CENTER FOR DRUG EVALUATION AND RESEARCH

FY 2023

GDUFA SCIENCE AND RESEARCH REPORT

U.S. FOOD & DRUG ADMINISTRATION

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INTRODUCTION

The U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) continually advances scientific understanding through research to ensure the safety, effectiveness, and quality of drugs in the United States. A research program established under the Generic Drug User Fee Amendments (GDUFA) helps to ensure that regulatory standards, recommendations, and decisions impacting generic drugs are supported by current scientific insights and modern tools. The GDUFA science and research program is particularly important for complex products because the program supports the development of innovative methodologies and efficient tools to establish the bioequivalence (BE) and quality of generic alternatives.

Specifically, GDUFA-funded research improves the efficiency with which generic drugs can be developed and assessed. This benefits public health in two critical ways: 1) making it feasible for manufacturers to develop generic drugs, which reduces the risk of drug shortages and facilitates competition; and 2) enhancing patient access to treatment by helping make these products widely available, allowing patients in the United States to obtain the medicines they need. Thus, the GDUFA science and research program is an essential component of FDA's mission to protect and promote public health.

Each year, multiple sources of public input help FDA identify specific generic drug science and research priorities that can help expand and accelerate patient access to generic drugs. FDA then advances research in those scientific areas and publishes annual reports describing the corresponding activities and outcomes. Eight scientific areas were identified as GDUFA Science and Research Priority Initiatives for Fiscal Year (FY) 2023. Accordingly, this FY 2023 GDUFA Science and Research report describes active research projects and outcomes organized in eight chapters corresponding to those eight priority areas for FY 2023, with a ninth chapter that reports on additional generic drug science and research.

In certain chapters, the reporting is sub-divided into sections that describe substantial activity in relevant scientific specialty areas. For example, Chapter 4 describes GDUFA science and research activities to enhance the efficiency of BE approaches for complex routes of delivery. This chapter is organized with separate sections focusing on locally acting gastrointestinal products and buccal/sublingual products, inhalation and nasal products, ophthalmic and otic products, and topical products.

In each scientific specialty area, we summarize the relevant research and typically highlight one research project that illustrates the types of scientific insights being developed. We also provide comprehensive lists of new, ongoing, and completed grants and contracts for research relevant to that area, as well as active FDA research and lists of the research outcomes in each specialty area from FY 2023. These outcomes include general guidances for industry and product-specific guidances (PSGs) published in FY 2023 that were supported by research in each area, as well as lists of scientific journal articles, posters, and presentations. When research projects impact multiple scientific areas, information about those projects and their outcomes is generally included or cross-referenced in each area impacted (e.g., research on physiologically based pharmacokinetic (PBPK) modeling of topical rectal and vaginal products is included in Chapter 4 (Complex Routes of Delivery: Topical Products) and in Chapter 7 (Quantitative Methods & Models: Locally Acting PBPK Modeling)).

The GDUFA science and research program is implemented through numerous extramural collaborations with leading experts at research institutions around the world, as well as extensive intramural research collaborations among FDA scientists. While both the Office of Generic Drugs (OGD) and the Office of Pharmaceutical Quality (OPQ) within CDER lead many of the GDUFA-funded research projects, the GDUFA science and research program involves coordination and collaboration among several offices and centers across FDA. These collaborators include the Office of Translational Sciences within CDER, FDA's Center for Devices and Radiological Health, FDA's National Center for Toxicological Research, and FDA's Office of Regulatory Affairs. The following Directors' Message is from the Director of OGD and the Director of OPQ, jointly and on behalf of FDA's GDUFA science and research program collaborators.

JOINT DIRECTORS' MESSAGE

Dr. Iilun Murphy

Dr. Michael Kopcha

The Generic Drug User Fee Amendments (GDUFA) science and research program facilitates patient access to high-quality, safe and effective generic drugs. It does this by advancing research in areas where generic product development has been limited due to scientific knowledge gaps. For example, an insufficient scientific understanding can create uncertainty about how to develop a complex generic product, or how to demonstrate that it is bioequivalent to its brand name reference listed drug product. Each fiscal year (FY), experts across the generic drug industry collaborate with FDA to establish research priorities for the most pressing scientific challenges they face with generic product development. Scientists and clinicians from industry, academia, and the U.S. Food and Drug Administration (FDA) then strategically design research projects and studies so that the research outcomes enable FDA to build scientific bridges across the knowledge gaps. The outcomes of this research help FDA establish efficient new approaches for pharmaceutical manufacturers to develop generic drugs that were previously challenging or unfeasible to develop, thus making these generic medicines available for patients.

Aligned with the GDUFA Science and Research Priority Initiatives for FY 2023, FDA awarded eight new grants and twelve new contracts during FY 2023 (not including supplements to existing projects) for innovative extramural research projects relevant to generic drugs. FDA also utilized its internal resources and expertise to conduct more than 70 research projects designed to facilitate generic product development and prepare FDA to assess information submitted in abbreviated new drug applications (ANDAs).

The outcomes from GDUFA-funded research expand our understanding of drug products, including complex products, and often contribute to the development of advanced methods to characterize product quality and performance. These methods enable efficient approaches for developing generic products and help FDA to assess the bioequivalence (BE) and quality of complex generic products. FDA's recommendations related to BE issues and product quality are communicated to the generic drug industry through the continual publication of new and revised product-specific guidances (PSGs), as well as general guidances for industry (GFIs).

In FY 2023, FDA issued 244 new and revised PSGs (174 of which were for complex products), which provided recommendations for developing generic drugs and generating the evidence to support ANDA approval. This included 146 PSGs for products with no approved ANDAs at the time of PSG publication (including 96 PSGs for complex products). Also, 37 PSGs were revised in FY 2023 to add an efficient in vitro BE option. All the new and revised PSGs issued during FY 2023 help prospective generic applicants understand FDA's expectations, focus their product development, prepare for ANDA submission, and mitigate certain risks associated with generic product development. The development of these PSGs also facilitates FDA's assessment of ANDAs

for the corresponding products, once submitted. The recommendations in many of these PSGs would not have been possible without the GDUFA science and research program.

For example, the PSGs issued during FY 2023 included more than 80 new and revised PSGs for topical products. The BE recommendations in these PSGs were uniformly and systematically updated for all relevant topical products based upon an expanding body of knowledge and the development of advanced test methods. Prior GDUFA research outcomes have enabled the development of efficient new BE approaches for certain generic topical products that contained the same component ingredients and formulation composition as their reference standard. The updated BE recommendations make it substantially more efficient to develop generic products applied to the skin, as well as vaginal, rectal, or anal routes of administration, and expand the eligibility for prospective generic applicants to utilize these efficient in vitro product characterization-based options to demonstrate BE. The revised eligibility criteria were the result of an array of scientific insights arising from ongoing GDUFA-funded research, now making it more efficient, as well as more feasible, for a prospective generic applicant to formulate a generic topical product that matches its reference standard product.

These topical PSGs were released in coordination with multiple new and revised GFIs on physicochemical and structural (Q3) characterization, in vitro release test (IVRT) studies, in vitro permeation test (IVPT) studies, and in vivo vasoconstrictor studies (for topical corticosteroids). These FDA guidances provide more detail and greater clarification about technical recommendations for relevant topical product characterization tests and studies. They also establish principles that prospective applicants can now utilize to develop generic topical products in a manner consistent with FDA's current thinking, even in the absence of a PSG for a specific topical product. The BE recommendations additionally included information about further expanding access to efficient BE approaches for a "Q3 Similar" generic topical product, which may contain certain differences in component ingredients or formulation composition compared to its reference standard product. The recommendations in these PSGs and GFIs were the direct result of GDUFA-funded research. The GDUFA research program has continually advanced our understanding of how specific characteristics of semisolid topical dosage forms can modulate the rate and extent to which an active ingredient becomes available at a local site of action. The resulting insights have elucidated how to control critical attributes of these dosage forms in a manner that ensures a generic topical product will be bioequivalent to its reference standard, and therapeutically equivalent for patients.

In addition to informing FDA guidances, GDUFA research also allows FDA to evaluate whether proposed BE approaches presented to FDA in pre-ANDA product development meetings are likely to be suitable. Specifically, GDUFA research outcomes enable FDA to provide prospective ANDA applicants with timely technical advice that helps them prepare their submissions in a manner compatible with the most current scientific insights and regulatory expectations. In FY 2023, FDA facilitated 64 such product development meetings.

Ultimately, GDUFA-funded research improved patient access to generic products that were practically unfeasible to develop as recently as a few years ago. It did this by establishing new BE approaches, informing generic product development, and preparing FDA to assess ANDAs once submitted.

For example, on July 6, 2023, FDA approved the first generic naltrexone extended-release injectable suspension (referencing Vivitrol®) to treat alcohol dependence and prevent relapse to opioid dependence. This is an important drug product that addresses two major public health needs affecting millions of individuals in the United States. This first generic approval is a notable achievement because of how scientifically challenging it was to develop, manufacture, and demonstrate bioequivalence. This generic product uses a long-acting injectable (LAI) biodegradable poly(lactide-co-glycolide) (PLGA) polymer microsphere technology. The PLGA formulation confers the product with a sustained effect that only necessitates patients to be dosed once a month. FDA approved the first PLGA product more than 30 years ago, and the complexity of developing and manufacturing PLGA products is so

great that there have been relatively few PLGA products approved during the interceding decades. This is the first naltrexone extended-release injectable suspension generic product to be approved, and also the first generic PLGA product to be approved.

FDA began GDUFA-funded research on PLGA-based LAI products in 2013, and ongoing research during the last decade has systematically advanced scientific insights and developed new tools that could support an efficient demonstration of BE for complex generic LAI products like this one. The research focused on developing analytical methods that would ultimately facilitate the reverse engineering, characterization, and selection of suitable PLGA polymers - a critical first step for generic product development. The GDUFA-funded research also focused on developing suitable in vitro drug release testing methods that ultimately elucidated how a drug is released from such a formulation and how different manufacturing processes and polymer characteristics can influence that drug release. FDA published BE recommendations for this product in a PSG and established criteria by which to assess the BE of a generic LAI PLGA product submitted in an ANDA. The GDUFA-funded research on polymer and formulation characterization thus helped to establish a viable scientific approach and regulatory pathway for generic PLGA-based products, directly supported generic product development, and prepared FDA to assess PLGA-based products when submitted in ANDAs.

The approval of this complex generic product exemplifies what can be achieved with effective coordination between FDA and the generic drug industry. The GDUFA science and research program fosters early engagement between FDA and industry to identify specific priority areas for GDUFA research. It then facilitates continued engagement through pre-ANDA meetings during product development to discuss how insights from GDUFA research can be leveraged. Following ANDA submission, it continues to support productive technical discussions in meetings between FDA and ANDA applicants on scientific matters. As part of FDA's commitment to expanding its collaboration and communication with industry, we also continued to work closely with the Center for Research on Complex Generics (CRCG) during FY 2023.

The CRCG solicited detailed feedback from generic drug industry representatives, which provided insights into specific scientific challenges and indicated the corresponding research needed to address these challenges. The feedback also clarified what technical methods, study designs, data analyses, and other scientific insights were necessary to help the generic drug industry successfully develop complex generics. To help generic drug industry stakeholders implement scientific insights from GDUFA research outcomes in a manner consistent with FDA's regulatory expectations, the CRCG hosted five scientific workshops as well as one training course during FY 2023. The CRCG also conducted research in GDUFA priority areas and played a central role in coordinating and enhancing generic drug industry engagement in the FY 2023 Generic Drug Science and Research Initiatives Public Workshop, which helped to inform the ongoing priority areas for the GDUFA science and research program.

We are deeply grateful to all our collaborators within FDA and at institutions around the world, and to many throughout the global generic drug industry, for the success of the GDUFA science and research program. The continual advances and emerging issues in pharmaceutical science and manufacturing provide ongoing challenges for generic product development. We remain confident that our collaborative engagements to advance the GDUFA science and research program are the most effective way to address these scientific challenges for generics. We also look forward with optimism, expecting that the outcomes of this research program will continue to promote generic competition as a key part of FDA's Drug Competition Action Plan and, ultimately, enhance patient access to high-quality, safe, and effective medicines.

On behalf of all our FDA collaborators,

Dr. Iilun Murphy, Director, Office of Generic Drugs and
Dr. Michael Kopcha, Director, Office of Pharmaceutical Quality

CHAPTER 1: IMPURITIES

A FY 2023 GDUFA science and research priority is to develop methods for generics to address impurities such as nitrosamines. The advancement of research in this area focuses on understanding how ingredients in drug products may either contribute to or mitigate the formation of potentially harmful impurities such as nitrosamines (e.g., nitrosamine drug substance related impurities (NDSRIs)), evaluating the risk of human exposure to these impurities, and developing methods for abbreviated new drug application (ANDA) applicants to efficiently address the potential risks. Research in this area is described below.

Summary of FY 2023 Activities

In FY 2023, research projects on impurities specifically focused on N-nitrosamines impurities including NDSRIs in drug products. FDA's research efforts involved one external research contract and one external research grant, as well as many internal research projects related to nitrosamines impurities. These research projects continued to develop analytical procedures for the quantitation of N-nitrosamine impurities (small molecule nitrosamines and NDSRIs) in pharmaceuticals, assessing the risk of forming these impurities, toxicological risks of these impurities, exploring strategies to prevent or mitigate their formation by reformulating drug products potentially with suitable antioxidants or pH modifiers, and weighing the potential impacts of reformulations on the bioequivalence of generic products.

As part of an internal FDA research project, scientists investigated the risk of forming N-nitrosamine impurities, including NDSRIs, and potential control strategies to mitigate the formation of these impurities in drug products containing bumetanide or metformin, as model drug products. Different antioxidants and pH modifiers were evaluated in this study for their potential to mitigate the formation of N-nitrosobumetanide (NBMT) and N-nitroso-dimethylamine (NDMA). Other nitrosamine research studies were established to study the effect of highly used excipients in metformin drug products on the formation of NDMA during manufacturing. Moreover, FDA scientists were also investigating the effect of secondary amine API with chemical structures that support the formation of NDSRIs in the drug product, using a selected model drug product. FDA scientists also engaged in developing analytical methods for detecting NDSRIs in different drug products. They constructed a liquid chromatography-high resolution mass spectrometry (LC-HRMS) analytical platform that can be broadly utilized for NDSRI analysis across a diverse range of drug products. The results obtained have not only shed light on the occurrence of NDSRIs in drug products but also allow further analysis to identify the underlying risk factors contributing to these contaminations. In addition, to understand the performance attributes of mass spectrometry-based analytical procedures for trace level nitrosamine analysis, FDA organized and led an inter-laboratory study including the laboratories from six regulatory agencies. The results demonstrated that quantitation of trace level nitrosamines can be achieved across multiple analytical procedures and provided insight into the performance attributes of a typical analytical procedure for the analysis of nitrosamines and other trace level impurities in pharmaceutical products.

The objective of the external research Contract (75F40119D10024-75F40122F19003) with Pharmaron (Exton) Lab Services LLC was to evaluate the impact of some frequently used antioxidants on the in vitro permeability of four biopharmaceutics classification system (BCS) III model drug substances using Caco-2 monolayer system. The external research Grant (3U01FD005978) with the Centers of Excellence in Regulatory Science and Innovation (CERSIs), a joint undertaking among University of California, San Francisco (UCSF), Stanford University, and the FDA, focused on assessing the potential effect of antioxidants on the transport function of three intestinal transport proteins - P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting peptide 2B1 (OATP2B1). The outcomes of these two external research projects aimed to provide fundamental information that could support an approach to ensure bioequivalence without in vivo bioavailability or bioequivalence studies, when appropriate. Specifically, this research evaluated the impact of adding antioxidants on factors that influence the bioavailability of different drugs.

