Diltiazem Extended Release Drug Products Using Physiologically Based Pharmacokinetic Analysis*. Poster Presentation at AAPS 2019 Pharmsci 360. San Antonio, TX, Nov. 5, 2019.
- Miao, L., Wu, F., Zhao, L., Raines, K., and Seo, P. *Using a Physiologically-based Pharmacokinetic Absorption Model to Establish Clinically Relevant Dissolution Safe space for Oseltamivir in Adult and Pediatrics*. Poster Presentation at AAPS 2019 Pharmsci 360. San Antonio, Texas, Nov. 6, 2019.
- Zou, L., Spanogiannopoulos, P., Chien, H., Pieper, L., Cai, W., Khuri, N., Pottel, J., Vora, B., Ni, Z., Tsakalozou, E., Zhang, W., Shoichet, B., Turnbaugh, P., and Giacomini, K. *Bacterial Metabolism Rescues the Inhibition of Intestinal Drug Absorption by Food and Drug Addictives*. Poster Presentation at 2020 Innovations in Regulatory Science Summit. San Francisco, CA, Jan. 12, 2020.
- Pawar, G., Wu, F., Zhao, L., Fang, L., Burckart, G., Feng, K., Mousa, Y., Naumann, F., and Batchelor, H. *Development of a Database Containing Clinical Data on Bioequivalence and Relative Bioavailability Studies Conducted in Pediatric Populations*. Poster presentation at 12TH Annual Conference European Paediatric Formulation Initiative (EUPFI). Virtual, Sept. 9–10, 2020.
- Chan, T., Ren, P., Yang W-C., Wang, Y., Luke M. C., Kim M-J., and Zhang Y. *Assessment on the Formulation Similarity of Approved Generic Drug Products and their Respective Reference Products Which are Considered as Potential BCS Class 3 Drugs*. Poster presentation at American College of Clinical Pharmacology (ACCP) 2020 Annual Meeting. Virtual, Sept. 21–23, 2020.

Presentations

- Wu, F. *Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs*. Presentation at AAPS 2019 Pharmsci 360. San Antonio, Texas, Nov. 6, 2019.
- Turner, D. *Updates to the Simcyp Simulator's ADAM / M-ADAM Models*. SIMCYP Webinar. Jan 29, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Arora, S. *Biopharmaceutic in Vitro In Vivo Extrapolation (IVIV_E) Informed PBPK Model of Ritonavir Norvir Tablet Absorption in Humans Under Fasted and Fed Conditions*. Simcyp Consortium Members Webinar. Jun. 18, 2020.
- Gong, X. *Alternatives to f2 Testing for Dissolution Similarity — f2 Bootstrapping and MSD Method*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.
- Wu, F. *Using Physiologically-Based Pharmacokinetic Absorption Modeling to Support Biopharmaceutics Classification System Class 3 Drug Waiver*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.
- Zhang, Y. *Biopharmaceutics Classification System Class 3 Waiver*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop. Virtual Meeting, Sept. 30, 2020.



Patient Substitution of Generic Drugs

Summary of FY2020 Activities

To better understand the substitutability of generic drug products for patients, FDA funds research projects 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.

One highlight was *Characterizing Safety and Efficacy of Brand and Generic Drugs Used to Treat Hypothyroidism Among Patients Who Switch Therapy Formulation* (U01FD005938). This was a retrospective study using national administrative claims database study to compare the effectiveness of generic versus brand-name L-thyroxine in achieving normal thyroid stimulating hormone levels. This study showed a similar proportion of generic versus brand L-thyroxine users achieved target thyroid stimulating hormone levels. The initiation of generic or brand L-thyroxine for mild thyroid dysfunction was found to be associated with similar rates of achieving target laboratory outcomes.

In addition to projects with external collaborators, an FDA internal research project on “Postmarket Surveillance of Advair Diskus and Wixela Inhub Using Sentinel” is being conducted using the administrative data of Sentinel’s data partners. The objective of the study is to proactively investigate the adoption and post-approval use of the first approved generic of Advair Diskus called Wixela Inhub. This study was divided into two parts. The first part of the study was designed to understand the treatment landscape in Sentinel’s data partners by studying the following: 1) number of users of inhaled corticosteroids (ICS)/long acting beta agonists (LABA) combination products and the baseline characteristics of these users; 2) follow-up time for users of ICS/LABA combination products; 3) duration of first continuous use for users of ICS/LABA combination products; and 4) switching patterns between Advair Diskus and other ICS/LABA products. This part of the study has been completed. It showed that there is substantial use of brand ICS/LABA products in Sentinel data and the pattern of use of different products has changed over time. There has been an increase in asthma diagnosis since September 2015 and this may be related to the conversion from International Classification of Diseases (ICD)-9 to ICD-10. Asthma and chronic obstructive pulmonary disease (COPD) cohorts are different with respect to factors such as age (asthma patients in their 50s; COPD patients in their 70s), sex (asthma patients 67% female; COPD patients 57% female), race (asthma 48% white and 9% Black; COPD 80% white and 8% Black), baseline conditions (respiratory failure in 3% asthma patients and in 23% COPD patients), and baseline medications use. The median duration of follow up for various products for asthma patients ranged from 241 days to 824 days and for COPD patients, the range was 342 days to 1,061 days. The duration of continuous ICS/LABA use is short (>50% of treatment episodes comprised of 1–2 prescription refills). The switching patterns between various products were similar; only a small proportion of Advair Diskus users switched to another ICS/LABA product and >50% of the switches occurred within 90 days. The second part of the study is designed to review the data for Wixela Inhub and the authorized generic for Advair Diskus. This part of the study will be conducted at a later date to allow for accrual of the usage data for Wixela Inhub and to allow for data delays in Sentinel.

Research Highlight

Two recently-completed studies demonstrate the comparability of treatment outcomes for generic vs. brand narrow therapeutic index (NTI) drug products, one in patients with hypothyroidism and another in a senior population treated with anticoagulation agents. The first study (see Brito et al., 2020) compared patient outcomes within 3 months after treatment with generic or brand name levothyroxine products, characterizing the proportions of patients with normal thyroid stimulating hormones (TSH) levels (4.5–19.9 mIU/L) or markedly abnormal TSH levels (<0.1mIU/L or >10mIU/L), in order to determine if there was a difference in the treatment effect or lack thereof, respectively. After 1:1 matching between the generic and brand-name drug initiators, the results showed that the proportion of patients with normal or markedly abnormal TSH level within 3 months of filling L-thyroxine prescriptions was similar for patients who received generic vs. brand L-thyroxine, 75.4% vs. 76.9% (Figure 1), $p=0.23$ or 4.1% vs. 3.9%, $p=0.65$, respectively. The second study, with warfarin (see Desai et al., 2020) showed a comparable effectiveness, safety, and risk of all-cause mortality between initiators of brand and generic warfarin products in the Medicare population. These studies provide real-world evidence to support public confidence in the generic NTI drugs.