To assess the toxicological risk of nitrosamines, CDER scientists from the Office of Pharmaceutical Quality (OPQ), Office of Generic Drugs (OGD), and other CDER offices are collaborating with scientists at the National Center for Toxicological Research (NCTR) on a research project that employs various combinations of Ames bacterial tester strains, incubation times, and metabolic activation systems to determine methods that work best for detecting the mutagenicity of nitrosamines including NDSRIs. The objective of this study is to identify methods that enhance detecting the mutagenicity of nitrosamines in the Ames test and, conversely, identify methods that are inappropriate for the sensitive detection of nitrosamine mutagenicity. Collaborative studies are also being conducted to develop in vitro methods that utilize human cells possessing endogenous human metabolic activity

(e.g., human lymphoblastoid TK6 cell lines and the human hepatoma HepaRG cell line expressing different cytochrome (CYP) P450 enzymes). These assays can potentially be used to follow-up on and/or confirm Ames test mutagenicity findings for small nitrosamine drug impurities and NDSRIs. Another important objective of these studies is to determine the specific CYP enzyme responsible for the bioactivation of a given NDSRI.

During FY 2023, to engage in discussions on scientific perspectives and relevant research, FDA and the Center for Research on Complex Generics (CRCG) co-hosted a public workshop titled "Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics" on June 15, 2023[1], to discuss the risks of NDSRIs formation in certain drug products, strategies to mitigate these risks, and considerations in assessing the safety of NDSRIs. The workshop also discussed the potential impacts of reformulations (e.g., adding a suitable antioxidant to the existing formulation to mitigate the formation of nitrosamine impurities) on the bioequivalence of generic products and strategies to utilize modeling and simulation approaches to assess the bio-inequivalence risks in the event of a reformulation.

[1] FDA/CRCG Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generic Products. https://www.complexgenerics.org/education-training/mitigation-strategies-for-nitrosamine-drug-substance-related-impurities-quality-and-bioequivalence-considerations-for-generic-products/

RESEARCH HIGHLIGHT

FDA determined that the level of nitrosamine impurities in some drug products exceeded FDA's recommended acceptable intake limit, which resulted in certain product recalls and impacted some drug shortages. An internal FDA research project investigated the risk of forming nitrosamine impurities, as well as potential control strategies to mitigate the formation of nitrosamine impurities. Bumetanide was used as a model drug in this study and research was conducted by FDA scientists to identify the risk for formation and ways to mitigate the formation of NBMT. Three antioxidants (ascorbic acid, caffeic acid, and ferulic acid) showed effective mitigation of NBMT formation in samples prepared by wet granulation, stored long-term (up to 6 months), and subjected to accelerated stability conditions (elevated heat and humidity). The highest inhibition of NBMT formation among the antioxidants was observed with ascorbic acid followed by caffeic acid, and then ferulic acid. Higher antioxidant concentrations improved the NBMT mitigation. In addition, use of an alkali modifier with sodium bicarbonate was most effective at inhibiting NBMT formation as shown in **Figure 1** below.

RESEARCH HIGHLIGHT *continued*

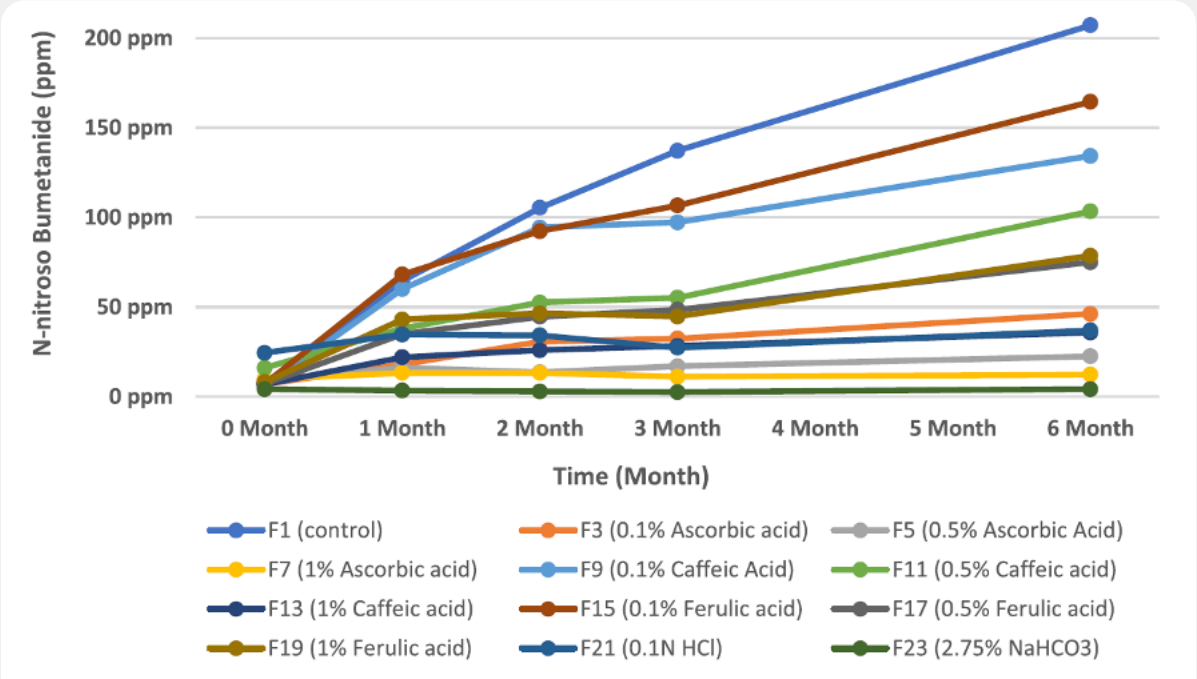

Figure 1: Comprehensive Profiles for N-Nitrosobumetanide Impurity in Stability Samples [Long Term Condition, (25 °C/60% RH)] This research was published in Shakleya D, Asmelash B, Alayoubi A, Abrigo N, Mohammad A, Wang J, Zhang J, Yang J, Marzan T, Li D, Shaklah M, Alsharif F, Desai S, Faustino P, Muhammad A, O'connor T, Vera M, Raw A, Sayeed V, and Keire D. *Bumetanide as a Model NDSRI Substrate: N-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets.* Journal of Pharmaceutical Sciences. (2023) S0022-3549(23): 00244-7.

Results from different published studies and internal research suggested that a small amount (1-2%, w/w) of an antioxidant in a drug product could potentially inhibit the formation of N-nitrosamine impurities. However, it is unknown whether antioxidants may have any impact on drug absorption through the gastrointestinal (GI) tract by affecting the permeability of the intestinal membrane or intestinal transporter functions, which dictate drug bioavailability and/or bioequivalence. The external research contract (75F40119D10024-75F40122F19003) with Pharmaron (Exton) Lab Services LLC investigated the impact of some frequently used antioxidants (e.g., ascorbic acid, alpha-tocopherol, propyl gallate, cysteine hydrochloride) on the in vitro permeability of four BCS III (high solubility and low permeability) model drugs such as ranitidine, atenolol, acyclovir, and cimetidine using “In Vitro Dissolution Absorption System (IDAS)” model supplemented with Caco-2 monolayer system. In brief, this in vitro study measured the rate of permeation of the model drugs (pre-dissolved) in the absence and presence of four antioxidants (one at a time), each at three concentrations (0.01 mg/mL, 0.02 mg/mL, 0.04 mg/mL). The model drug atenolol was always co-incubated with the other three model drugs in the permeation study; atenolol is commonly used as a cell monolayer integrity marker in Caco-2 monolayer systems. The result of this permeation study is shown in **Table 1** below. The four antioxidants did not have any significant impact on the permeability of these model BCS III drugs in the antioxidant concentration ranges evaluated.

RESEARCH HIGHLIGHT *continued*

Table 1: The effects of antioxidants on the in vitro permeability of selected BCS III drugs

Treatment		Mean P_{app} (10^{-6} cm/s)			
		Acyclovir	Atenolol	Ranitidine	Cimetidine
Ascorbic acid	Control	0.28	0.396	0.448	0.931
	0.01 mg/mL	0.278	0.364	0.438	0.952
	0.02 mg/mL	0.262	0.363	0.443	0.928
	0.04 mg/mL	0.216	0.296	0.469	0.933
Cysteine	Control	0.275	0.297	0.406	0.883
	0.01 mg/mL	0.307	0.357	0.419	0.845
	0.02 mg/mL	0.362	0.355	0.461	0.861
	0.04 mg/mL	0.347	0.352	0.507	0.836
Propyl Gallate	Control	0.425	0.445	0.409	0.619
	0.01 mg/mL	0.435	0.429	0.405	0.605
	0.02 mg/mL	0.362	0.364	0.386	0.727
	0.04 mg/mL	0.372	0.37	0.348	0.66
α-Tocopherol	Control	0.295	0.283	0.381	0.678
	0.01 mg/mL	0.285	0.287	0.354	0.622
	0.02 mg/mL	0.285	0.287	0.383	0.802
	0.04 mg/mL	0.259	0.259	0.378	0.764

Note: The high test concentration of antioxidant (i.e., 0.04 mg/mL) is based on the assumption of a 500 mg dosage unit weight; 2% of 500 mg is 10 mg, and 10 mg in 250 mL is 0.04 mg/mL. The mid test concentration is 50% of the high test concentration; and the low test concentration is 50% of the mid test concentration.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grant(s) and Contract(s)

- Grant (3U01FD005978) *Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters* with Dr. Sook Wah Yee at UCSF

Completed Grant(s) and Contract(s)

- Contract (75F40119D10024-75F40122F19003) *Quality and Bioequivalence Considerations for Generic Drug Reformulation to Mitigate Nitrosamine Risks* with Dr. Chris Bode at Pharmaron

Active FDA Research

- *Assessing the Prevalence of NDSRI Contamination in Pharmaceutical Products and Gaining Insights into the Contributing Factors for the Contamination by Screening NDSRIs in Various Drug Products*
- *Evaluating the Mutagenicity of Nitrosamines and NDSRIs Using Different In Vitro Assay Methods*
- *Excipient-Mediated Nitrosamine Formation in Pharmaceuticals: Approaches to Risk Assessment and Mitigation*
- *Investigation of N-Nitroso Compounds Formation in Pharmaceuticals: Risk Assessment, Approaches and Analytical Methods*
- *In Vitro and In Silico Modeling Approaches for Supporting Biowaiver for Non Q1/Q2 BCS Class 3 Drug Products*
- *Mitigation Studies of Nitrosamine Formation in Metformin and Bumetanide Drug Products*
- *Roles of Excipients in the Formation of NDMA in Metformin Drug Products*

OUTCOMES

General Guidance

- FDA Guidance for Industry. *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities.* August 2023. Link to Posting

Articles

- Li X, He X, Le Y, Guo X, Bryant M, Atrakchi A, Mcgovern T, Davis Bruno K, Keire D, Heflich R, and Mei N. *Genotoxicity Evaluation of Nitrosamine Impurities using Human TK6 Cells Transduced with Cytochrome P450s.* Archives of Toxicology. (2022) 96(11). https://doi.org/10.1007/s00204-022-03347-6. PMID: 35882637.
- Li X, Le Y, Seo J, Guo X, Li Y, Chen S, Mittelstaedt R, Moore N, Guerrero S, Sims A, King S, Atrakchi A, Mcgovern T, Davis Bruno K, Keire D, Elespuru R, Heflich R, and Mei N. *Revisiting the Mutagenicity and Genotoxicity of N-nitroso Propranolol in Bacterial and Human in Vitro Assays.* Regulatory Toxicology and Pharmacology. (2023) 141(105410). https://doi.org/10.1016/j.yrtph.2023.105410. PMID: 37210026.

OUTCOMES *continued*

- Shakleya D, Asmelash B, Alayoubi A, Abrigo N, Mohammad A, Wang J, Zhang J, Yang J, Marzan T, Li D, Shaklah M, Alsharif F, Desai S, Faustino P, Muhammad A, O'connor T, Vera M, Raw A, Sayeed V, and Keire D. *Bumetanide as a Model NDSRI Substrate: N-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets.* Journal of Pharmaceutical Sciences. (2023) S0022-3549(23): 00244-7. https:/doi.org/10.1016/j.xphs.2023.06.013. PMID: 37364772.

- Yang J, Kakarla R, Marzan T, Sherwin T, George M, Bennett J, Basutto J, Su Y, Ollerenshaw J, Morin J, Rebiere H, Maggio A, Kermaidic A, Gervela E, Breniew C, Civade C, Chauvey D, Duperray F, Wollein U, Conti M, Tromp J, Meyer S, Wanko R, Wierer M, Bertrand M, Rodriguez J, Sommers C, and Keire D. *Performance Characteristics of Mass Spectrometry-Based Analytical Procedures for Quantitation of Nitrosamines in Pharmaceuticals: Insights from an Inter-laboratory Study.* Journal of Pharmaceutical Sciences. (2023) 112 (10) 2685-2695. https://doi.org/10.1016/j.xphs.2023.07.022. PMID: 37524228.

Posters

- Li X, Le Y, Seo J, Guo X, Atrakchi A, Mcgovern T, Davisburno K, Keire D, Heflich R, and Mei N. *Assessing the In Vitro Mutagenicity and Genotoxicity of Nitrosamine Drug Substance-Related Impurities (NDSRIs): A Case Study on N-nitroso Propranolol.* Poster Presentation at the 54th Annual Meeting of Environmental Mutagenesis and Genomics Society (EMGS). Chicago, IL, Sep. 10, 2023.

- Koleske M, Kulkarni C, Alam K, Raw A, Rege B, Zhao L, Lu D, Zhang L, Giacomini K, Kroetz D, and Yee S. *Effects of Antioxidants in Drug Products on Intestinal Drug Transporters.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2023 Annual Meeting. Atlanta, GA, Mar. 23, 2023.

- Li X, He X, Le Y, Guo X, Bryant M, Atrakchi A, Mcgovern T, Davis Bruno K, Keire D, Heflich R, and Mei N. *Nitrosamine Drug Impurities Induce Genotoxicity in Human Lymphoblastoid TK6 Cells.* Poster Presentation at the 62nd Annual Meeting of Society of Toxicology (SOT). Nashville, TN, Mar. 19, 2023.

- Seo J, Yu J, Mei N, Heflich R, and Guo X. *Assessment of DNA Damage–induced by 10 Nitrosamine Impurities using 2D and 3D HepaRG Models.* Poster Presentation at the 62nd Annual Meeting of Society of Toxicology (SOT). Nashville, TN, Mar. 19, 2023.

Presentations

- Li Li X. *Genotoxicity Assessment of Eight Nitrosamine Impurities using 2D and 3D HepaRG Cell Models.* Presentation at the 54th Annual Meeting of Environmental Mutagenesis and Genomics Society (EMGS). Chicago, IL, Sep. 09, 2023.

- Heflich R. *Nitrosamine Drug Impurities and Nitrosamine Drug Substance Related Impurities: Optimizing Mutagenicity Testing.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting. Rockville, MD, Jun. 15, 2023.

OUTCOMES *continued*

- Kruhlak N. *Using Structure-Activity Relationships to Inform Setting Acceptable Intakes for Nitrosamine Impurities.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Lu D. *FDA Guidance - Control of Nitrosamines in Human Drugs.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Shakleya D. *Effectiveness of Antioxidants in Selected Model Drugs: Mitigation Strategy and Impact of Reformulation in their Stability.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting. Rockville, MD, Jun. 15, 2023.
- Wu F. *Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling to Evaluate the Impact of Excipients on Bioequivalence of BCS Class III Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Yang J. *Performance Characteristics of Mass Spectrometry Based Methods for Quantitation of Nitrosamines: Insight from an Inter-laboratory Study.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Heflich R. *FDA/NCTR Activities: Ames Optimization Effort and In Vitro Alternatives.* Presentation at the FDA and the Health and Environmental Science Institute (HESI) Workshop on Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs. Virtual Meeting, May 31, 2023.
- Shakleya D. *Nitrosamine Additives Mitigation Studies.* Presentation at the Fiscal Year (FY) 2023 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, May 11, 2023.
- Heflich R. *Work Being Done at FDA/NCTR with HepaRG cells.* Presentation at the Health and Environmental Sciences Institute (HESI)- Genetic Toxicology Technical Committee (GTTC) Annual Meeting. Hybrid Meeting. Washington, DC, May 08, 2023.
- Keire D. *Mitigation Studies for Nitrosamines in Pharmaceutical Formulations.* Presentation at Small Business and Industry Assistance (SBIA) - Generic Drugs Forum (GDF) 2023: Celebrating 10 Years of the GDF. Virtual Meeting, Apr. 13, 2023.
- Shakleya D. *Development and Validation of Ion Chromatography Methods for the Evaluation of Nitrosamine Precursors (Nitrite, Nitrate, and Dimethylamine).* Presentation at American Chemical Society (ACS) Spring 2023: Crossroads of Chemistry. Indianapolis, IN, Mar. 26, 2023.
- Heflich R. *Research Being Conducted at NCTR/FDA on N-Nitrosamine Impurities.* Presentation at the 2022 Association for Affordable Medicines (AAM): GRx + Biosims Conference. North Bethesda, MD, Nov. 07, 2022.