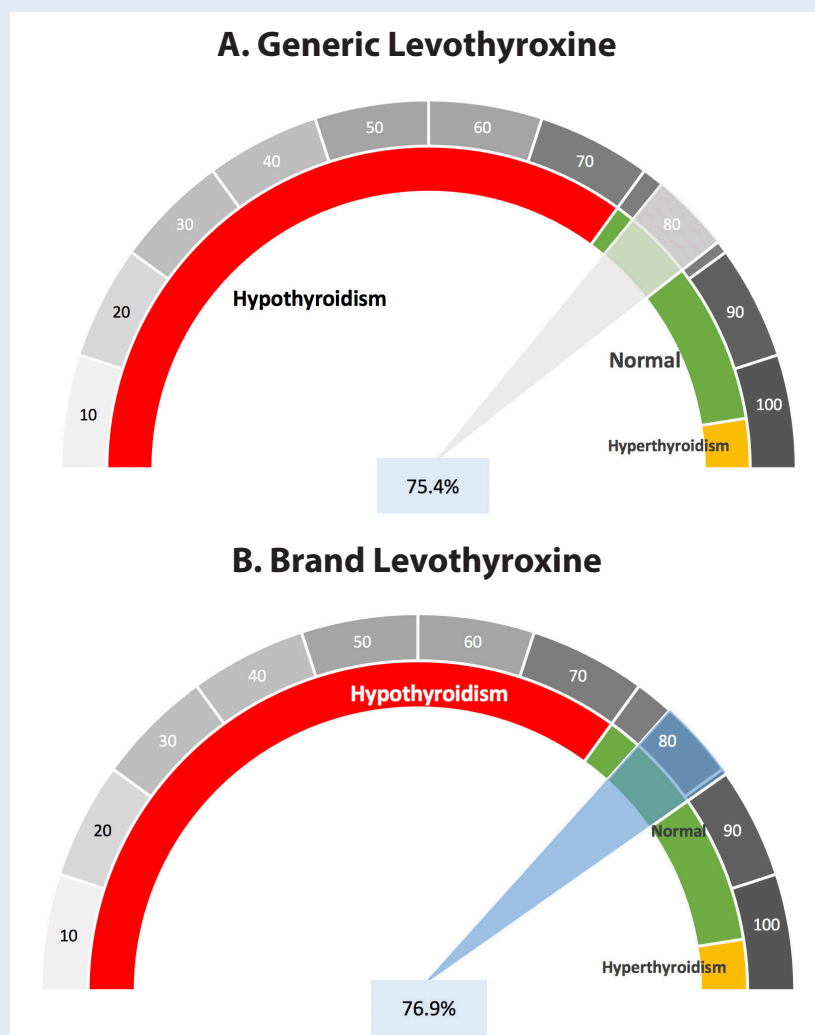


Figure 1: Comparison of generic vs. brand-name levothyroxine in restoring normal levels of thyroid stimulating hormone (TSH) levels. In the images shown here, the spectrum of gray shades indicates lower levels of thyroid hormone (lighter gray, from left of spectrum) to higher levels of thyroid hormone (with abnormally high hormone levels at the far right). The percentages (75.4% in A, and 76.9% in B) indicate, respectively, that generic and brand-name levothyroxine products achieved comparable restoration of thyroid levels in patients. The lower and upper bounds (95% confidence interval) of these estimated proportions are shown by the edges of the wedge (gray in A, blue in B), with the average displayed at the center of each wedge.

Research Projects and Collaborations

New Grants and Contracts

- Contract (75F40120F19005) *A Randomized, Open Label, Two Treatment, Four Period, Single Dose, Fully Replicate, Crossover Bioequivalence (BE) Study of Tacrolimus Capsules 5 Mg* with Kathleen Doisy at Biopharma

Continuing Grants and Contracts

- 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 (1U01FD005938-A2) *Characterizing Use, Safety and Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross and Nilay Shah at Yale-Mayo CERSI

Completed Grants and Contracts

- Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Robert 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 (1U01FD005442-01) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence of Leuprolide Acetate Injection* with Robert Ward at University of Utah
- 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 at Yale-Mayo CERSI
- 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

Active FDA Research

- *Postmarket Surveillance of Advair Diskus and Wixela Inhub Using Sentinel*

Outcomes

Articles

- Barenie, R., Kesselheim, A., Gagne, J., Lu, Z., Campbell, E., Dutcher, S., Jiang, W., and Sarpatwari, A. *Preferences for and Experiences with Pill Appearance Changes: National Surveys of Patients and Pharmacists*. The American Journal of Managed Care. (2020) 26(8):340{347. doi: [10.37765/ajmc.2020.44070](https://doi.org/10.37765/ajmc.2020.44070). PMID: [32835461](https://pubmed.ncbi.nlm.nih.gov/32835461/).
- Brito, J., Ross, J., Sangaralingham, L., Dutcher, S., Graham, D., Wang, Z., Wu, Y., Yao, X., Smallridge, R., Bernet, V., Shah, N., and Lipska, K. *Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels*. JAMA Network Open (2020); 3 (9): doi: [10.1001/jamanetworkopen.2020.17645](https://doi.org/10.1001/jamanetworkopen.2020.17645). PMID: [32997127](https://pubmed.ncbi.nlm.nih.gov/32997127/).
- Desai, R., Gopalakrishnan, C., Dejene, S., Sarpatwari, A., Levin, R., Dutcher, S., Wang, Z., Wittayanukorn, S., Franklin, J., and Gagne, J. *Comparative Outcomes of Treatment Initiation with Brand vs. Generic Warfarin in Older Patients*. Clin Pharmacol Ther. 2020 Jun;107(6):1334–1342. doi: [10.1002/cpt.1743](https://doi.org/10.1002/cpt.1743). Epub 2020 Jan 19. PMID: [31872419](https://pubmed.ncbi.nlm.nih.gov/31872419/).
- Li, C., Chen, L., Huo, N., Mishuk, A., Hansen, R., Harris, I., Kiptanui, Z., Wang, Z., and Qian, J. *Generic Escitalopram Initiation and Substitution Among Medicare Beneficiaries: A New User Cohort Study*. PLoS One. 2020 Apr 30;15(4): e0232226. doi: [10.1371/journal.pone.0232226](https://doi.org/10.1371/journal.pone.0232226). PMID: [32353006](https://pubmed.ncbi.nlm.nih.gov/32353006/).
- Chen, L., Li, C., Huo, N., Mishuk, A., Hansen, R., Harris, I., Kiptanui, Z., and Qian J. *Oral Generic Tacrolimus Initiation and Substitution in the Medicaid Population: A New User Cohort Study*. Curr Med Res Opin. 2020 Jul 22:1–8. doi: [10.1080/03007995.2020.1793750](https://doi.org/10.1080/03007995.2020.1793750). Epub ahead of print. PMID: [32644886](https://pubmed.ncbi.nlm.nih.gov/32644886/).

Presentations

- Babiskin, A. *Assessing Bioequivalence for Generic Extended Release Formulations*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
- Gomeni, R. *Drug-Disease Modeling Approach to Describe the Relationship Between Long-Acting Methylphenidate Exposure and Clinical Response*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
- Spencer, T., Biederman, J., Faraone, S., Childress, A., Gomeni, R., Babiskin, A., and Fang, L. *Comparative, Crossover PD Study of Different Formulations of Extended Release MPH*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
- Brown, J. *Real-World Data Approaches for Early Detection of Potential Safety and Effectiveness Signals for Generic Substitution: A Metoprolol Extended Release Case Study*. Presentation at Association of Corporate Citizenship Professionals (ACCP) 2020 Conference. Orlando, FL, Mar. 12, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.



Quantitative Clinical Pharmacology

Summary of FY2020 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 aid in the development of clinically relevant bioequivalence (BE) criteria, design efficient BE studies, and explore alternate BE approaches. QCP approaches are used in various regulatory activities including development of product-specific guidances (PSGs), pre-ANDA meetings, controlled correspondences, abbreviated new drug application (ANDA) consultations, and citizen petition assessments.

Population pharmacokinetic (PK) model-integrated approaches can potentially provide an alternative means of BE evaluation by generating model-integrated evidence when non-compartmental analysis (NCA) becomes challenging, e.g., for long-acting injectables and/or products with sparse PK sampling. For instance, long-acting injectable (LAI) products is an area where conducting BE studies has been a challenge due to their long duration and high subject dropout rate. Model-integrated approaches are being developed to facilitate BE assessment of LAI products (Contract# 75F40119C10018) such as:

- Developing a surrogate BE criterion for shortened switchover BE study designs
- Developing a BE evaluation method that accounts for the effect of related covariates, in addition to formulation, on the PK variations
- Developing a model-based BE evaluation method for shortened switchover or parallel BE studies, in which population PK models will be fitted to observed data and are further used for the simulations of BE trials on which subsequent BE assessment will be conducted
- Developing optimal BE study design methodologies that can increase the precision of PK metric measurements using NCA analysis

As part of another contract (HHSF223201710015C), a user-friendly R package has been developed that will incorporate both NCA-based BE analysis and model-based BE methods for situations where NCA is practically challenging. This R package will help to support alternative BE study designs, reduce sample size, and/or reduce study duration for products such as LAI products.

Innovative approaches using QCP tools are being applied to account for potential batch-to-batch variability of certain products such as oral powder inhalation products (Contract# 75F40119C10068) in the BE assessment. This research aims to evaluate and develop BE methodologies that could facilitate BE assessment of generics to overcome uncertainty associated with potential batch-to-batch PK variability.

Because of the model-integrated BE methodology development and advancement, the Office of Generic Drugs (OGD) is able to respond rapidly to challenges in generic drug development due to COVID-19 pandemic and provide guidance to applicants. A quantitative modeling and simulation-based framework is being developed to assist FDA in making timely decisions for generic drug approval with confidence and providing the necessary guidance to the industry based on risk assessment supported by modeling and simulation approaches.

Research Highlight

The objective of this project is to develop, evaluate and compare model-based (MB) methods to analyze bioequivalence (BE) studies with sparse pharmacokinetic (PK) sampling designs with the aim to find adequate statistical approaches to control type I errors and to achieve enough power to conclude BE using nonlinear mixed-effects models (NLMEM). The standard BE analysis uses two one-sided tests (TOST) on the area under the concentration-time curve and the maximal concentration derived using a non-compartmental approach (NCA). While this method is associated with fewer assumptions/hypotheses and perform adequately well in majority of cases, it requires dense PK samples for all individuals in the study, which is not always feasible, such as in studies involving patients. An MB approach, using NLMEM can be possible, but previous research showed that application of MB-TOST using asymptotic standard errors (SE) can lead to an increase in type I error. In this research work, three alternative approaches for calculation of SE were proposed and assessed. The alternative approaches include i) an adaptation of the correction proposed by Gallant to NLMEM, ii) an a posteriori distribution of the treatment coefficient using the Hamiltonian Monte Carlo algorithm using Stan, and iii) parametric random effects and residual errors bootstrap. Simulations were conducted to evaluate these approaches with parallel and cross-over designs, with rich ($n=10$) and sparse ($n=3$) PK sampling per subject under the null (H_0) and the alternative (H_1) hypotheses (Figure 1). As shown in Figure 2, all proposed approaches controlled the type I error within 5% (within 95% prediction interval of 0.050 i.e., 0.0326 – 0.0729) in PK studies with sparse sampling designs ($n=3$) and had similar control of type I error for PK studies with rich sampling designs ($n=10$). Accurate estimation of treatment effect and correction for the SE are critical to control MB-TOST type I error especially for study designs with sparse sampling. This work demonstrated that for PK BE studies with a sparse sampling design, where NCA approach is practically challenging, MB-TOST, with the proposed non-asymptotic SE approach may serve as an alternative approach.