CHAPTER 2: COMPLEX APIs

A major GDUFA science and research priority is to enhance the efficiency of equivalence approaches for complex active pharmaceutical ingredients (APIs), such as peptides and oligonucleotides. The advancement of research in this area focuses on improving advanced orthogonal methods for the characterization of chemical compositions, molecular structures, and distributions of complex APIs and associated impurity profiles. These methods can be used to elucidate attributes of complex APIs and support immunogenicity risk assessments that may be critical to their performance and, thereby, support the development of efficient characterization-based bioequivalence (BE) and pharmaceutical equivalence (PE) approaches. Research in this area is described below.

Summary of FY 2023 Activities

In FY 2023, research efforts continued to focus on the characterization of complex API drug products with an emphasis on peptide, oligonucleotide, and other polymeric APIs. FDA has seen an increase in the approval of drug products with complex APIs, and the availability of generic versions of these products are critical to increasing public access to important medications. The characterization of complex APIs and related impurities is challenging and requires highly sensitive and precise analytical techniques to demonstrate sameness between the active ingredient in a proposed generic drug product and the brand drug product.

Physicochemical characterization of peptides requires analytical techniques that interrogate the primary sequence and probe higher order structures (HOS). Differences in peptide HOS can inhibit receptor binding, expose immunogenic epitopes, and give rise to aggregation. A multivariate nuclear magnetic resonance (NMR) method was developed to assess HOS. The method was applied to recently approved peptide drugs, including the first generics of glucagon, calcitonin salmon, and other shorter peptide drugs such as icatibant and leuprolide. Additionally, as presented in the **Research Highlight** section below, diffusion ordered spectroscopy (DOSY)-NMR and dynamic light scattering (DLS) methods were developed to assess oligomerization of chemically modified peptides.

Synthetic oligonucleotides therapeutics (ONTs) contain a class of complex APIs that have the potential to open new treatment pathways for rare life-threatening diseases previously considered “undruggable”. However, the complex molecular and impurity profiles inherent in ONTs lead to analytical and regulatory challenges. FDA laboratories developed a liquid chromatography high resolution mass spectrometry-based multi-attribute method for oligonucleotides (MAMO). It is a quality control analytical platform that can be used throughout an ONT product life cycle. FDA continues to engage with external collaborators to develop analytical methods to analyze diastereomeric compositions of ONTs with phosphorothioate linkages, which includes supporting research through a Grant (1U01FD007651) to the University of Maryland, Baltimore to investigate the diastereomeric composition of inotersen injection.

The orphan drug Elmiron® (pentosan polysulfate sodium [PPS]) is used to treat bladder pain syndrome, which is also known as interstitial cystitis. The complex API, PPS, is a heterogenous mixture of chemically modified polysaccharides. PPS is sourced from the beechwood tree, followed by chemical processing to yield a mixture of 4–6 kDa poly-xylose with branched 4-O-methyl-glucuronate (MGA). Quality attributes (QA) of PPS, which are expected to be similar between brand and generic products, include polymer length distribution, monosaccharide composition, sequence effect, reducing end heterogeneity, degrees of sulfation, and acetylation. FDA research using 2D NMR spectroscopy assessed the QAs and evaluated lot-to-lot variability of the brand drug.

RESEARCH HIGHLIGHT

DLS and DOSY-NMR methods were developed to assess oligomerization in peptide drug formulations. These methods provide information about molecular size of peptide oligomers by measuring their diffusion coefficient (D). A linear correlation of log(D) vs. log(MW_{hd}) was established to derive hydrodynamic MW (MW_{hd}) based on experimental D, where MW_{hd} is a new representation of the hydrodynamic volume. The MW_{hd} was directly used to assess oligomerization of the peptide in a formulation. Two peptide drug products, liraglutide and semaglutide, were studied. Different oligomer species were shown in the multi-exponential signal decay curves for liraglutide (**Figure 1a**) and semaglutide (**Figure 1b**). The DLS measured MW_{hd} can be compared to the expected monomeric MW_{hd} value to predict oligomerization through the ratio values. Here, the D_{dls} predicted MW_{hd} of liraglutide in formulation was 20 kDa, 5.3-fold more than the monomeric MW_{hd} value of 3.8 kDa. Therefore, the primary species of liraglutide in formulation could be either a pentamer or a hexamer. Similarly, the D_{dls} predicted MW_{hd} of semaglutide in formulation was 10 kDa, 2.4-fold more than the monomeric MW_{hd} of 4.1 kDa. Therefore, the primary species of semaglutide was predicted to be either a dimer or a trimer. DOSY-NMR was also used to measure the average diffusion coefficient among the fast-exchanging species for liraglutide (**Figure 1c**) and semaglutide (**Figure 1d**) and only one apparent diffusion coefficient was obtained for each measurement. The D_{nmr} results were between the primary and secondary species of D_{dls}. When the D_{nmr} results were converted to MW_{hd}, the DOSY-NMR-derived MW_{hd} values were larger than the DLS-derived MW_{hd} for the primary species. Therefore, within the DOSY diffusion time of 0.5 s, peptides were exchanging between oligomeric species, slowing down the translation diffusion coefficient D_{nmr}. By contrast, in the DLS measurement window of 0.1 s, the chemical exchange was not effectively averaged.

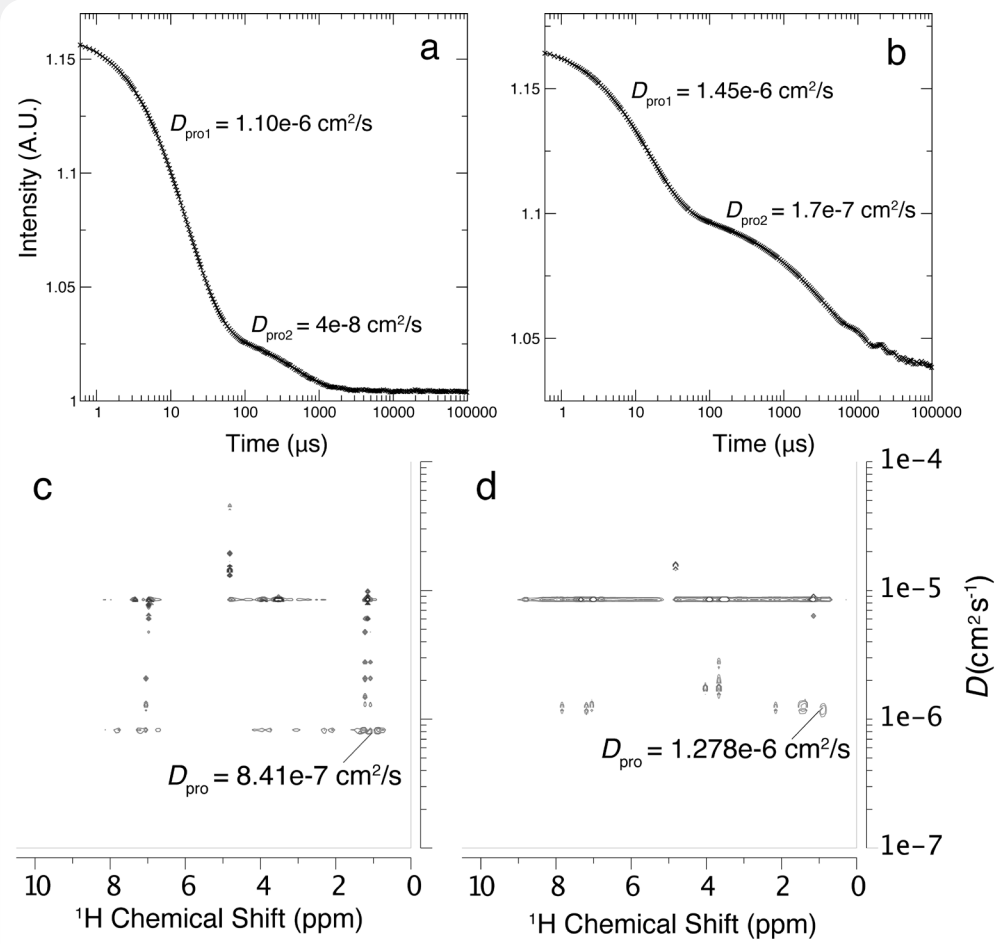

Figure 1. Comparison of orthogonal DLS decay curves (a, b) and DOSY-NMR spectra (c, d) used to measure diffusion coefficients (D) for liraglutide (a, c) and semaglutide (b, d). The diffusion coefficients provide information about molecular size of peptide oligomers.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40123C00118) *Investigating the Impact of API Purity, Lipid Source and Manufacturing Process on Performance and Quality of Complex siRNA Lipid Nanoparticles* with Xiuling Lu at University of Connecticut

Continuing Grant(s) and Contract(s)

- Grant (1U01FD007651) *Multidimensional Analytical and Computational Approach to Determine Diastereomer Compositions in Oligonucleotide Drug Products* with Jace Jones at University of Maryland Baltimore

Active FDA Research

- *Analytical Characterization of Recombinant and Synthetic Peptide Product Impurities*
- *API Characterization and Impurity Profiling of Synthetic Oligonucleotides Using MS-based Multi-Attribute Method for Oligonucleotides (MAMO) Platform*
- *Assessment of Higher Order Structure Equivalence between Reference Peptide/Protein/Nucleic Acid Drug and its Follow-on/Generic/Biosimilar products using NMR Spectroscopy*
- *Characterization of Active Pharmaceutical Ingredients in Premarin (Conjugated Estrogen Creams)*
- *Developing High-resolution NMR Methods for Characterizing Multi-attributes of Complex API Mixtures*
- *Development and Optimization of Bioassays to Assess Immunogenicity Risk of Product and Process Related Impurities*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *In Vitro Innate Immune Response Assessment*
- *Process-Related Impurity Profile Characterization in Peptide Drug Products*

OUTCOMES

General Guidance

- FDA Draft Guidance for Industry. *Sameness Evaluations in an ANDA — Active Ingredients.* November 2022. Link to posting

Product-Specific Guidances

There were 15 new and 1 revised product-specific guidances (PSGs) published in FY 2023 related to *Complex Active Ingredient* products. PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Calcitonin Salmon Injection Injectable.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Casimersen Intravenous Solution.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Defibrotide Sodium Intravenous Solution.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Eteplirsen Intravenous Solution.* (Nov. 17, 2022) Link to Posting

OUTCOMES *continued*

- *New Draft Guidance for Givosiran Sodium Subcutaneous Solution.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Glucagon Nasal Powder.* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Glucagon Subcutaneous Solution.* (Aug. 21, 2023) Link to Posting
- *New Draft Guidance for Golodirsen Intravenous Solution.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Inclisiran Sodium Subcutaneous Solution.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Inotersen Sodium Subcutaneous Solution.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Lumasiran Sodium Subcutaneous Solution.* (Aug. 21, 2023) Link to Posting
- *New Draft Guidance for Patisiran Sodium Intravenous Solution.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Tirzepatide Subcutaneous Solution.* (Aug. 21, 2023) Link to Posting
- *New Draft Guidance for Viltolarsen Intravenous Solution.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Vosoritide Subcutaneous Powder.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Vutrisiran Sodium Subcutaneous Solution.* (Aug. 21, 2023) Link to Posting

Articles

- Chen K, and Smith C. *Best Practices for Submission of NMR Data to Support Higher Order Structure Assessment of Generic Peptide Drugs.* The AAPS Journal. (2023) 25. https://doi.org/10.1208/s12248-023-00782-w. PMID: 36670271.
- De Groot A, Roberts B, Mattei A, Lalias S, Boyle C, and Martin W. *Immunogenicity Risk Assessment of Synthetic Peptide Drugs and Their Impurities.* Drug Discovery Today. (2023) 28(103714). https://doi.org/10.1016/j.drudis.2023.103714. PMID: 37467878.
- Henry SP, Arfvidsson C, Arrington J, Canadi J, Crowe D, Gupta S, Lohmann S, Massonnet B, Mytych D, Rogers T, Rogers H, Stebbins C, Stovold C, Verthelyi D, Vigil A, Xuan C, Xu Y, Yu R, Klem T. *Assessment of the Immunogenicity Potential for Oligonucleotide-Based Drugs.* Nucleic Acid Therapeutics. 2022 Oct;32(5):369-377. https://doi.org/10.1089/nat.2021.0112. PMID: 36178478
- Jani D, Marsden R, Gunsior M, Hay L, Ward B, Cowan K, Azadeh M, Barker B, Cao L, Closson K, Coble K, Dholakiya S, Dusseault J, Hays A, Herl C, Hodson M, Irvin S, Kirshner S, Kolaitis G, Kulagina N, Kumar S, Lai C, Lipari F, Liu S, Merdek K, Moldovan I, Mozaffari R, Pan L, Place C, Snoeck V, Manning M, Stocker D, Tary-Lehmann M, Turner A, Vainshtein I, Verthelyi D, Williams W, Yan H, Yan W, Yang L, Yang L, Zemo J, and Zhong Z. *Anti-drug Antibody Sample Testing and Reporting Harmonization.* The AAPS Journal. (2022) 24: 113. https://doi.org/10.1208/s12248-022-00762-6. PMID: 36307592.

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- Wang K, and Chen K. *Direct Assessment of Oligomerization of Chemically Modified Peptides and Proteins in Formulations using DLS and DOSY-NMR.* Pharmaceutical Research. (2023) 40(6): 1329-1339. https://doi.org/10.1007/s11095-022-03468-8. PMID: 36627448.

OUTCOMES *continued*

- Wang K, Dai W, Qian K, Scott B, and Chen K. *A Precise qNMR Method for the Rapid Quantification of Lot-To-Lot Variations in Multiple Quality Attributes of Pentosan Polysulfate Sodium.* The AAPS Journal. (2023). 25(3). https://doi.org/10.1208/s12248-023-00815-4. PMID: 37147461.
- Wang D, Su Y, and Chen K. *Fast Dynamics of Difluprednate in Micelles or Swollen-Micelles Revealed by 19F Nuclear Magnetic Resonance Spin Relaxation Rates.* The Journal of Physical Chemistry Letters. (2023) 14: 4837-4841. https://doi.org/10.1021/acs.jpclett.3c00846. PMID: 37193655.

Posters

- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Otte A, Xu X, Jhon Y, Qin B, and Wang Y. *Scanning Analysis of Semi-solvent Vapor Impact (SAVI): Microstructural and Compositional Analysis of Leuprolide-loaded Poly(lactide-co-glycolide) Microparticles.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Dieke N, Shipman J, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *High-Resolution Ion Mobility Mass Spectrometry (IMMS) for Oligonucleotide Impurity Analysis.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Islam M, Abdullah A, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *Validation of HILIC-HRMS Method for Oligonucleotide Analysis.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Islam A, Abdullah A, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *Validation of HILIC-HRMS Method for Quantitative Oligonucleotide Analysis.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 71st Conference on Mass Spectrometry and Allied Topics. Houston, TX, Jun. 04, 2023.
- Pang E, Liao K, Holley C, Dobrovolskaia M, and Verthelyi D. *In-Vitro Assessment of Comparative Immunogenicity for Generic Synthetic Peptide Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Chen, K. *NMR as a Multi-Attribute Method in Complex Drug Analysis: Pentosan Polysulfate Sodium.* Presentation at the 30th Symposium on Glycosaminoglycans. Hybrid Meeting. Loveno di Menaggio, Italy, Sep. 21, 2023.
- Al Ghabeish M. *Q1 and Q2 Recommendations: Sucralfate Oral Suspension.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Pang E. *PSG Recommendations for Risk-based Comparative Immunogenicity and Impurity Profile Assessment.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.

OUTCOMES *continued*

- Yang K. *LC-HRMS-based Multi-Attribute Method for Oligonucleotides (MAMO) to Resolve Complexities.* Presentation at the 3rd Chinese American Society Mass Spectrometry Annual Conference. Virtual Meeting, Aug. 28, 2023.
- Verthelyi, D. *Tools to Assess Immunogenicity Risk and New Computational Methods.* Presentation at the 17th Workshops on Recent Issues in Bioanalysis (WRIB). Orlando, FL, Jun. 20, 2023.
- Abdullah A. *Comprehensive Impurities Profiling in Synthetic Oligonucleotides by High-resolution Mass Spectrometry Intact Mass Data Processing.* Presentation at the American Society for Mass Spectrometry (ASMS) - 71st Conference on Mass Spectrometry and Allied Topics. Houston, TX, Jun. 08, 2023.
- Yang K, Abdhullah A, Islam R, Dieke N, Sommers C, Rodriguez J, Zhang D, Kozak D, and Keire D. *LC-HRMS-based Multi-Attribute Method for Oligonucleotides (MAMO).* Presentation at the American Society for Mass Spectrometry (ASMS) - 71st Conference on Mass Spectrometry and Allied Topics. Houston, TX, Jun. 08, 2023.
- Dieke N, Shipman J, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *High-Resolution Ion Mobility Mass Spectrometry for Oligonucleotide Impurity Analysis.* Presentation at the American Society for Mass Spectrometry (ASMS) - 71st Conference on Mass Spectrometry and Allied Topics. Houston, TX, Jun. 06, 2023.
- Verthelyi, D. *Innate Immune Response Modulating Impurities Testing for Generics and Biosimilars: Where We Are and What We Are Missing.* Presentation at the 19th Annual PEGS BOSTON Summit – the Essential Protein and Antibody Engineering. Boston, MA, May 15, 2023.
- Chen, K. *Direct Assessment of Oligomerization of Chemically Modified Peptides and Proteins in Formulations using DLS and DOSY-NMR.* Presentation at the Analytical Technologies Europe: Symposium on Analytical Sciences and Regulatory Trends in the Biopharmaceutical Industry 2023. Rotterdam, Netherlands, May 12, 2023.
- Verthelyi, D. *Current FDA Thinking on the use of Non-Clinical Tools in Immunogenicity Risk Assessments: Possibilities and Challenges.* Presentation at the 14th Open Scientific EIP Symposium on Immunogenicity of Biopharmaceuticals. Lisbon, Portugal, Apr. 27, 2023
- Chen K. *High Resolution 1D and 2D NMR in Complex Drug Analysis: Pentosan Polysulfate Sodium.* Presentation at the Pharmaceutical Analysis and Characterization-Center of Excellence. Virtual Meeting, Mar. 17, 2023.
- Chen, K. *2D HSQC Peak Profile Method to Compare Chemical Differences between Batches of Pentosan Polysulfate Sodium.* Presentation at the 2nd USP qNMR Symposium. Virtual Meeting, Jan. 09, 2023.
- Hu M. *Use of Data Analytics Approaches to Support Regulatory Assessment - from FDA Perspective.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.

CHAPTER 3: COMPLEX DOSAGE FORMS & FORMULATIONS

A major GDUFA science and research priority is to enhance the efficiency of bioequivalence (BE) approaches for complex dosage forms and formulations, such as long-acting injectable, insertable or implantable (collectively, LAI) products, and nanotechnology products. The advancement of research in this area focuses on improving efficient characterization-based (in vitro) BE approaches for complex dosage forms by identifying relevant critical quality attributes (CQAs) to characterize and developing suitable test methods. Research in this area is described below, highlighting LAI products and nanotechnology products independently in separate sub-sections.

LONG-ACTING INJECTABLE, INSERTABLE, OR IMPLANTABLE PRODUCTS

Summary of FY 2023 Activities

In FY 2023, the LAI product research program investigated poly (lactide-co-glycolide) (PLG) polymers-based products (i.e., microspheres, in situ forming implants, solid implants), ethylene-vinyl acetate (EVA)-based implants, drug substance-based injectable suspensions, multivesicular liposomes (MVL), and intrauterine systems (IUSs).

For the PLG polymer-based products, research efforts included 1) developing new analytical tools for separating and characterizing PLG polymer mixtures, 2) investigating the impact of raw materials and manufacturing parameters on formulation performance, and 3) exploring in vitro-in vivo correlation (IVIVC) using advanced imaging tools. GDUFA-funded research on biodegradable PLG)-based long-acting injectable (LAI) products during the last decade has focused on developing analytical methods to facilitate the reverse engineering, characterization, and selection of suitable PLGA polymers - a critical first step for generic product development. The research also focused on developing suitable in vitro drug release testing methods that elucidated how a drug is released from such a formulation and how different manufacturing processes and polymer characteristics can influence that drug release.

This research enabled FDA to publish and update recommendations in product-specific guidances (PSGs) for such products, and established criteria that prepared FDA to assess the BE of a generic LAI PLGA product in an abbreviated new drug application (ANDA) submission. This led to the approval on July 6, 2023, of the first generic naltrexone extended-release injectable suspension (referencing Vivitrol®) which uses an LAI PLGA polymer microsphere technology. This first generic approval is notable not only because of how scientifically challenging it was to develop, manufacture, and demonstrate BE for this product, but also because this product treats alcohol dependence and prevents relapse to opioid dependence - two major public health issues affecting millions of individuals in the United States.

A method based on sequential semi-solvent showed the potential to effectively separate PLG mixtures in a formulation when the polymers differ in the ratio of lactide and glycolide[1]. In addition, analytical and characterization methods were developed and published for reverse engineering a dexamethasone intravitreal ophthalmic implant referencing OZURDEX[2], risperidone PLG-based in situ forming implant referencing PERSERIS[3], and PLG microspheres containing leuprolide acetate refencing LUPRON DEPOT[4]. The results of investigations into the mechanism of drug release from the dexamethasone intravitreal implant and the in vivo drug release characteristics of the risperidone in situ forming implant

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1 Garner J, Skidmore S, Hadar J, Park H, Park K, Qin B, Wang Y. *Surface Analysis of Sequential Semi-Solvent Vapor Impact (SAVI) for Studying Microstructural Arrangements of Poly (Lactide-Co-Glycolide) Microparticles.* Journal of Controlled Release. (2022) 350: 600-612. https://doi.org/10.1016/j.jconrel.2022.08.052. PMID: 36057396.

2 Costello M, Liu J, Wang Y, Bin Q, Xu X, Li Q, Lynd N, and Zhang F. *Reverse Engineering the Ozurdex Dexamethasone Intravitreal Implant.* International Journal of Pharmaceutics. (2023) 634: 122625. https://doi.org/10.1016/j.ijpharm.2023.122625 PMID: 36690129.

3 Wang X, Bao Q, Wang R, Wan B, Wang Y, and Qin B. *Reverse Engineering of Perseris and Development of Compositionally Equivalent Formulations.* International Journal of Pharmaceutics. (2023) 639: 122948. https://doi.org/10.1016/j.ijpharm.2023.122948. PMID: 37044228.

4 Schutzman R, Shi N, Olsen K, Ackermann R, Tang J, Liu Y, Hong J, Wang Y, Qin B, Schwendeman A, and Schwendeman S. *Mechanistic Evaluation of the Initial Burst Release of Leuprolide from Spray-Dried PLGA Microspheres.* Journal of Controlled Release. (2023) 361: 297-313. https://doi.org/10.1016/j.jconrel.2023.06.016. PMID: 37343723.

were also published[5,6]. Advanced imaging techniques, including focused ion beam scanning electron microscopy (FIB-SEM), X-ray microtomography, microcomputed tomography (microCT), and 3D laser scanning microscopy, were employed to explore IVIVCs for PLG microspheres, in situ forming implants, and solid implants.

In addition, preliminary data were generated showing the potential impact of raw materials and manufacturing parameters on drug release kinetics from EVA-based implants prepared using hot-melt extrusion. Progress was also made in the development of accelerated in vitro drug release testing (IVRT) conditions and real time IVRT for IUS products. One of the main objectives was to develop an accelerated IVRT method that correlates with the real time drug release. The development of this method could support a demonstration BE and facilitate product development by potentially shortening the time to conduct an IVRT, compared to performing real time IVRT.

An IVIVC for medroxyprogesterone acetate suspensions was developed using a rabbit model. The study results provided insights on critical formulation attributes and drug release kinetics which are helpful to further explore an in vitro BE approach and develop a physiologically based (mechanistic) approach to establish IVIVC for drug substance suspensions[7]. The research efforts on injectable drug substance suspension are continuing and will focus on developing physiologically based pharmacokinetic (PBPK) models.

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[6] Wang X, Bao Q, Wang R, Kwok O, Maurus K, Wang Y, Qin B, and Burgess D. *In Situ Forming Risperidone Implants: Effect of PLGA Attributes on Product Performance.* Journal of Controlled Release. (2023) 361: 777-791. https://doi.org/10.1016/j.jconrel.2023.08.029. PMID: 37591464.

[7] Bao Q, Wang X, Wan B, Zou Y, Wang Y, and Burgess D. *Development of In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* International Journal of Pharmaceutics. (2023) 634: 122642. https://doi.org/10.1016/j.ijpharm.2023.122642. PMID: 36709013.

RESEARCH HIGHLIGHT

Among complex products, LAIs present unique challenges to generic product development involving various aspects of complexity. Formulation design is generally complex, and clinical approaches by which to demonstrate BE are generally unfeasible. To promote generic product development, research efforts sought to understand the impact of variation in raw materials and manufacturing parameters on PLG-based implants using hot melt extrusion. A dexamethasone intravitreal ophthalmic implant was thoroughly characterized to enable the reverse engineering of the commercial product, OZURDEX (**Figure 1**). Advanced imaging techniques such as SEM and microCT revealed that the implant exhibits an irregular surface and an internal porosity of approximately 6%. Thermal and spectroscopic analyses showed limited interaction between the dexamethasone and the PLG mixture, resulting in a two-phase system of dexamethasone crystals embedded within a PLG matrix. IVRT was carried out to determine drug release mechanisms from the implant (**Figure 2**). The implant exhibited a triphasic release profile in 37 °C normal saline and 11.9 mM phosphate buffered saline (PBS) pH 7.4 with a burst release phase, a lag phase, and secondary steady state release phase where the remainder of the dexamethasone was released. The overall dexamethasone release was accelerated in saline compared to PBS due to the absence of pH buffering, which led to auto-catalysis of PLG degradation. Drug release and total implant mass loss was closely related indicating that the release was mainly driven by polymer degradation. In addition, it was interesting to observe that the surface and the core of the implant showed different kinetics of hydration and degradation which was likely due to diffusional limitations, autocatalytic hydrolysis, and osmotic effects. These findings will be helpful for generic product development and for the development of more efficient BE approaches.

RESEARCH HIGHLIGHT *continued*

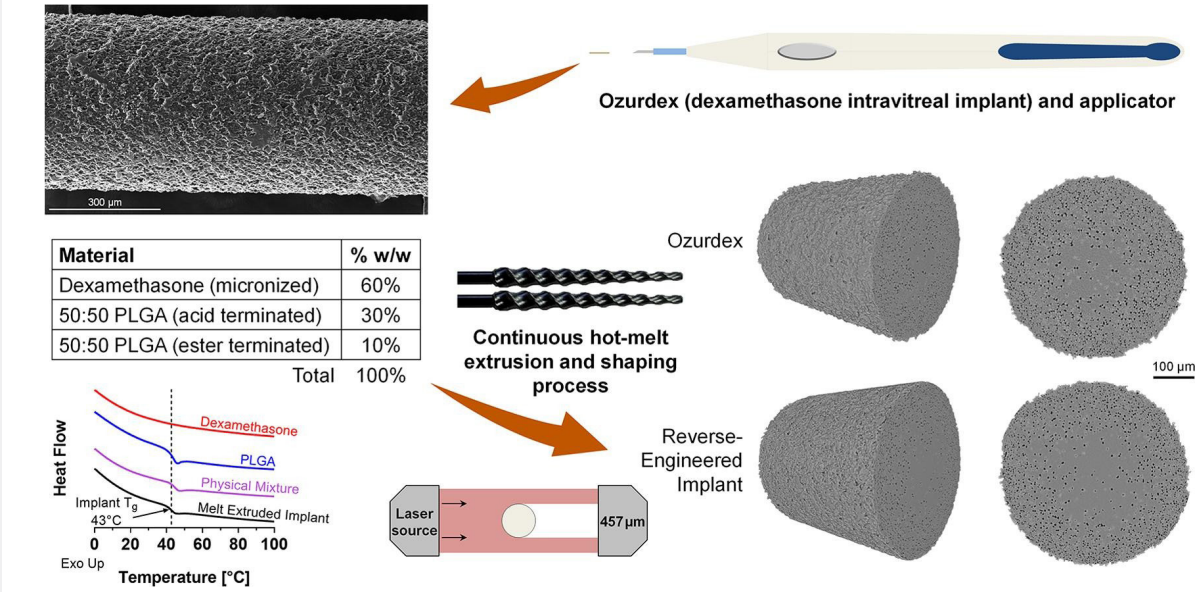

Figure 1. Graphical abstract illustrating the reverse engineering of an OZURDEX implant.

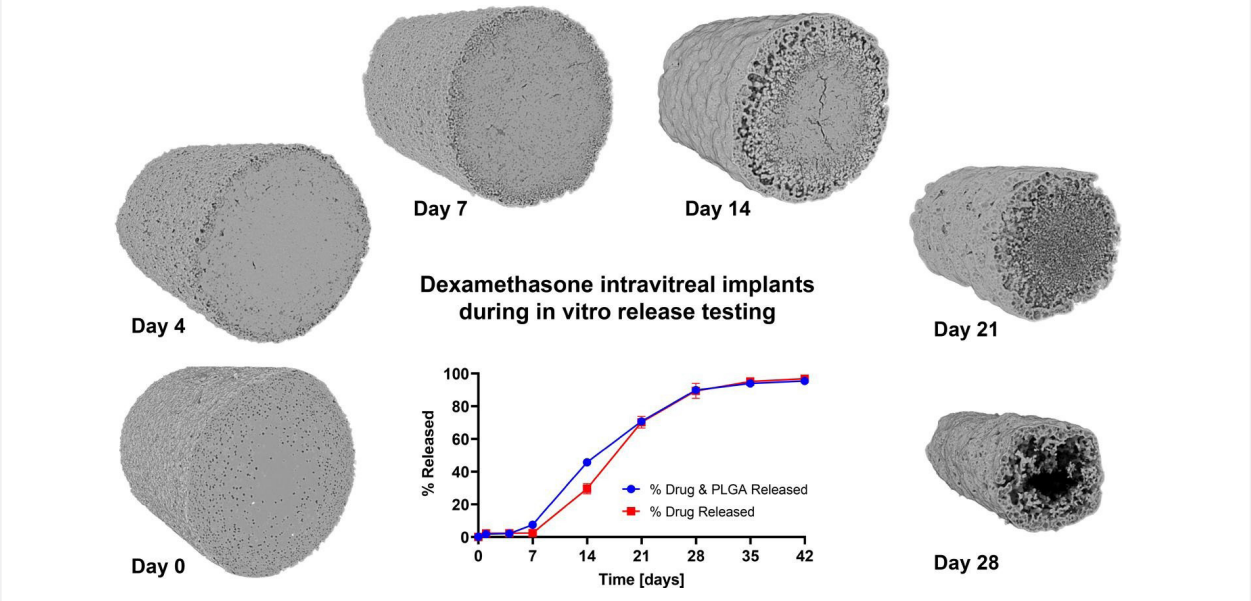

Figure 2. Graphical abstract illustrating dexamethasone release from the implant, and morphological changes during release testing.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40123C00142) *Impact of API CQAs on In Situ Forming Implants and Understanding In Vitro and In Vivo Performance Differences* with Diane J. Burgess at University of Connecticut
- Contract (75F40123C00196) *In Vitro and In Vivo Assessment of Buprenorphine Extended Release Injection for Generic Product Equivalence* with Qingguo Xu at Virginia Commonwealth University
- Contract (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina

Continuing Grants and Contracts

- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane J Burgess at University of Connecticut
- Contract (75F40120C00136) *Assessing Long-Acting Injectable Formulations Using In Vivo Imaging* with Xiuling Lu at University of Connecticut
- Contract (75F40120C00127) *Characterization of Exparel, Understanding of Critical Manufacturing Process Parameters and Characterization of Drug Release Mechanisms In Vitro and In Vivo* with Anna Schwendeman at Regents of the University of Michigan
- Contract (75F40122C00019) *Correlation Between Material Properties Manufacturing Process Structural Properties and Quality Attributes of Long-acting Biodurable Implants Study* with Feng Zhang at University of Texas at Austin
- Contract (75F40122C00163) *Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation* with Shawn Zhang at DigiM Solution LLC
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* with Feng Zhang at University of Texas at Austin
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate their Generic Development* with Diane J 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 Regents of the University of Michigan, College of Pharmacy

Completed 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 J. Burgess at University of Connecticut

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Active FDA Research

- *AI-Assisted Regulatory Tool to Improve the Quality and Assessment of PLGA Formulations*
- *Characterization and Manufacturing Process Evaluation of Multivesicular Liposomes*
- *Characterization of Bupivacaine HCL Implant, Understanding Impact of Variations in Raw Materials and Critical Manufacturing Process Parameters on Formulation Performance*
- *Characterization of Dexamethasone Ophthalmic Insert, Understanding of Raw Materials and Critical Manufacturing Process Parameters and Determination of Drug Release Mechanisms*
- *Comparing the Performance of Neural ODE and Population PK Models in Modeling Long-acting Injectable Products*
- *Evaluation and Development of Model-Integrated Bioequivalence Analysis Strategies*
- *Model Integrated Evidence Based Bioequivalence Using In-Silico Dosing to Steady State for Long Acting Injectable*
- *Product and Process Understanding of Long-acting Intrauterine System and Development of Accelerated In Vitro Release Testing Methods*

OUTCOMES

Product-Specific Guidances

There were eight new and three revised PSGs published in FY 2023 related to *Injectable, Insertable, or Implantable* products. PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Afamelanotide Subcutaneous Implant. (*Feb. 16, 2023) Link to posting
- *New Draft Guidance for Bimatoprost Ophthalmic Implant.* (May 18, 2023) Link to posting
- *New Draft Guidance for Cabotegravir Intramuscular Suspension.* (May 18, 2023) Link to posting
- *New Draft Guidance for Cabotegravir; Rilpivirine Intramuscular Suspension.* (Feb. 16, 2023) Link to posting
- *New Draft Guidance for Ethinyl Estradiol; Segesterone Acetate Vaginal Ring.* (May 18, 2023) Link to posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant.* (NDA 019726) (Nov. 17, 2022) Link to posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant.* (NDA 020578) (Nov. 17, 2022) Link to posting
- *New Draft Guidance for Leuprolide Mesylate Subcutaneous Emulsion.* (Feb. 16, 2023) Link to posting
- *Revised Draft Guidance for Paliperidone Palmitate Intramuscular Suspension.* (May 18, 2023) Link to posting
- *New Draft Guidance for Triamcinolone Acetonide Injectable Suspension.* (Feb. 16, 2023) Link to posting
- *New Draft Guidance for Triamcinolone Acetonide Intra-Articular Suspension.* (Nov. 17, 2022) Link to posting

OUTCOMES *continued*

Articles

- Fanse S, Bao Q, and Burgess D. *Long-Acting Intrauterine Systems: Recent Advances, Current Challenges, and Future Opportunities.* Advanced Drug Delivery Reviews. 191: 114581. https://doi.org/10.1016/j.addr.2022.114581. PMID: 36270490.

- Bao Q, Wang X, Wan B, Zou Y, Wang Y, and Burgess D. *Development of In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* International Journal of Pharmaceutics. (2023) 634: 122642. https://doi.org/10.1016/j.ijpharm.2023.122642. PMID: 36709013.

- Chandrashekar A, Beig A, Wang Y, and Schwendeman S. *In Vitro Performance of Composition-Equivalent PLGA Microspheres Encapsulating Exenatide Acetate by Solvent Evaporation.* International Journal of Pharmaceutics. (2023) 643: 123213. https://doi.org/10.1016/j.ijpharm.2023.123213. PMID: 37423376.

- Clark A, Wang R, Lomeo J, Wang Y, Zhu A, Shen M, Bao Q, Burgess D, Qin B, and Zhang S. *Investigating Structural Attributes of Drug Encapsulated Microspheres with Quantitative X - ray Imaging.* Journal of Controlled Release. (2023) 358: 626-635. https://doi.org/10.1016/j.jconrel.2023.05.019. PMID: 37209962.

- Costello M, Liu J, Chen B, Wang Y, Qin B, Xu X, Li Q, Lynd N, and Zhang F. *Drug Release Mechanisms of High-Drug-Load, Melt-Extruded Dexamethasone Intravitreal Implants.* European Journal of Pharmaceutics and Biopharmaceutics. (2023) 187: 46-56. https://doi.org/10.1016/j.ejpb.2023.04.003. PMID: 37037387.

- Costello M, Liu J, Wang Y, Bin Q, Xu X, Li Q, Lynd N, and Zhang F. *Reverse Engineering the Ozurdex Dexamethasone Intravitreal Implant.* International Journal of Pharmaceutics. (2023) 634: 122625. https://doi.org/10.1016/j.ijpharm.2023.122625. PMID: 36690129.

- Gong Y, Zhang P, Yoon M, Zhu H, Kohojkar A, Hooker A, Ducharme M, Gobburu J, Celliere G, Gajjar P, Li B, Velagapudi R, Tsang Y, Schwendeman A, Poli J, Fang L, Lionberger R, and Zhao L. *Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products: Summary of Workshop.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12: 624 - 630. https://doi.org/10.1002/psp4.12931. PMID: 36710372.

- Hong J, Schutzman R, Olsen K, Chandrashekar A, and Schwendeman S. *Mapping In Vivo Microclimate pH Distribution in Exenatide-Encapsulated PLGA Microspheres.* Journal of Controlled Release. (2023) 352: 438-449. https://doi.org/10.1016/j.jconrel.2022.08.043. PMID: 36030989.

- Schutzman R, Shi N, Olsen K, Ackermann R, Tang J, Liu Y, Hong J, Wang Y, Qin B, Schwendeman A, and Schwendeman S. *Mechanistic Evaluation of the Initial Burst Release of Leuprolide from Spray-Dried PLGA Microspheres.* Journal of Controlled Release. (2023) 361: 297-313. https://doi.org/10.1016/j.jconrel.2023.06.016. PMID: 37343723.

- Wang R, Bao Q, Clark A, Wang Y, Zhang S, and Burgess D. *Characterization and In Vitro Release of Minocycline Hydrochloride Microspheres Prepared via Coacervation.* International Journal of Pharmaceutics. (2022) 628: 122292. https://doi.org/10.1016/j.ijpharm.2022.122292. PMID: 36252639.

- Wang X, Bao Q, Wang R, Kwok O, Maurus K, Wang Y, Qin B, and Burgess D. *In Situ Forming Risperidone Implants: Effect of PLGA Attributes on Product Performance.* Journal of Controlled Release. (2023) 361: 777-791. https://doi.org/10.1016/j.jconrel.2023.08.029. PMID: 37591464.

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- Wang X, Bao Q, Wang R, Li T, Wang Y, Qin B, Li Q, and Burgess D. *In Vivo Characterization of Perseris and Compositionally Equivalent Formulations.* International Journal of Pharmaceutics. (2023) 642: 123170. https://doi.org/10.1016/j.ijpharm.2023.123170. PMID: 37354927.

- Wang X, Bao Q, Wang R, Wan B, Wang Y, and Qin B. *Reverse Engineering of Perseris and Development of Compositionally Equivalent Formulations.* International Journal of Pharmaceutics. (2023) 639: 122948. https://doi.org/10.1016/j.ijpharm.2023.122948. PMID: 37044228.

- Yilmaz H, Ahmed S, Rodriguez J, and Willett D. *Scanning Electron-Raman Cryomicroscopy for Characterization of Nanoparticle-Albumin Drug Products.* Analytical Chemistry. (2023) 95(5): 2633-2638. https://doi.org/10.1021/acs.analchem.2c03826. PMID: 36693238.

- Yu M, Yuan W, Xia Z, Liu Y, Wang Y, Xu X, Zheng J, and Schwendeman A. *Characterization of Exparel Bupivacaine Multivesicular Liposomes.* International Journal of Pharmaceutics. (2023) 639: 122952. https://doi.org/10.1016/j.ijpharm.2023.122952. PMID: 37054926.

- Zhou J, Schutzman R, Shi N, Ackermann R, Olsen K, Wang Y, and Schwendeman S. *Influence of Encapsulation Variables on Formation of Leuprolide-Loaded PLGA Microsphere.* Journal of Colloid and Interface Science. (2023) 636: 401-412. https://doi.org/10.1016/j.jcis.2022.11.122. PMID: 36640551.

Posters

- Zhao J., Tian G, Smith W, Wang Y., and Xu X. *Impact of Shear Rate on the Flocculation State and Dissolution of Injectable Suspensions: A Numerical Study.* Poster Presentation at the FDA 2023 Scientific Computing Days. Virtual Meeting, Sep. 12, 2023.

- Clark A, Wang R, Wang Y, Qin B, Burgess D, and Zhang S. *Assessing the Impact of Formulation on Microstructure Critical Quality Attributes in PLGA Microspheres.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Das J, Hasan M, Smith W, Graner J, Qin B, Wang Y, Park K, Tian G, and Xu X. *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Lin X, Zouabi N, Ward L, Zhen Z, Masese F, Hargrove D, Yuan H, Beringhs AO, Kasi R, Bin Q, Wang Y, and Lu X. *Assessing In Situ Forming Implant Formulations Using In Vivo Imaging.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Qin B, Wang Y, Zhang Q, Li Q, and Kozak D. *What do We Know About PLGA Polymers in FDA-approved Drug Products: A Journey of Characterizing PLGA Polymers and Formulations.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Wang R, Clark A, Bao A, Wang Y, Qin B, Zhang S, and Burgess D. *Impact of Microstructural Properties on Drug Release from PLGA Microspheres.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

OUTCOMES *continued*

- Nejad HB, Zaman R, Smith W, Wu K, Feng X, O'Reilly Beringhs AO, Wang Y, Kozak D, and Xu X. *Impact of Material and Manufacturing Process on Performance of an Ophthalmic Implant.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Lin X, O'Reilly Beringhs AO, Hargrove D, Jay M, Wang Y, Bin Q, and Lu X. *Assessing In Situ Forming Implant Formulations Using In Vivo Imaging.* Poster Presentation at the 2022 NIPTE Research Conference. Virtual Meeting, Nov. 29, 2022.
- Anno K, Zhang L, and Jiang W. *Generic Long-acting Injectable Product Availability and Approval Standards.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Role of Excipients on Drug Release from Long-Acting Intrauterine Systems.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Lin X, O'Reilly Beringhs AO, Hargrove D, Jay M, Wang Y, Bin Q, and Lu X. *Assessing In Situ Forming Implants Using Real-Time Imaging.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Silva D, Bao Q, Wan B, Malavia N, Burgess D, and Lukacova V. *Establishment of Preclinical Mechanistic In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Wang R, Bao Q, Clark A, Wang Y, Qin B, Zhang S, and Burgess D. *Effect of Coacervation Processing Parameters on In vitro Drug Release from Minocycline Hydrochloride Microspheres.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Zhang Q. *In Vitro Approaches for Injectable Suspension Products: Medroxyprogesterone Acetate & Triamcinolone Acetate.* Presentation at Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Clark A. *Correlating Microstructure to Performance of PLGA Microspheres Using X Ray Microscopy and AI Based Image Analysis.* Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 27, 2023.
- Fanse S. *Enabling the Rational Development of Long-Acting Contraceptive Levonorgestrel Intrauterine Systems.* Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 27, 2023.
- Lu X. *Novel In Vitro, Ex Vivo and In Vivo Assessment of Ophthalmic Semi-Solid Drug Products.* Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 27, 2023.

OUTCOMES *continued*

- Wang Y. *Scientific and Regulatory Considerations on In Vitro Release Testing (IVRT) and In Vitro In Vivo Correlation (IVIVC) for Complex Long-Acting Drug Suspensions.* Presentation at the IQ Webinar: Scientific and Regulatory Considerations for Long-acting Injectable Suspensions. Virtual Meeting, Jul. 21, 2023.
- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2023. North Bethesda, MD, Jun. 04, 2023.
- Kuehster L. *Stochastic and Deterministic Analysis of Reactivity Ratios in the Partially Reversible Copolymerization of Lactide and Glycolide.* Presentation at The American Institute of Chemical Engineers (AIChE) Annual Meeting. Phoenix, AZ, Nov. 13, 2022.
- Zhao L. *Generating Model-integrated Evidence for Developing and Approving Complex Generic LAI Products.* Presentation at the American Conference on Pharmacometrics (ACoP) 2022. Aurora, CO, Nov. 02, 2022.
- Hooker A. *A Population PK Based Model-Integrated BE Platform.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Lukacova V. *Application of Modeling and Simulation in Long-Acting Injectable Product Development.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Zhang F. *Melt-Extruded Dexamethasone Ophthalmic Implants: Process, Structure and In Vitro Drug Release.* Presentation at the 4th Annual Formulation and Drug Delivery USA Conference. San Diego, CA, Oct. 11, 2022.
- Lukacova V. *Current Status and Gaps in Mechanistic In-Silico Modeling for Clinical Translation and Performance.* Presentation at the American Association of Pharmaceutical Scientists (AAPS): Patient-Centric Design of Long-Acting Injectable Drug Products. Virtual Meeting, Oct. 10, 2022.

NANOTECHNOLOGY PRODUCTS

Summary of FY 2023 Activities

In FY 2023, external and internal research projects on nanomaterials continued to focus on developing new characterization methods for nanomaterial-containing drug products. Lipid nanoparticles (LNPs) are one example of an emerging nanomaterial delivery system. This type of nanomaterial system has been used in the recently FDA-approved COVID-19 vaccines and ONPATTRO® (patisiran sodium), an siRNA LNP drug product. To facilitate generic product development of this new class of nanomaterials, FDA initiated a new research project in FY 2023 that sought to understand the impact of active ingredient impurities, lipid sources, and manufacturing processes on the performance and quality of siRNA LNP.

FDA continued to collaborate with Purdue University (Contract 75F40121C00189) and the University of Maryland, Baltimore (Grant 1U01FD007363) to develop and validate analytical methods to analyze colloidal iron-carbohydrate products ferric carboxymaltose and ferric derisomaltose, respectively. Nuclear magnetic resonance (NMR) and mass spectrometry (MS) methods are being developed to characterize the carbohydrate components in the drug products and the interactions between the carbohydrates and the iron core. The research projects will also provide insights on how variations in manufacturing processes affect the performance of colloidal iron-carbohydrate products. Additional external research conducted in FY 2023 included developing an in silico systems-based multiscale model to capture the various biological and physicochemical events that affect the transport and residence of nanoparticles and their active ingredient cargo among different extracellular and intracellular compartments (Contract 75F40119C10139).

Within the FDA, efforts to investigate novel techniques for post manufacturing physicochemical characterization are ongoing. Improved analytical methods to provide better characterization of nanomaterials, such as use of asymmetrical flow field-flow fractionation (AF4) and advanced imaging and spectroscopy (see **Research Highlight** below) are being developed. Correlation of product physicochemical properties and critical quality attributes with release behavior is being assessed through the continuing effort to develop in vitro drug release testing methods, such as adaptive perfusion. An ultra-high-performance liquid chromatography-high-resolution MS approach was developed to separate, identify and quantify the phospholipids and triacylglycerols in intravenous lipid emulsions. This method can be used to determine both the lipids and their degradation products and would be beneficial for the development of generic intravenous lipid emulsions, as well as to support evaluations of manufacturing, stability and storage conditions.