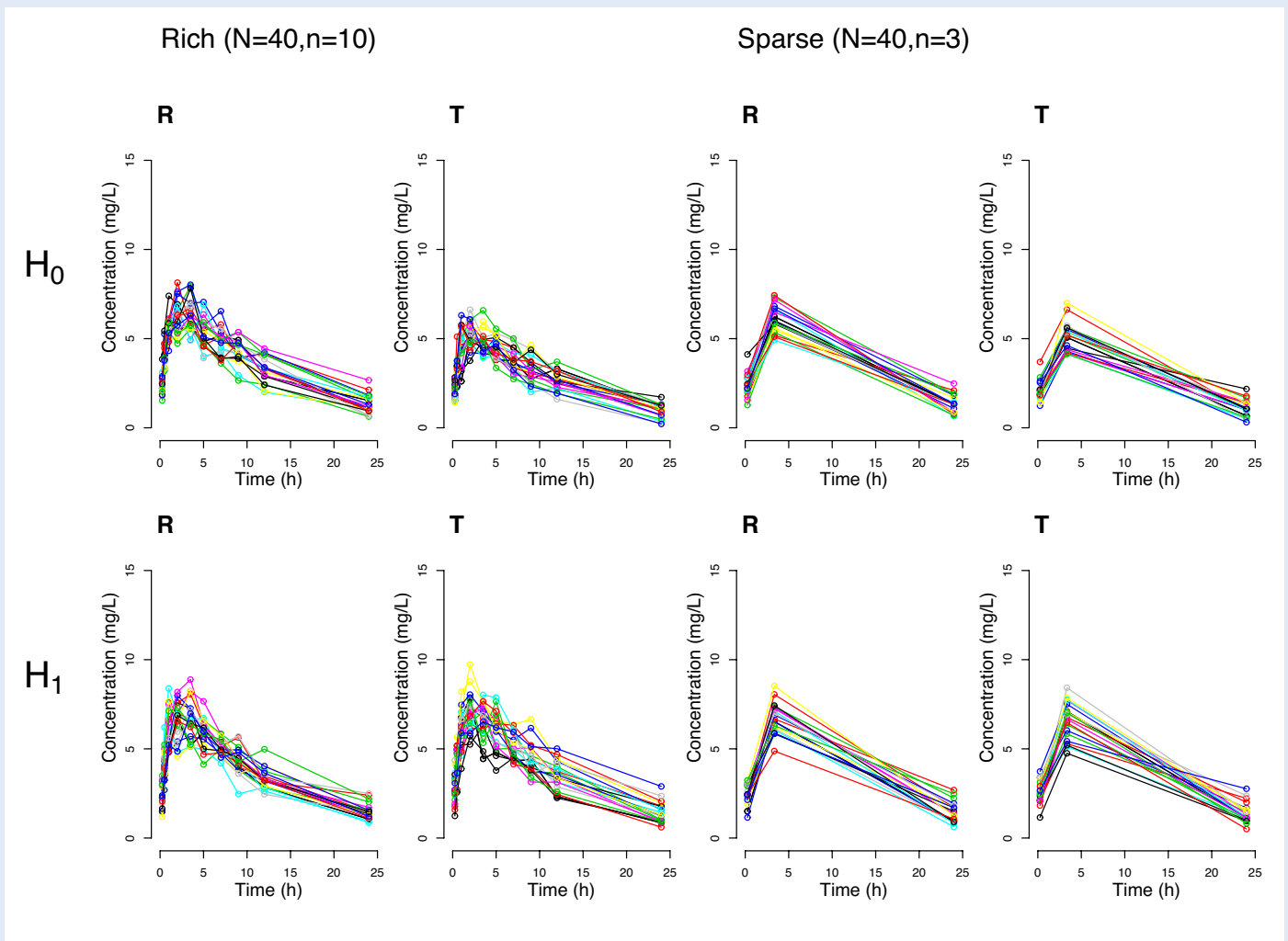


Figure 1: Spaghetti plots of simulated concentrations versus time for the two-arms parallel design under H_0 (top) and H_1 (bottom) for rich (columns 1 and 2) and sparse (columns 3 and 4) designs, in the reference (R, columns 1 and 3) and the test (T, columns 2 and 4) treatment groups.

* H_0 = Null hypothesis

H_1 = Alternative hypothesis

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30 Loingeville, Florence et al., *New model-based Bioequivalence Statistical Approaches for Pharmacokinetic Studies with Sparse Sampling*. AAPS Journal, 22, 141 (2020) (<https://pubmed.ncbi.nlm.nih.gov/33125589/>).

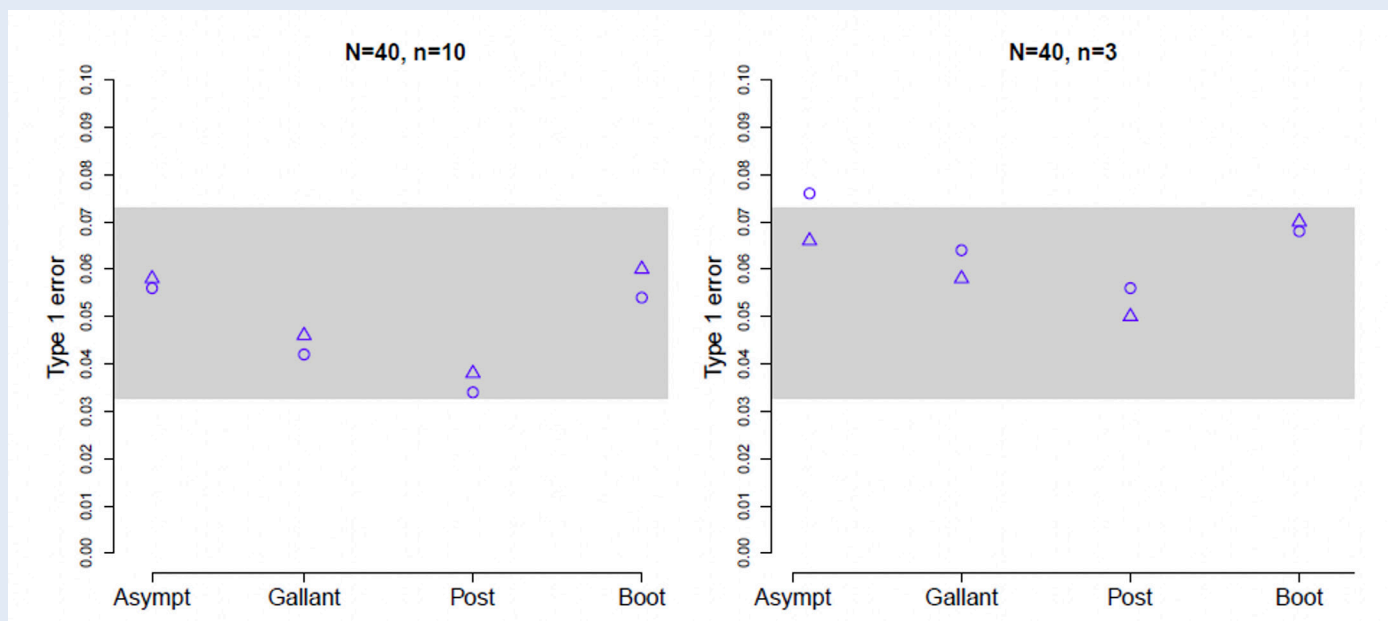


Figure 2: Type I errors of MB-TOST on coefficient of the treatment for AUC (β_{Tr_AUC} (o)) and on coefficient of the treatment for Cmax (β_{Tr_Cmax} (Δ)) using the different SE calculations on the parallel rich (left), and sparse (right) designs. The 95% prediction interval (PI) around 0.050 for 500 simulated data sets is indicated in grey (PI95%(0.050) = [0.0326; 0.0729]) (N = number of subjects, n = sampling time points). With permission from AAPS Journal.

Research Projects and Collaborations

Continuing Grants and Contracts

- Grant (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael N. Neely at Children's Hospital of Los Angeles
- Contract (75F40119C10018) *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 (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 (75F40119C10068) *Batch to Batch Variability: Exploring Solutions for Generic BE Pathway* with Joga Gobburu at University of Maryland

Completed Grants and Contracts

- Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Catherine Mary Turner Sherwin 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 Catherine Mary Turner Sherwin at University of Utah
- Contract (HHSF223201710015C) *Evaluation and Development of Model-based Bioequivalence Analysis Strategies* with Andrew Hooker at Uppsala University

Active FDA Research

- *Assessment of Variability and Dose Sensitivity of FEV1 in Comparative Clinical Endpoint BE Studies of OIDs*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*
- *Model-Based Assessment on Bioequivalence Limits for Anticoagulants*
- *Model-Based Adaptive Learning Design in BE Assessments*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Quantitative Analysis of PKPD Relationship of Abuse Deterrent Opioid Products Clinical Trial Simulation for Clinical Endpoint Bioequivalence Studies*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based Supports for Bioequivalence Assessment During the COVID-19 Public Health Emergency*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-Based Approach*

Outcomes

Product-Specific Guidances (PSGs)

There were seven new and nine revised PSGs published in FY2020 related to quantitative clinical pharmacology. All of these PSGs were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance on Albuterol Sulfate Inhalation Aerosol, Metered. (Mar. 2, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Albuterol Sulfate Inhalation Powder, Metered. (Mar. 2, 2020) [Link to Posting](#).*
- *New Draft Guidance on Copper Intrauterine Device. (Nov. 21, 2019) [Link to Posting](#).*
- *New Draft Guidance on Glycopyrrolate; Indacaterol Maleate Inhalation Powder. (June 3, 2020) [Link to Posting](#).*
- *Revised Draft Guidance on Levalbuterol Tartrate Inhalation Aerosol, Metered. (Mar. 2, 2020) [Link to Posting](#).*

- *Revised Draft Guidance on Levonorgestrel Intrauterine Device.* (Jan. 22, 2020) [Link to Posting](#).
- *New Draft Guidance on Methylphenidate Hydrochloride Oral Capsule, Extended Release (NDA 209311).* (June 3, 2020) [Link to Posting](#).
- *New Draft Guidance on Methylphenidate Hydrochloride Oral Capsule, Extended Release (NDA 212038).* (June 3, 2020) [Link to Posting](#).
- *Revised Draft Guidance on Nitrofurantoin, Macrocrystalline Oral Capsule.* (Nov. 21, 2019) [Link to Posting](#).
- *Revised Draft Guidance on Nitrofurantoin; Nitrofurantoin, Macrocrystalline Oral Capsule.* (Nov. 21, 2019) [Link to Posting](#).
- *Revised Draft Guidance on Scopolamine Transdermal Film, Extended Release.* (Nov. 21, 2019) [Link to Posting](#).
- *New Draft Guidance on Tacrolimus Oral for Suspension.* (Mar. 2, 2020) [Link to Posting](#).
- *Revised Draft Guidance on Theophylline Oral Tablet, Extended Release.* (Aug. 28, 2020) [Link to Posting](#).
- *Revised Draft Guidance on Theophylline Oral Capsule, Extended Release.* (Aug. 28, 2020) [Link to Posting](#).
- *New Draft Guidance on Umeclidinium Bromide; Vilanterol Trifenatate Inhalation Powder.* (Mar. 2, 2020) [Link to Posting](#).
- *New Draft Guidance on Buprenorphine Solution, Extended Release (NDA 209819).* (June 3, 2020) [Link to Posting](#).

Articles

- Kohno, M., Andhariya, J., Wan, B., Bao, Q., Rothstein, S., Hezel, M., Wang, Y., and Burgess, D. *The Effect of PLGA Molecular Weight Differences on Risperidone Release from Microspheres.* International Journal of Pharmaceutics. (2020) 582: doi: [10.1016/j.ijpharm.2020.119339](https://doi.org/10.1016/j.ijpharm.2020.119339). PMID: [32305366](https://pubmed.ncbi.nlm.nih.gov/32305366/).
- Lee, J., Feng, K., Xu, M., Gong, X., Sun, W., Kim, J., Zhang, Z., Wang, M., Fang, L., and Zhao, L. *Applications of Adaptive Designs in Generic Drug Development.* Clinical Pharmacology & Therapeutics. (2020): doi: [10.1002/cpt.2050](https://doi.org/10.1002/cpt.2050). PMID: [32940349](https://pubmed.ncbi.nlm.nih.gov/32940349/).
- *Modeling Tools Could Modernize Generic Drug Development,* In: Regulatory Science in Action, Regulatory Science Impact Story. Available at [Impact Story: Modeling Tools Could Modernize Generic Drug Development | FDA](#). Content current as of 06/02/2020.

- Mollenhoff, K., Loingeville, F., Bertrand, J., Nguyen, T., Sharan, S., Zhao, L., Fang, L., Sun, G., Grosser, S., Mentre, F., and Dette, H. *Efficient Model-Based Bioequivalence Testing*. *Biostatistics*. (2020): 1–14. doi: [10.1093/biostatistics/kxaa026](https://doi.org/10.1093/biostatistics/kxaa026). PMID: [32696053](https://pubmed.ncbi.nlm.nih.gov/32696053/).

Posters

- Miao, L., Wu, F., Yang, X., Ramamoorthy, A., Lee, S., Raines, K., Zhang, L., and Seo, P. *Application of Dissolution Profile Comparison for Gastric pH-Dependent Drug-Drug Interaction Prediction*. Poster Presentation at American College of Clinical Pharmacy (ACCP) 2019 Annual Meeting. New York City, NY, Oct. 26, 2019.
- Kohno, M., Andhariya, J., Rothstein, S., Wang, Y., Qin, B., and Burgess, D. *The Effect of PLGA Molecular Weight on Drug Release from Microspheres*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) 2019 Pharmsci 360. San Antonio, TX, Nov. 4, 2019.
- Pawar, G., Wu, F., Zhao, L., Fang, L., Burckart, G., Feng, K., Mousa, Y., Naumann, F., and Batchelor, H. *Development of a Database Containing Clinical Data on Bioequivalence and Relative Bioavailability Studies Conducted in Pediatric Populations*. Poster Presentation at European Pediatric Formulation Initiative Conference 2020. Virtual Meeting. Sept. 9, 2020.