RESEARCH HIGHLIGHT

Physicochemical and structural characterization of the drug product is essential to ensure the quality and equivalence of nanomaterial-containing drug products. This is because CQAs such as size, morphology, surface chemistry, and composition can govern the product's in vivo behavior. Multi-attribute characterization is of interest as it enables characterization of multiple CQAs from a single study. Through an internal project, FDA labs developed a novel method using scanning electron Raman cryo-microscopy (SERCM), which is capable of measuring morphology, particle size, and composition of a nanomaterial. Using an albumin-bound paclitaxel nanoparticle formulation as a model drug, FDA scientists optimized a sample fixation method for scanning electron cryo-microscopy (cryo EM) through comparing different strategies, including filtration, plunge freezing (PF), high pressure freezing (HPF), and freeze substitution (FS) (**Figure 1**). Filtration using a centrifugation filter was found useful for the separation of monomer or oligomeric forms of albumin from the formulation, and for characterization of formulations with components within a certain size range. Plunge freezing using liquid nitrogen slush was found effective, but it led to moderate particle aggregation. Despite being a labor-intensive method, high-pressure freezing enabled the characterization of components in the formulation in their native state, while freeze substitution required dilution of the sample which changed particle size and distribution. When in-SEM Raman spectroscopy (a Raman structural and chemical analyzer unit integrated into SEM chamber) was added to cryo EM as a chemical characterization technique, the cooperative approach, namely SERCM, was capable of confirming the chemical composition of particles observed in cryo-fixed samples (**Figure 2**).[8] This multi-attribute method has the potential to be used for characterization of albumin-based nanoparticles drug products.

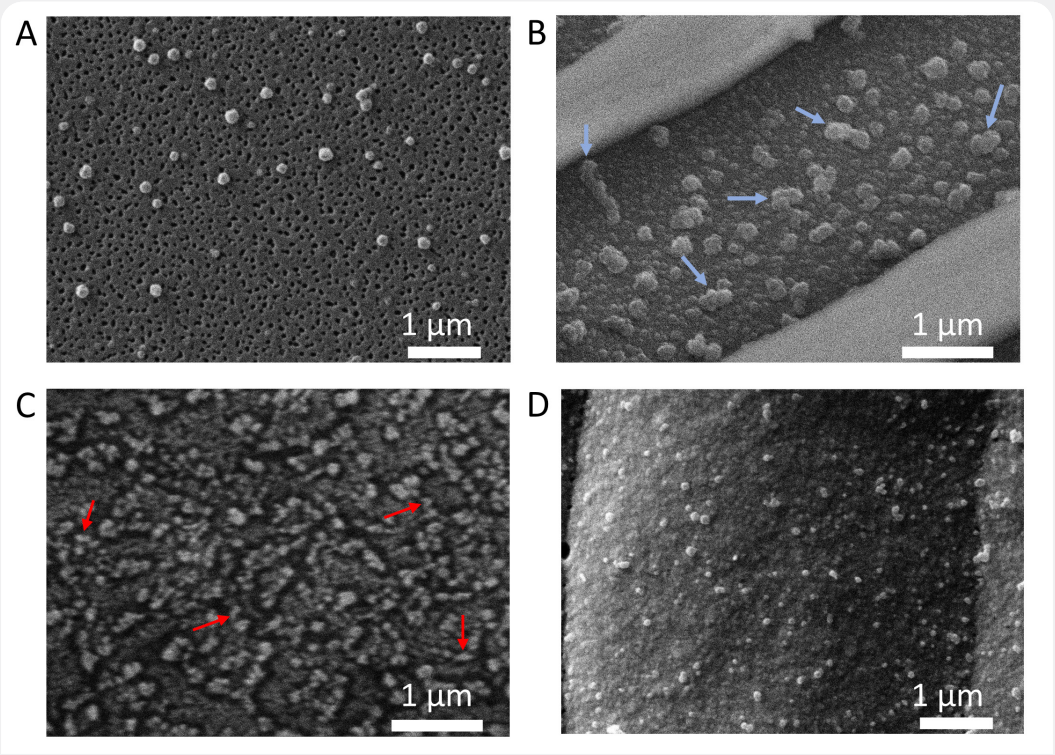

Figure 1. Effect of various cryo-fixation methods on size and morphology of albumin-bound paclitaxel nanoparticle formulation. SEM images for comparison of different shape descriptors for filtered (A), plunge freezing (B), high pressure freezing (C) and freeze substitution (D).

[8] Yilmaz H, Ahmed S, Rodriguez J, and Willett D. *Scanning Electron-Raman Cryomicroscopy for Characterization of Nanoparticle-Albumin Drug Products.* Analytical Chemistry. 95(5): 2633-2638. https://doi.org/10.1021/acs.analchem.2c03826. PMID: 36693238

RESEARCH HIGHLIGHT *continued*

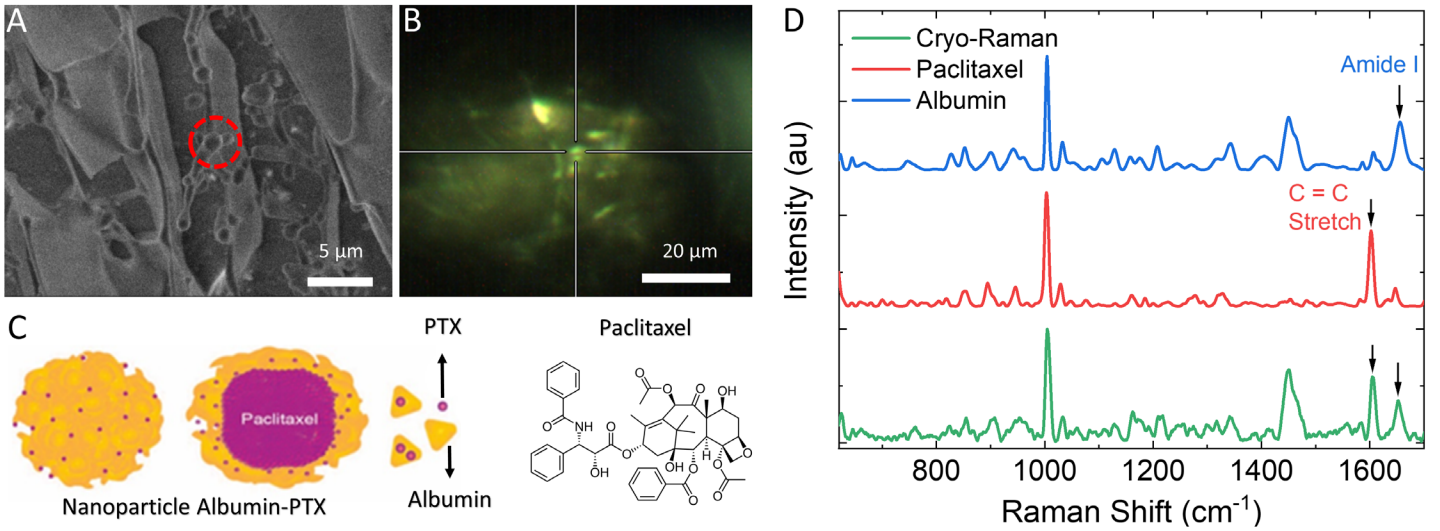

Figure 2. SERCM for characterization of nab-paclitaxel. (A, B) Cryo EM and optical images of the sample. (C) Hypothesized composition of albumin-paclitaxel complexes and albumin encapsulated paclitaxel nanoparticles. (D) Raman spectra of albumin and paclitaxel reference standards (blue and red, respectively) and particles observed in cryo EM (green).

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (IAA-75F40123S30031) *Confinement and Error Model Enhanced Nanoparticle Tracking Analysis (CEMENT)* with Samuel M. Stavis at National Institute of Standard and Technology
- Contract (75F40123C00118) *Investigating the Impact of API Purity, Lipid Source and Manufacturing Process on Performance and Quality of Complex siRNA Lipid Nanoparticles* with Xiuling Lu at University of Connecticut

Continuing Grants and Contracts

- Grant (1U01FD007363) *Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex - Ferric Derisomaltose* with Sarah L. Michel at the University of Maryland, Baltimore
- Contract (75F40121C00189) *Characterization of Carboxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes* with Eric J. Munson at Purdue University
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie Au at IQSP - Institute of Quantitative Systems Pharmacology

Completed Grants and Contracts

- Grant (5U01FD005946) *Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics* with Taylor Woehl at the University of Maryland, College Park

Active FDA Research

- *Adaptive Perfusion a Novel In Vitro Release Test Method for Assessing Dissolution, Release, and Drug Distribution*
- *Assessing New Analytical Methods for Characterization of Complex Nanotechnology Drug Products*
- *Assessment of Asymmetric Flow Field-Flow Fractionation Methodologies for the Evaluation of Nanoparticle Morphology*
- *Investigations into the Continuous Manufacturing of Lipid Nanoparticle and Liposomal Products*
- *Novel Imaging and Spectroscopy Methods for Characterizing Size, Chemical Composition, and Morphology of Nanomaterials*

OUTCOMES

Product-Specific Guidances

There were two new and three revised PSGs published in FY 2023 related to *Nanomaterials* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *Revised Draft Guidance on Daunorubicin Citrate Injection Injectable Liposomal.* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance on Ferric Oxyhydroxide Injection Injectable.* (NDA 017441) (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance on Ferric Oxyhydroxide Injection Injectable.* (NDA 020955) (Nov. 17, 2022) Link to Posting
- *New Draft Guidance on Patisiran Sodium Intravenous Solution.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance on Sirolimus Intravenous Powder.* (May 18, 2023) Link to Posting

Articles

- Banstola B, Gamage P, Jiang W, and Mudalige T. *Analysis of Phospholipids and Triacylglycerols in Intravenous Lipid Emulsions.* Journal of Pharmaceutical and Biomedical Analysis. (2023) 222: 115112. https://doi.org/10.1016/j.jpba.2022.115112. PMID: 36274478.
- Naageshwaran V, Bigonne H, Gum G, Malla S, Sol C, Bon C, Xu X, Vo A, Smith W, O'Reilly Beringhs AO, Kozak D, Tan M-L, Babiskin A, Babiskin A, Urtti A, Amo E, and Ranta V. *Topical Pharmacokinetics of Brinzolamide Suspensions in Rabbits and Variability Analysis for Sample Size and Design Considerations.* International Journal of Pharmaceutics. (2023) 642(123183). https://doi.org/10.1016/j.ijpharm.2023.123183. PMID: 37369289.
- Simon C, Borgos S, Calzolai L, Nelson B, Parot J, Petersen E, Roesslein M, Xu X, and Caputo F. *Orthogonal and Complementary Measurements of Properties of Drug Products Containing Nanomaterials.* Journal of Controlled Release. 354: 120-127. https://doi.org/10.1016/j.jconrel.2022.12.049. PMID: 36581261.
- Yilmaz H, Ahmed S, Rodriguez J, and Willett D. *Scanning Electron-Raman Cryomicroscopy for Characterization of Nanoparticle-Albumin Drug Products.* Analytical Chemistry. 95(5): 2633-2638. https://doi.org/10.1021/acs.analchem.2c03826. PMID: 36693238.

Posters

- Burroughs L, Yenduri G, Smith W, Patri A, and Xu X. *Continuous Processing of Liposomal Nanoparticles as Potential Reference Materials for Drug Product Development.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Smith W, Liu H, Wang Y, Kozak D, and Xu X. *Phytonadione Injectables: Understanding Dosage Form and Formulation Processes.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

OUTCOMES *continued*

- Smith W, Qu H, Costa A, Burgess D, and Xu X. *Investigation of Advanced Separation Techniques in the Assessment of Liposomal Drug Products Produced via Continuous Manufacturing.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Smith W, Qu H, Costa A, Burgess D, and Xu X. *Assessing Morphological Variation in Liposomal Drug Products using Asymmetrical Flow Field-Flow Fractionation.* Poster Presentation at Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Xu X, Wang Y, Kozak D, Smith W, and Liu H. *Understanding Formulation Processes and Implications for Dosage Form Determination of Phytonadione Injectables.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Smith W, Liu H, Wang Y, Kozak D, and Xu X. *Understanding Formulation Processes and Implications for Dosage Form Determination of Phytonadione Injectables.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jul. 13, 2023.
- Jayaraj S, Jiang W, and Mudalige T. *Doxorubicin HCl Release from Liposomal Doxorubicin Formulations Autonomous Capillary Electrophoretic (CE) In Vitro Release Test (IVRT) Method.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Zhu D, Zhang Y, Patel D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: A Novel In Vitro Drug Release Testing System for Complex Drug.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 13, 2023.
- Gan J, Juang V, Wang K, Hong K, Xia Z, Ackermman R, Olsen K, Wang Y, Liang J, Zheng J, Xu X, Park J, and Schwendeman A. *Characterization and Quantification Analysis of Onivyde Irinotecan Liposome Injection.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Kumar S, Cook N, Gum G, Manza L, Naageshwaran V, Lyulkin M, Xu X, Patel D, Qu H, Walenga R, Tan M-L, Babiskin A, Kasiar M. *Impact of Changes in Ophthalmic Emulsion Globule Size Distribution and Viscosity on Tear Film Thickness and Menisci Characteristics.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Smith W, Liu H, Wang Y, Kozak D, and Xu X. *Impact of Formulation Processes on Dosage Form Determination of Phytonadione Injectables.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Zhu D, Zhang Y, Kozak D, Ashraf M, Xu X. *Automated Adaptive Perfusion: A Novel In Vitro Release Testing System for Complex Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Xu X. *Future of Continuous Manufacturing in Drug Products Containing Nanomaterials.* Poster Presentation at the FDA NanoDay Symposium 2022. Virtual Meeting, Oct. 11, 2022.

OUTCOMES *continued*

Presentations

- Qin B. *Amphotericin B Liposome: Revisions of the Product Specific Guidance.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Fan Q, and Harigaya Y. *Cyclosporine & Difluprednate Opthalmic Emulsions.* Presentation at Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Smith W. *Phytonadione - Self-Assembled System & Thermodynamics Systems.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Xu X. *Opportunities in Continuous Manufacturing of Nanomaterials.* Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Xu X. *Roundtable Discussion: Dissolution Testing of Nanoparticles.* Presentation at the SelectScience Webinar. Virtual Meeting, Jun. 07, 2023.
- Jiang W. *Complex Generics Containing Nanomaterials: What's Next in the Pipeline?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) - Chicagoland Pharmaceutical Discussion Group (CPDG). Chicago, IL, May 19, 2023.
- Xu X. *In Vitro Release Test for Complex Drug Product: What is Your Perspective?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) - Chicagoland Pharmaceutical Discussion Group (CPDG). Chicago, IL, May 19, 2023.
- Xu X. *Opportunities in Continuous Manufacturing of Nanomaterials.* Presentation at Research Center Pharmaceutical Engineering (RCPE): Accelerating Access to Medicines Workshop. Washington, DC, Mar. 28, 2023.
- Xu X. *Challenges and Opportunities of Continuous Manufacturing inf Nanomaterials.* Presentation at National Nanotechnology Initiative Workshop. Hybrid Meeting. Washington, DC, Mar. 23, 2023.
- Xu X. *Complex Equilibria and Complex Drug Products: Role of Fundamentals in Advancing Regulatory Science.* Presentation at the University of Connecticut. Virtual Meeting, Nov. 28, 2022.
- Kozak D. *Considerations for Post-Approval Changes to Complex Generic Drug Products.* Presentation at the 2022 Association for Affordable Medicines (AAM): GRx + Biosims Conference. North Bethesda, MD, Nov. 08, 2022.
- Xu X. *One Size Does Not Fit All: Challenges of Particle Size Measurement in Pharmaceutical Applications.* Presentation at Bureau International des Poids et Mesures CCQM Workshop on Particle Metrology. Virtual Meeting, Oct. 26, 2022.
- Kozak D. *Development and Characterization of Generic Drug Products Containing Nanomaterials.* Presentation at the FDA NanoDay Symposium 2022. Virtual Meeting, Oct. 11, 2022.
- Xu X. *Future of Continuous Manufacturing in Drug Products Containing Nanomaterials.* Presentation at the FDA NanoDay Symposium 2022. Virtual Meeting, Oct. 11, 2022.

CHAPTER 4: COMPLEX ROUTES OF DELIVERY

A major GDUFA science and research priority is to enhance the efficiency of bioequivalence (BE) approaches for complex routes of delivery, such as locally acting gastrointestinal (GI), buccal, sublingual, inhalation, nasal, ophthalmic, otic, topical dermatological, vaginal, and rectal products. Research in this area is described in this Chapter in separate sub-sections. Specifically, advances in this area include research on understanding how the ingredients and other physicochemical properties of a formulation influence drug absorption. This Chapter will also describe advancements in research aimed at building in vivo predictive models and identifying potential failure modes for BE. Ultimately this research aims to support the development of more efficient BE approaches for these complex products.