Presentations

- Chen, X., Hooker, A., Nyberg, H., Karlsson, M., and Hooker, A. *Model-Based Bioequivalence Evaluation for Ophthalmic Products Using Model Averaging Approaches*. Presentation at American Conference on Pharmacometrics (ACoP10). Orlando, FL, Oct. 22, 2019.
- Hooker, A., Nyberg, H., Karlsson, M., and Chen, X. *Development and Comparison of Model-Based Bioequivalence Analysis Methods on Sparse Data*. Presentation at American Conference on Pharmacometrics (ACoP10). Orlando, FL, Oct. 22, 2019.
- Mentre, F., Loingeville, F., Rakez, M., Nguyen, T., Bertrant, J., Mollenhoff K., Dette, H., Sharan, S., Sun, G., Grosser, S.,

- Zhao, L., and Fang, L. *Model-Based Statistical Approaches for Pharmacokinetic Bioequivalence Studies with Sparse Sampling and Extension to Two-Stage Designs*. Presentation at American Conference on Pharmacometrics (ACoP10). Orlando, FL, Oct. 22, 2019.
- Zhao, L. *Regulatory Challenges and Opportunities for Model-Based Approaches for Patient Pharmacokinetic (PK) Studies with Sparse Sampling Design*. Presentation at American Conference on Pharmacometrics (ACoP10). Orlando, FL, Oct. 22, 2019.
 - Zhao, L. *FEV1 based Bioequivalence Study for Inhaled Corticosteroids*. Presentation at American Association of Pharmaceutical Scientists (AAPS) and The European Federation for Pharmaceutical Sciences (EUFEPS), FDA Co-Sponsored Global Bioequivalence Harmonization Initiative (GBHI): 4th International Workshop. Bethesda, MD, Dec. 13, 2019.
 - Babiskin, A. *Assessing Bioequivalence for Generic Extended Release Formulations*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
 - Gomeni, R. *Drug-Disease Modeling Approach to Describe the Relationship Between Long-Acting Methylphenidate Exposure and Clinical Response*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
 - Spencer, T. *Comparative, Crossover PD Study of Different Formulations of Extended Release MPH*. Presentation at the American Professional Society of ADHD and Related Disorders (APSARD) 2020 Annual Meeting. Washington, DC, Jan. 18, 2020.
 - Lukacova, V. *What Does It Take to Develop a PBPK Model That Mimics In Vivo Behavior of LAIs*. Presentation at 3rd Long-Acting Injectables & Implantables Conference. La Jolla, CA, Feb. 6, 2020.

- Brown, J. *Real-World Data Approaches for Early Detection of Potential Safety and Effectiveness Signals for Generic Substitution: A Metoprolol Extended Release Case Study*. Presentation at American College of Clinical Pharmacology (ACCP) 2020 Virtual Journal Club. Orlando, FL, Mar. 11, 2020.
- Zhao, L. *Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program*. Presentation at FY2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
- Hamadeh, A. *A Workflow for Mechanistic Dermal Model Optimization and In Vitro-In Vivo Inference*. Presentation at the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) and FDA Co-Sponsored Topical Drug Development: Evolution of Science and Regulatory Policy II Workshop. Virtual Meeting, July 23, 2020.
- Fang, L. *Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice*. Presentation at American College of Clinical Pharmacology (ACCP) 2020 Annual Meeting (Virtual), Sept. 23, 2020.
- Fang, L. *Current Status for pAUC Recommendations in Product-specific Guidance & Case Examples*. Presentation at American College of Clinical Pharmacology (ACCP) 2020 Annual Meeting (Virtual), Sept. 23, 2020.
- Zhao, L. *Introduction to Partial Area Under the Curve (pAUC) Recommendations: A Regulatory Perspective*. Presentation at American College of Clinical Pharmacology (ACCP) 2020 Annual Meeting (Virtual), Sept. 23, 2020.
- Sharan, S. *Model-Informed and Model-Integrated Approach in BE Assessment of Long-Acting Injectable Products*. Presentation at CDER Small Business and Industry (SBIA) 2020 Regulatory Education for Industry (REdI): Advancing Innovative Science in Generic Drug Development Workshop 2020 Meeting. Virtual Meeting, Sept. 30, 2020.



Topical Dermatological Products

Summary of FY2020 Activities

Multiple Generic Drug User Fee Amendments (GDUFA)-funded research initiatives are underway to support the development of efficient bioequivalence (BE) approaches for topical dermatological drug products, as part of an effort to facilitate generic drug development and enhance patient access to these topical products. One strategy has been to develop generic products that are essentially identical to the reference product in all respects; this strategy necessitated the development of scientific approaches to comprehensively characterize the arrangement of matter (Q3) in the reference (R) product so that a prospective generic product developer could use these comparative Q3 tests and performance characterizations to demonstrate that a prospective generic test (T) product is as closely matched to the R product as batches of the R product are to each other — thereby ensuring BE by design.

During FY2020, ongoing research projects advancing this strategy were focused on expanding characterization-based BE approaches to all classes of topical dermatological products. To achieve this goal, in vitro research was performed by the University of Mississippi (Grant# 1U01FD005233) on solution- and emulsion-based topical foam products and by the University of South Australia (Grant# 1U01FD005226) and FDA laboratories on tretinoin topical gel and cream products. In parallel, research conducted by FDA laboratories identified the critical Q3 characteristics of microsponges in Retin-A-Micro[®] gel and the corresponding specific analytical matrices for them. In parallel, the in vitro and in vivo performance of metronidazole gel and cream products were assessed at the University of Maryland (Baltimore) (Grant# 1U01FD004947) to develop an in vitro-in vivo relationship between the results of in vitro permeation test (IVPT) and in vivo systemic pharmacokinetics (PK) studies with the same set of products. A new research project was also initiated at the University of Rhode Island (Grant# 1U01FD006721) to develop characterization-based approaches for vaginal and rectal products. FDA laboratories also developed comparative testing methodologies for estradiol vaginal inserts by providing an understanding of the correlation between the product's critical quality attributes and its in vivo performance at the site of action to support the assessment of generic versions of the drug product. Collectively, these research groups studied various approaches to characterize critical aspects of multiple classes of different topical dosage forms.

As a related component of this strategy, FDA sought to understand the mechanisms that allow T and R topical products to be clinically bioequivalent even when they are not necessarily identical, but are similar in components, composition, and/or Q3 attributes (analogous to the similarity of pre-change and post-change R products that undergo post-approval changes, for example). To elucidate these mechanisms, in vitro experiments and in silico modeling and simulation were advanced in FDA collaborations with the University of South Australia (Grant# 1U01FD006496) as well as the University of Mississippi (Grant# 1U01FD006507). These independent research collaborations sought to understand how compositional changes of inactive ingredients in a topical solution can change the thermodynamic activity of the drug; how the metamorphosis of the dosage form can modulate that thermodynamic activity; and the resulting influence on the rate and extent to which the drug is delivered and becomes available in the skin. Additionally, a research collaboration with the University of Queensland (Grant# 1U01FD006700) studied how specific Q3 attributes of topical dermatological products may be perceived by human subjects (e.g., how the rate of evaporation of an applied product contributes to a cooling sensation) and designed instrumental tests to

assess whether T and R products that are compositionally different may have comparable sensorial attributes and be therapeutically equivalent.

Another strategy to develop efficient BE approaches for topical dermatological products was to explore the development of efficient PK-based methods to directly monitor the rate and extent of a drug's bioavailability at or near its site(s) of action in the skin. While PK-based BE approaches are routinely utilized to demonstrate BE for systemically-acting drug products (like oral tablets), such approaches had not been previously considered feasible for locally-acting topical drug products. However, GDUFA-funded research in recent years has illustrated the feasibility of cutaneous PK-based approaches to support a demonstration of BE, both in vitro and in vivo. During FY2020, in vivo BE studies in human subjects were successfully performed at Joanneum Research (Grant# 1U01FD005861) using dermal open flow microperfusion (dOFM) for lidocaine and prilocaine gel and cream products. Independently, research at the University of Bath (Grant# 1U01FD006533) and Massachusetts General Hospital/Harvard Medical School (Grant# 1U01FD006698) have been developing non-invasive cutaneous PK-based methods using advanced confocal Raman imaging techniques.

FDA's laboratories have also been evaluating the safety risk encountered with unintentional drug transfer from a dosed person to non-dosed individuals through skin-to-skin contact after the application of semisolid hormonal drug products. An in vitro permeation method was developed for prediction of this risk. Ongoing research in this area is designed to correlate the formulation and manufacturing parameters of semisolid hormonal drug products to the extent of skin-to-skin drug transfer.

Research Highlight

Dermal open flow microperfusion (dOFM) can directly and continuously sample interstitial fluid from the dermis and characterize the cutaneous (dermal) PK of topically applied drug products. By dosing several products in parallel on the same subject, dOFM may be able to support a demonstration of BE for a prospective generic product by comparing the rate and extent of bioavailability at or near the site(s) of action in the skin. A clinical study performed at Joanneum Research (Grant# 1U01FD005861) with 20 healthy subjects was conducted to compare the dermal PK of the R product, EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 % to itself (R vs. R) and to an approved generic version of lidocaine and prilocaine cream, 2.5%; 2.5% (T_{generic} vs. R). Both of these comparisons (R vs. R and T_{generic} vs. R) served as positive controls for BE to assess the accuracy and reproducibility of such a dOFM BE study. In addition, the R product was also directly compared to a different dosage form with the same drugs at the same strengths, Oraqix® (lidocaine; prilocaine) gel, 2.5%; 2.5% ($T_{\text{non-equ}}$ vs. R as well as $T_{\text{non-equ}}$ vs. T_{generic}). These comparisons served as negative controls for BE to assess the discrimination sensitivity of such a dOFM BE study (Figure 1). All products were administered at a product dose of 15 mg/cm² and removed from the skin after 3 hours of application, after which the dOFM sampling was continued.

The dOFM sampling technique was accurately and reproducibly able to demonstrate comparable cutaneous PK profiles for the R vs. R products as well as the T_{generic} vs. R products. The dOFM sampling technique was also successfully able to differentiate the cutaneous PK profiles of the $T_{\text{non-equ}}$ vs. R as well as the $T_{\text{non-equ}}$ vs. T_{generic} (Figure 2). A scaled average bioequivalence (SABE) statistical analysis was used to analyze the BE of lidocaine and prilocaine from the various product comparisons based on PK endpoints of area under the curve (AUC_{0-12h}) and maximum dermal concentration (C_{max}). The geometric mean ratios for AUC_{0-12h} and C_{max} for both lidocaine and prilocaine were within the BE limits of 0.8 and 1.25 for both positive controls (R vs. R and T_{generic} vs. R) confirming that the R product is bioequivalent to itself as well as to the T_{generic} product, while the $T_{\text{non-equ}}$ product was not found to be bioequivalent to either the R or the T_{generic} product based on both PK endpoints.

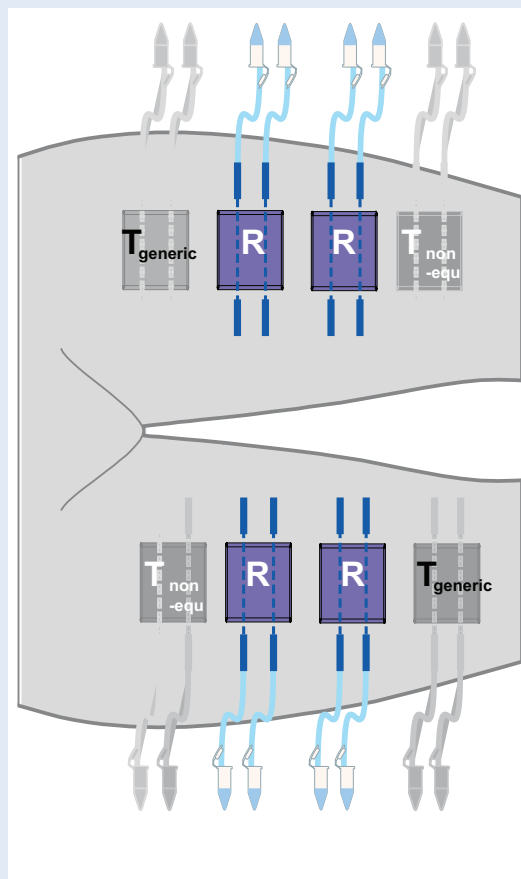


Figure 1: Schematic representation of the application sites in the dOFM BE study. The following products were applied on each application site: EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 % (R), generic lidocaine and prilocaine cream, 2.5%; 2.5% (T_{generic}), Oraqix® (lidocaine and prilocaine) dental gel, 2.5%; 2.5% ($T_{\text{non-equ}}$).