LOCALLY ACTING GI PRODUCTS AND BUCCAL/ SUBLINGUAL PRODUCTS

Summary of FY 2023 Activities

In FY 2023, research for locally acting GI drugs focused on improving in vitro BE methods and developing a predictive in silico model. In addition, this subsection covers the FY 2023 research effort on buccal and sublingual drug products.

The work funded by an FY 2022 Grant 1U01FD007660 aims to develop a validated physiologically based pharmacokinetics (PBPK) model to provide supportive evidence (e.g., PBPK model based virtual BE trial simulations) when evaluating the BE of locally acting GI drug products. The goal will be achieved through both in vitro and in silico components. In vitro dissolution of marketed locally acting GI drug products including budesonide, sulfasalazine, and mesalamine products will be measured in biorelevant dissolution media mimicking the gut physiology of heathy subjects and of patients with ulcerative colitis or Crohn's disease. Additionally, formulation variants related to the excipient level and excipient type in the formulation, as well as the manufacturing will be created for three (3) active pharmaceutical ingredients (APIs) (i.e., budesonide, sulfasalazine, and mesalamine). Their dissolution properties will be tested using the same in vitro dissolution test method as the marketed products. This effort will provide an investigation into the correlation between product quality or performance attributes (e.g., dissolution) and in vivo API release in patients. In parallel, a PBPK model will be developed to account for GI disease conditions.

The aim of another FY 2022 Grant (1U01FD007662) is to develop a practical, multi-stage in vitro dissolution method to characterize formulation performance from the stomach to the colon under both fasting and fed conditions, and to incorporate these in vitro data into PBPK models to assess the relationship between systemic and local drug exposures for drugs targeting the GI tract. To support this goal, in vitro biopharmaceutic data including solubility and dissolution data will be generated for locally acting GI drug products. In addition, using the generated in vitro biopharmaceutics data, a model-based virtual BE evaluation will be simulated in healthy adults and Crohn's disease patients.

Ongoing internal research aims to identify the scientific gaps in the in vitro studies recommended for establishing BE for locally acting GI drugs and to improve quantitative tools and methodologies for evaluating the BE of prospective generic drugs.

Research also continued on buccal/sublingual products. The goal of an ongoing research contract (75F40120C00150) was to develop a predictive in silico modeling and simulation platform for drug products delivered via the oral cavity (e.g., buccal and sublingual tablets). Under this project, permeability of APIs (e.g., zolpidem, fentanyl, sufentanil, buprenorphine, etc.) was measured though the use of a cellular model and dynamic in vitro dissolution and absorption model (DIVDAM) to understand the potential impact of excipients in the permeation of API through buccal/ sublingual mucosa. Another key goal was to establish a PBPK model-based in vitro-in vivo correlation (IVIVC) of oral cavity drug products by taking into account the in vitro dissolution and absorption, and the clinical PK data of oral cavity drug products.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grant(s) and Contract(s)

- Grant (1U01FD007662) *Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract* with Rodrigo Cristofoletti at University of Florida
- Grant (1U01FD007660) *Development of PBBM Framework to Support an Assessment of Bioequivalence for Locally Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients* with Nikoletta Fotaki at University of Bath
- 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 University of Health Sciences and Pharmacy in St. Louis

Active FDA Research

- *Best Practice for Using PBPK Modeling for Orally Absorbed Generic Drug Products*
- *GDUFA III Product-Specific Guidance Improvement for Oral Products*

OUTCOMES

Product-Specific Guidances

There were two new and three revised PSGs published in FY 2023 related to *Locally Acting GI Drugs and Buccal and Sublingual* products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride Oral Tablet, Chewable & Oral Tablet, Capsule.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Budesonide Oral Capsule, Delayed Release.* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Rifaximin Oral Tablet.* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Sucralfate Oral Suspension.* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Sucralfate Oral Tablet.* (Feb. 16, 2023) Link to Posting

Posters

- Ren P, Yang W, Choi SJ, and Zhang Y. *Impact of Solubility and Dissolution Performance on Bioequivalence Recommendations for Immediate-Release Locally Acting Gastrointestinal Drug Products.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sep. 10, 2023.

OUTCOMES *continued*

Presentations

- Al Ghabeish M. *Q1 and Q2 Recommendations: Sucralfate Oral Suspension.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Dandamudi S. *Non-Q2 Sucralfate Suspension Approval.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Sun W. *Bioequivalence for Oral Locally Acting Gastrointestinal Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Wu F. *OGD Perspectives on PBBM Applications for Generics.* Presentation at the FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling Workshop. Rockville, MD, Aug. 31, 2023.

INHALATION AND NASAL PRODUCTS

Summary of FY 2023 Activities

The evaluation of potential alternative methods to conducting the comparative clinical endpoint (CCEP) BE studies recommended in FDA product-specific guidances (PSGs) for orally inhaled and nasal drug products has been a continuing area of research. In FY 2023, the results from research conducted by the University of Florida and Nanopharm (Contracts HHSF223201310220C and 75F40120C00036, respectively) supported the revision of nine PSGs on locally acting nasal spray suspension products. Based on the dissolution and PK studies conducted under these contracts, which demonstrated their sensitivity to particle size distribution (PSD) differences, the revised PSGs now provide two options to establish BE. The first option is a new in vitro only option based on formulation sameness and includes a dissolution study, an option the prospective applicants with a generic product similarly formulated to the reference listed drug formulation can choose. The second option includes in vitro and in vivo BE studies for generic products not similarly formulated to the reference listed drug.

In April 2023, experts from industry, academia, and FDA gathered at a two-day workshop hosted by FDA and the Center for Research on Complex Generics (CRCG) to discuss the current scientific and regulatory perspectives for using in vitro, in vivo, and in silico studies as alternatives to CCEP and pharmacodynamic (PD) BE studies for orally inhaled drug product (OIDPs). Many of the presentations were supported by 10 years of GDUFA research from multiple external collaborators and over 25 grants and contracts. Through small group discussions, in-person participants provided greater clarity and consensus on the roles current alternative BE approaches can play for establishing local drug delivery equivalence for suspension-based metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

During FY 2023, there were two notable scientific publications related to in silico modeling studies that focused on regional lung and nasal deposition predictions using computational fluid dynamics (CFD). One publication[1] described research by the University of Iowa (Grant 1U01FD005837) that constructed a CFD model to predict regional lung deposition following administration of beclomethasone dipropionate inhalation metered aerosol, where the model was used to test the sensitivity of deposition predictions to differences in the amount of ethanol in the formulation. Another publication[2] described research by Virginia Commonwealth University (Contract HHSF223201810144C) to assess the sensitivity of regional nasal deposition to differences with in vitro metrics, and the results suggested that spray cone angle and plume ovality may have the most significant impact.

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[1] Rajaraman P, Choi J, Babiskin A, Walenga R, and Lin C. *Transport and Deposition of Beclomethasone Dipropionate Drug Aerosols with Varying Ethanol Concentration in Severe Asthmatic Subjects.* International Journal of Pharmaceutics. (2023) 636: 122805. https://doi.org/10.1016/j.ijpharm.2023.122805. PMID: 36898619.

[2] Kolanjiyil A, Walenga R, Babiskin A, Golshahi L, Hindle M, and Longest W. *Establishing Quantitative Relationships Between Changes in Nasal Spray In Vitro Metrics and Drug Delivery to the Posterior Nasal Region.* International Journal of Pharmaceutics. (2023) 635: 122718. https://doi.org/10.1016/j.ijpharm.2023.122718. PMID: 36781083.

RESEARCH HIGHLIGHT

The quality and performance of OIDPs are determined by complex interactions between the formulation, device design characteristics, and patient factors. The PSD of API emitted from an OIDP is an example of an attribute that can influence drug delivery, dissolution, and pharmacokinetics. Current FDA guidance on MDIs and DPIs recommends measuring aerodynamic PSD using inertial cascade impactors coupled with chromatography, but there has been interest in using alternative approaches, including laser diffraction (LD), to collect PSD data. ADASUVE (loxapine, 10 mg) inhalation powder is a single-use inhaler that rapidly heats a thin film of an excipient-free API, forming a drug vapor that quickly nucleates and grows into microscale aerosol particles after breath actuation. ADASUVE is a good candidate for LD analysis because it is excipient-free, allowing direct measurement of API PSD without chromatographic analysis. To identify the critical study method parameters for assessing BE, the effects from changes in inspiratory flow on ADASUVE performance were studied using LD under different inhalation conditions. **Figure 1** shows the PSD of ADASUVE inhalation powder is inhalation flow rate dependent, with higher flow rates generating smaller particles. This work also shows that mass median aerodynamic diameter (MMAD) can be calculated from LD data (**Figure 2**), and these MMAD data showed a similar trend to published ADASUVE MMAD data collected using a Next Generation Impactor[3]. This research also provided data on analytical considerations of LD methods for characterizing ADASUVE PSD, including detector saturation issues. The results from this research supported FDA's development of a draft PSG on Loxapine Inhalation Powder.

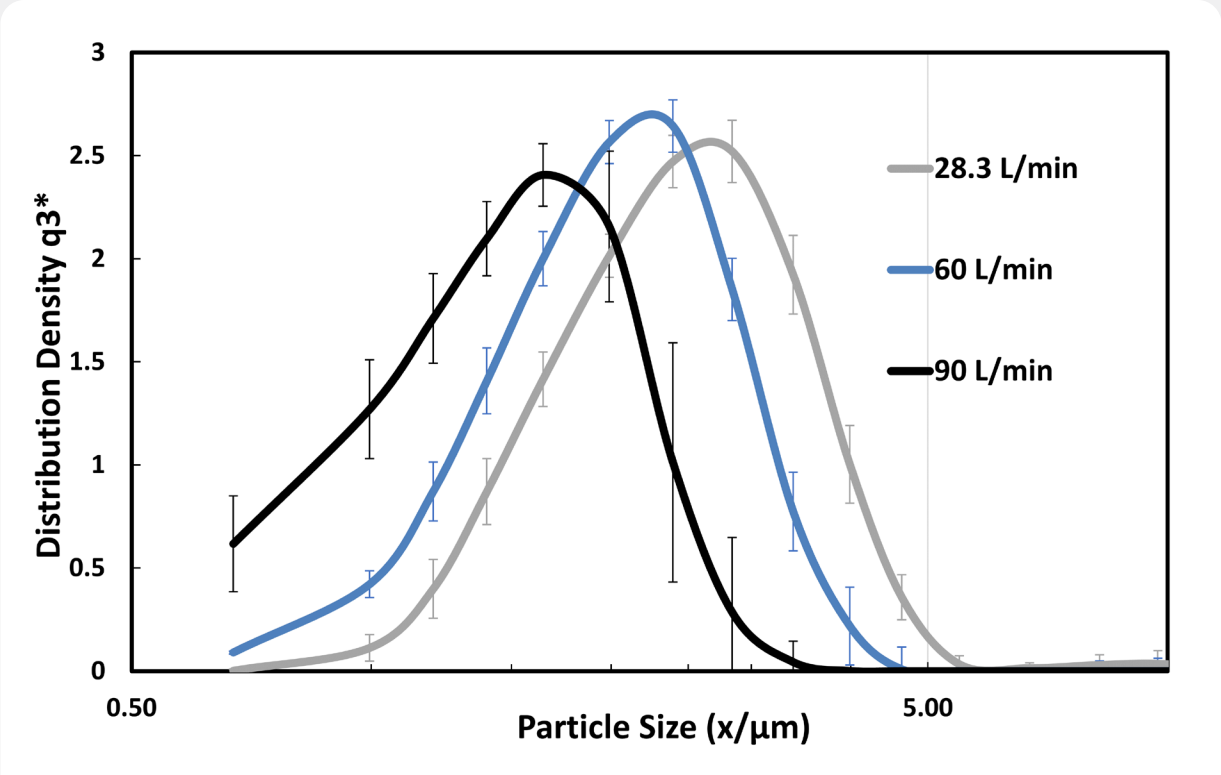

Figure 1. Laser diffraction PSD for inhalation flow rates of 28.3, 60, and 90 L/min. Each data point is the average value of five runs (N=5) and error bars represent the standard deviation (± SD). Data were averaged in the percent optical concentration range of 35 to 10.

[3] Dinh KV, Myers DJ, Noymer PD, Cassella JV. *In Vitro Aerosol Deposition in the Oropharyngeal Region for Staccato Loxapine.* J Aerosol Med Pulm Drug Deliv. 2010 Aug;23(4):253-60. doi: https://doi.org/10.1089/jamp.2009.0814. PMID: 20528148.

RESEARCH HIGHLIGHT *continued*

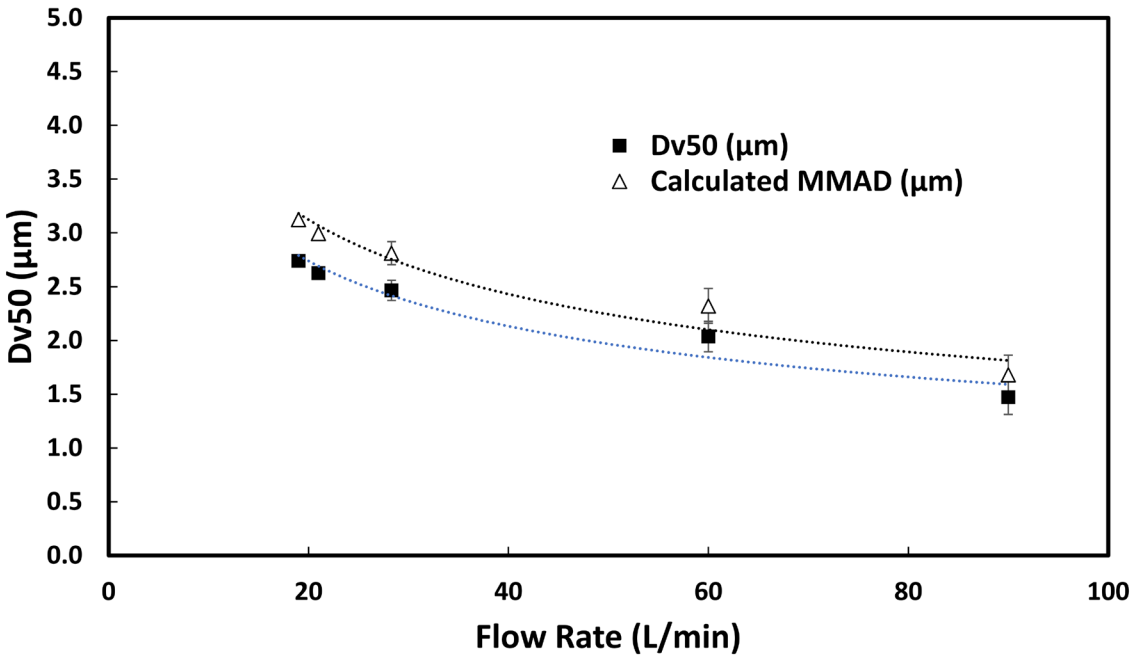

Figure 2. The median particle size by volume/mass (Dv50) of ADASUVE was measured using LD at inhalation flow rates of 19, 21, 28.3, 60, and 90 L/min. A trendline was fit to the Dv50 and MMAD data using a power function.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007987) *A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods* with Benjamin Lavon at Fluidda, Inc.
- Grant (1U01FD007936) *Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic Data of Generic OIDPs via Population Pharmacokinetic Modeling and Non-Compartmental Approaches* with Jurgen Bulitta at University of Florida
- Contract (75F40123C00201) *Development of a Laser-based Testing Platform for Generic Dry Powder Inhaler (DPI) Evaluation and In-silico Model Validation* with Agisilaos Kourmatzis at University of Sydney
- Contract (75F40123C00186) *Research Challenges Related to Environmentally Friendly Propellants In Metered Dose Inhalers* with Jagdeep Shur at Nanopharm

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Continuing Grants and Contracts