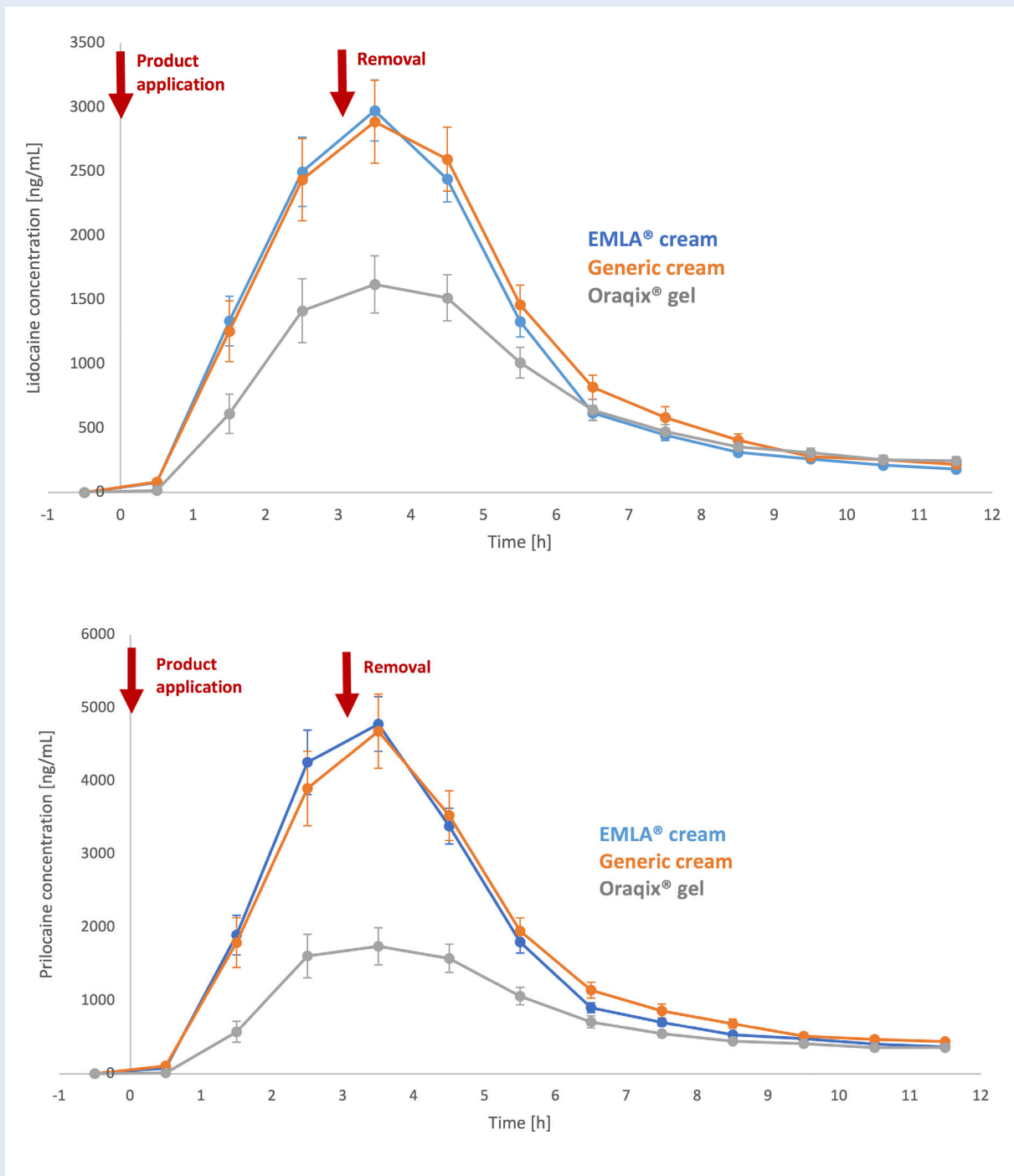


Figure 2: Mean lidocaine and prilocaine dermal concentration-time profiles (\pm SE) for EMLA® (lidocaine; prilocaine) topical cream, 2.5%; 2.5 %, generic lidocaine and prilocaine cream, 2.5%; 2.5%, and Oraqix® (lidocaine and prilocaine) dental gel, 2.5%; 2.5%. The cutaneous PK profiles for lidocaine and prilocaine were comparable between the subjects and showed relatively low inter- and intra-subject variability. The reference and generic creams were shown to have similar cutaneous bioavailability, whereas the PK profile of Oraqix® gel was well-differentiated from those of the reference and generic creams, and not found to be bioequivalent to either the reference or generic creams.

Research Projects and Collaborations

New Grants and Contracts

- Grant (1U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with Grazia Stagni at Long Island University

Continuing Grants and Contracts

- Grant (1U01FD004947) *Bioequivalence of Topical Drug Products: In Vitro-In Vivo Correlations* with Audra Stinchcomb at University of Maryland
- 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 (1U01FD006533) *Assessing the Skin Pharmacokinetics of Topical Drugs, and the Bio(in)equivalence of Topical Drug Products, Using Non-Invasive Techniques* with Richard Guy at University of Bath
- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Grant (1U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at University of South Australia
- Grant (1U01FD006507) *Impact of Formulation Composition on the Structure and Performance Attributes of Topical Products* with Sathyanarayana Murthy at University of Mississippi
- 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 (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
- Grant (1U01FD006526) *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations* with Jessica Spires at Simulations Plus, Inc.
- Grant (1U01FD006721) *Bioequivalence Considerations of Topical Rectal and Vaginal Suppositories* with Jie Shen at University of Rhode Island
- Grant (1U01FD006700) *Elucidating Sensorial and Functional Characteristics of Topical Formulations* with Yousuf Mohammed at University of Queensland

Completed Grants and Contracts

- Grant (1U01FD005233) *Topical Products and Critical Quality Attributes* with Sathyanarayana Murthy at University of Mississippi.
- Grant (1U01FD005862) *Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products* with Grazia Stagni at Long Island University.
- 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.

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *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 Novel In Vitro Method to Predict the Safety Risk Due to Skin-to-Skin Drug Transfer During Transdermal Hormonal Replacement Therapy*
- *Evaluation of the In Vitro Performance and Other Product Quality Attributes of Imvexxy® (estradiol) Vaginal Insert*

- *Q3 Pharmaceutical Characterization-Based BE Approach for Test Products Referencing Retin-A-Micro® (Tretinoin) Topical Gel, 0.04%, 0.06%, 0.08% or 0.1%*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-Based Approach*

Outcomes

Guidances for Industry (GFI)

GFI Research Outcomes

- *Draft Guidance on Industry: Transdermal and Topical Delivery Systems — Product Development and Quality Considerations. (November 2019) [Link to Posting.](#)*

Product-Specific Guidances (PSGs)

There were 8 new and 47 revised PSGs published in FY2020 related to topical products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance on Clindamycin Phosphate Topical Gel (NDA 050615). (Nov. 21, 2019) [Link to Posting.](#)*
- *Revised Draft Guidance on Clindamycin Phosphate Topical Gel (NDA 050782). (Jun. 3, 2020) [Link to Posting.](#)*
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- 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 American Association of Pharmaceutical Scientists (AAPS) 2019 PharmSci 360. San Antonio, TX, Nov. 4, 2019.
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- Arora, S. *Formulation Drug Product Quality Attributes Additions in Dermal PBPK Model*. Presentation at the 10th Annual Simcyp Virtual Seminar. Webinar, Oct. 24, 2019.

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- Raney, S. *A Generic Drugs Perspective on the Use of In Vitro Assessment Methods: Bridging Results from the Maximum Use Trials with Sunscreen Reformulations*. Presentation at New York Society of Cosmetic Chemists Meeting. Iselin, NJ, Jan. 29, 2020.
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- Kozak, D., *GDUFA Regulator Science Research on In Vitro Bioequivalence Methods*. Presentation at FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop. Virtual Meeting, May 4, 2020.
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