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina at Chapel Hill
- Grant (1U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University
- Grant (1U01FD007657) *Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data* with Kayode Ogungbenro at University of Manchester
- Contract (75F40122C00182) *Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs* with Rodrigo Cristofoletti at University of Florida
- Contract (75F40122C00197) *DissolvIt® – An In Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution- and Absorption of Drugs Administered via the Inhalation Route* with Maria Malmlof at Inhalation Sciences Sweden AB (ISAB)
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University
- Contract (75F40122C00202) *Identification of Drug Distribution in Aerosols: A Nanospectroscopy and Nanothermal Analysis* with Hak Kim Chan at the University of Sydney
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Completed Grants and Contracts

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at University of Iowa
- Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and its Origins in Dry Powder Inhalers* with Hugh D C Smyth at The University of Texas at Austin, College of Pharmacy
- 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 (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 (75F40120C00036) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Jag Shur at Nanopharm
- Contract (75F40119C10154) *Systematic Evaluation of the Ex-Throat Plume Properties of MDI Formulations* with Guenther Hochhaus at University of Florida and S5 Consulting

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Active FDA Research

- *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways*
- *Alternative BE Approach Assessment for Orally Inhaled Drug Products*
- *CFD Models of Soft Mist Inhalers*
- *Characterizing ADASUVE (loxapine, 10 mg) Staccato Inhalation Powder Particle Size Distribution*
- *Characterizing XERESE Cream (5% Acyclovir and 1% Hydrocortisone) Using MDRS*
- *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*
- *Development of a Nasal PBPK Modeling Platform*
- *Dissolution for Inhalation Products*
- *Evaluating Process-Relevant Quality Attributes of Inhalation Powders*
- *Evaluation of the Staccato Drug Delivery Platform*
- *Explore the Use of Lung-On-A-Chip to Obtain Physiologically Relevant Parameters for Orally Inhaled Drug Products*
- *In Vitro Performance Testing of Soft Mist Inhalers*
- *Measurement of Delivered Dose Performance of Spiriva Handihaler*
- *Morphological and Performance Evaluation of Spray-dried Phospholipid Porous Particles*
- *Optimization of an In Vitro Method for Regional Deposition Prediction of Nasal Powders*
- *Predicting APSD Parameters of Orally Inhaled Drug Products using Artificial Intelligence and Machine Learning Algorithms*
- *Scientific Investigation of the Low Target Delivery Dose for Unit Dose Dry Powder Inhalers*

OUTCOMES

There were two new and nine revised PSGs published in FY2023 related to *Inhalation and Nasal* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

Product-Specific Guidances

- *Revised Draft Guidance for Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Beclomethasone Dipropionate Monohydrate Nasal Spray, Metered.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Budesonide Nasal Spray, Metered.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Ciclesonide Nasal Spray, Metered.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Fluticasone Furoate Nasal Spray, Metered.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate Nasal Spray, Metered.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Loxapine Inhalation Powder.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Mometasone Furoate Nasal Spray, Metered.* (NDA 215712) (Nov. 17, 2022) Link to Posting

OUTCOMES *continued*

- *Revised Draft Guidance for Mometasone Furoate Nasal Spray, Metered.* (NDA 020762) (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Mometasone Furoate; Olopatadine Hydrochloride Nasal Spray, Metered.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetonide Nasal Spray, Metered.* (Aug. 21, 2023) Link to Posting

Articles

- Amini E, Berger S, Schilling U, Jiao Y, Chen M, Bachhav S, Baumstein S, Tang Y, Al-Humiari M, Leon Astudillo C, Drescher S, Iley T, Shur J, Price R, Carrasco C, Conti D, Delvadia R, Oguntimein O, Witzmann K, Absar M, Luke M, Boc S, Dhapare S, Saluja B, Bielski E, Newman B, Bulitta J, and Hochhaus G. *Sensitivity of Pharmacokinetics to Differences in the Particle Size Distribution for Formulations of Locally Acting Mometasone Furoate Suspension-Based Nasal Sprays.* Molecular Pharmaceutics. (2023) 20(11):5690-5700. https://doi.org/10.1021/acs.molpharmaceut.3c00553. PMID: 37773975.
- Kimbell J, Garcia G, Schroeter J, Sheth P, Vallorz-III E, Saluja B, Babiskin A, Tian G, and Walenga R. *Nasal Steroid Spray Simulations Using Measured Spray Characteristics in Healthy and Rhinitic Nasal Passages.* Journal of Aerosol Science. (2023) 174:106246. https://doi.org/10.1016/j.jaerosci.2023.106246.
- Kolanjiyil A, Walenga R, Babiskin A, Golshahi L, Hindle M, and Longest W. *Establishing Quantitative Relationships Between Changes in Nasal Spray In Vitro Metrics and Drug Delivery to the Posterior Nasal Region.* International Journal of Pharmaceutics. (2023) 635: 122718. https://doi.org/10.1016/j.ijpharm.2023.122718. PMID: 36781083.
- Mohan A, Wang Q, Dhapare S, Bielski E, Kaviratna A, Han L, Boc S, and Newman B. *Advancements in the Design and Development of Dry Powder Inhalers and Potential Implications for Generic Development.* Pharmaceutics. (2022) 14(11):2495. https://doi.org/10.3390/pharmaceutics14112495. PMID: 36432683.
- Rajaraman P, Choi J, Babiskin A, Walenga R, and Lin C. *Transport and Deposition of Beclomethasone Dipropionate Drug Aerosols with Varying Ethanol Concentration in Severe Asthmatic Subjects.* International Journal of Pharmaceutics. (2023) 636: 122805. https://doi.org/10.1016/j.ijpharm.2023.122805. PMID: 36898619.
- Tang P, Kakhi M, Albariqi A, Behara S, Walenga R, Yang R, and Chan H. *The Role of Capsule Aperture Size on the Dispersion of Carrier-based Formulation at Different Air Flowrates.* International Journal of Phramaceutics. (2023) 642(123152). https://doi.org/10.1016/j.ijpharm.2023.123152. PMID: 37339687.
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Posters

- Chakma M, Usmani O, Meah S, Biddiscombe M, Bielski E, Feibus K, Natarajan K, Li K, Kinjo M, Illoh O, Han L, Newman B, and Murnane D. *The Importance of Inter-patient Peak Inspiratory Flow Variance in Simplifying DPI Prescribing in COPD: A Meta-Analysis.* Poster Presentation at the European Respiratory Society (ERS) International Congress 2023. Milan, Italy, Sep. 09, 2023.
- Mohan A, Dhapare S, Newman B, Svensson M, Elfman P, Stuckel J, Sandell D, Winner L, Bulitta J, and Hochhaus G. *Effect of Coating of Andersen Cascade Impactor and Next Generation Impactor on the Aerodynamic Particle Size Distribution of Nine Commercial Metered Dose Inhalers.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 17, 2022.
- Nair V, Hefnawy A, Herpin M, Feng K, Reed N, Ma T, Bielski E, Dhapare S, Newman B, Boc S, and Smyth H. *Development of a Low-Volume In-Vitro Dissolution Method for Assessing Variability in Fine Particle Doses of Dry Powder Inhalers.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Bielski E. *The Current Status and Considerations for Dissolution Testing of Orally Inhaled Drug Products (OIDPs).* Presentation at The Society for Pharmaceutical Dissolution Science USA (SPDS-US) – Webinar. Virtual Meeting, Sep. 15, 2023.
- Walenga R. *Predicting Regional Deposition, Local and Systemic Pharmacokinetics of Orally Inhaled Drug Products.* Presentation at The Society for Pharmaceutical Dissolution Science USA (SPDS-US) – Webinar. Sep. 15, 2023.
- Chopski S. *Innovative Technology: Particle Image Velocimetry (PIV) and High Speed Imaging to Support Approval of Generic Orally Inhaled Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Clerman A. *Post-Approval Impact of Generic Fluticasone Propionate & Salmeterol Inhalation Powder.* Presentation at Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Bielski E and Reed N. *Loxapine Inhalation Powder: OTR Research Conducted to Inform the PSG Recommendations.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Boc S. *Complex Nasal Suspension PSGs: Utilization of Newly Recommended In Vitro Only Bioequivalence Option.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Walenga R. *Complex Nasal Suspensions: Utilization of In Silico Studies to Support Development and Approval.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Lee J. *In Silico Study of the Effect of Including Lactose Fines in Modeling Dry Powder Inhaler Performance.* Presentation at the FDA 2023 Scientific Computing Days. Virtual Meeting, Sep. 12, 2023.

OUTCOMES *continued*

- Newman B. *Challenges & Considerations for the Transition to Low Global Warming Potential (LGWP) Propellants with Metered Dose Inhalers.* Presentation at the Next Gen Inhalation Delivery Summit. Boston, MA, Jun. 21, 2023.
- Bielski E. *Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products.* Presentation at the American Thoracic Society (ATS) International Conference 2023. Washington, DC, May 22, 2023.
- Walenga R. *Utilizing In Vitro and In Silico Methods to Accelerate Product Development for Generic Nasal Drug Products.* Presentation at Novel Nasal Formulation and Delivery Summit 2023. San Diego, CA, May 18, 2023.
- Holtgrewe N. *Alternative In Vitro Bioequivalence Methods for Testing Generic Orally Inhaled Drug Products.* Presentation at the Fiscal Year (FY) 2023 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, May 12, 2023.
- Newman B. *Design Considerations for Alternative Bioequivalence Approaches for Generic Orally Inhaled Drug Products.* Presentation at the Respiratory Drug Delivery (RDD) Europe 2023. Antibes (Nice), France, May 05, 2023.
- Bulitta J. *Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic (PK) Data of Generic OIDPs via Population PK.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.
- Feng K. *Acceptability of Using Alternative Pk Metrics from Systemic Pharmacokinetic (Pk) Data to Inform Regional Deposition for Orally Inhaled Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.
- Holtgrewe N. *Alternative Bioequivalence Approach Using Morphologically-Directed Raman Spectroscopy (MDRS) on Nasal Spray Suspensions.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.
- Lin C. *Cluster-Informed In Silico and In Vivo Regional Deposition Assessments.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.
- Shur J. *Understanding Time-Evolved Changed in Morphology of Pharmaceutical Aerosol Systems.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.

OUTCOMES *continued*

- Bielski E. *Considerations and Challenges for Dissolution Testing of Orally Inhaled Drug Products (OIDPs).* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Boc S. *Considerations for Conducting More Realistic Aerodynamic Particle Size Distribution Testing for Orally Inhaled Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Gong Y. *Considerations for FEV1-based Comparative Clinical Endpoint or Pharmacodynamic Bioequivalence Studies for Orally Inhaled Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Hochhaus G. *Dissolution Tests for OIDPs: Opportunities and Challenges.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Newman B. *Designing Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies – Does One Approach Fit All for Generic Orally Inhaled Drug Products?* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Ren K. *Challenges and General Considerations of Conducting Pharmacodynamic Equivalence Studies for Albuterol Sulfate Metered Dose Inhalers.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Soukup S. *Challenges and Recommendations in Comparative Clinical Endpoint Bioequivalence Studies in Dry Powder Inhaler Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Svensson M. *Which Test and Handling Factors Affect the MDI Performance?* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.

OUTCOMES *continued*

- Walenga R. *Model Purpose and Selection for Supporting Development and Approval of Generic Locally Acting Orally Inhaled Drug Products in the United States.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Holl M. *Materials for Aerosol Treatment of Disease: New Microscopy for Bioequivalence and Improving Therapeutic Index.* Presentation at the University of Alabama Cystic Fibrosis Research Center (CFRC). Virtual Meeting, Jan. 24, 2023.
- Kaviratna A. *General Considerations for the Quantitative Sameness Evaluation of a Proposed Generic Formulation.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Bielski E. *Regulatory Science in the Field of Respiratory Medicine: Current Challenges and New Frontiers with Generics.* Presentation at the 2022 Virginia Commonwealth University Pharmaceutics Seminar. Virtual Meeting, Nov. 04, 2022.

OPHTHALMIC & OTIC PRODUCTS

Summary of FY 2023 Activities

FDA's FY 2023 research efforts focused on addressing challenges associated with the development and evaluation of generic ophthalmic and otic products converging on two major areas of interest, (1) identification and characterization of critical physicochemical and structural properties that affect in vitro, ex vivo, and in vivo performance; and (2) the advancement and integration of in silico approaches to enable a deeper understanding of the relationship between drug product physicochemical and structural properties, pharmacokinetics (PK), and pharmacodynamics (PD).

In collaboration with Pharmaron (Contract 75F40119D10024-75F40120F19002), the impact of variations in the critical quality attributes (CQAs) of ophthalmic suspension drug products indicated for reduction of intraocular pressure were evaluated as a function of ocular PK/PD. Similarly formulated ophthalmic suspensions with varying drug particle size and formulation viscosity, provided critical insights into how these two product CQAs impact the in vivo performance of these locally acting ophthalmic products. With respect to ophthalmic ointments, the University of Connecticut (Contract HHSF223201810114C) investigated the CQAs of complex ointment dispersions with multiple active ingredients and established in vivo and in vitro relationships to estimate product performance as a function of particle size distribution, rheology, and release kinetics. Additionally, research in collaboration with Akina, Inc. (Contract 75F40119C10096) focused on using molecular topology fractionation for the separation of complex polymeric mixtures to develop and validate novel approaches to support the establishment of inactive ingredient sameness for certain polymer-based ophthalmic implants and inserts.

GDUFA research in this area also focused on leveraging in silico approaches to help establish more clinically relevant BE criteria for complex ophthalmic products. The development of a robust framework, that utilizes multiple ocular models featuring different levels of spatial resolution, was completed in collaboration with CFD Research Corporation (Grant 1U01FD006929). The purpose of this framework was to facilitate interspecies physiologically based extrapolation of ophthalmic PK/PD models from rabbits to humans. Lastly, a research collaboration with Simulations Plus, Inc. (Grant 1U01FD006927) focused on developing and validating a physiologically based PK/PD modeling strategy to further support the interspecies translation of rabbit ocular models to humans. The goal was to achieve interspecies translation by amplifying the models' capacity to perform human extrapolation utilizing rabbit and monkey preclinical PK/PD data. Details of this work are provided in the **Research Highlight** below.

Additional GDUFA research in this area during FY 2023, that is continuing into FY 2024, focuses on (1) understanding and characterizing polymeric blockiness in long-acting ophthalmic implants (Contract 75F40120C00198), (2) advancing BE approaches using in silico strategies (Contract 75F40123C00072), and (3) evaluating the CQAs of a dexamethasone intracanalicular insert (internal FDA research project).

RESEARCH HIGHLIGHT

The complex structure and the dynamic nature of ocular physiology creates significant challenges in assessing the bioequivalence of complex locally acting ophthalmic drug products. Preclinical models are often used in the development of ophthalmic products; however, physiological factors (e.g., tear turnover and film dynamics, pH, corneal and conjunctival permeability) and anatomical differences between human and preclinical animal models can hinder the understanding and interpretation of preclinical PK/PD studies. Modeling strategies have been explored to advance FDA's understanding of the dynamics of ocular bioavailability (BA)/BE for complex products, and potential interspecies translational approaches, through a completed Grant (1U01FD006929, CFD Research Corporation) and an ongoing Grant (1U01FD006927, Simulations Plus, Inc.).

The ongoing research (1U01FD006927) focused on the expansion and validation of an Ocular Compartmental Absorption and Transit (OCAT™) model within the commercial GastroPlus® software platform, with the goal of predicting human ocular PK and PD through interspecies extrapolation. The rabbit models were first developed and validated using publicly available data. The validated rabbit models were then extrapolated into human models by incorporating differences in ocular anatomy and physiology between rabbits and humans. This physiologically based PBPK-based extrapolation strategy is illustrated in **Figure 1**.

Ophthalmic solution formulations were first studied with the purpose of certifying that human ocular PK can be scaled from rabbit preclinical PK data using the developed PBPK modeling approach. The extrapolated PBPK models were successfully applied to predict human PK in multiple ocular tissues for a variety of topical ophthalmic solutions. The drugs studied included, but was not limited to, levofloxacin, moxifloxacin, and gatifloxacin ophthalmic solutions.[4] Subsequently, complex ophthalmic suspensions, including dexamethasone, besifloxacin and fluorometholone are being investigated. Additionally, an intraocular pressure PD baseline model was developed that accounts for the circadian rhythm in aqueous humor production as well as the aqueous humor elimination using both uveoscleral and trabecular outflow pathways, and for related interspecies variations between rabbits, monkeys, and humans.

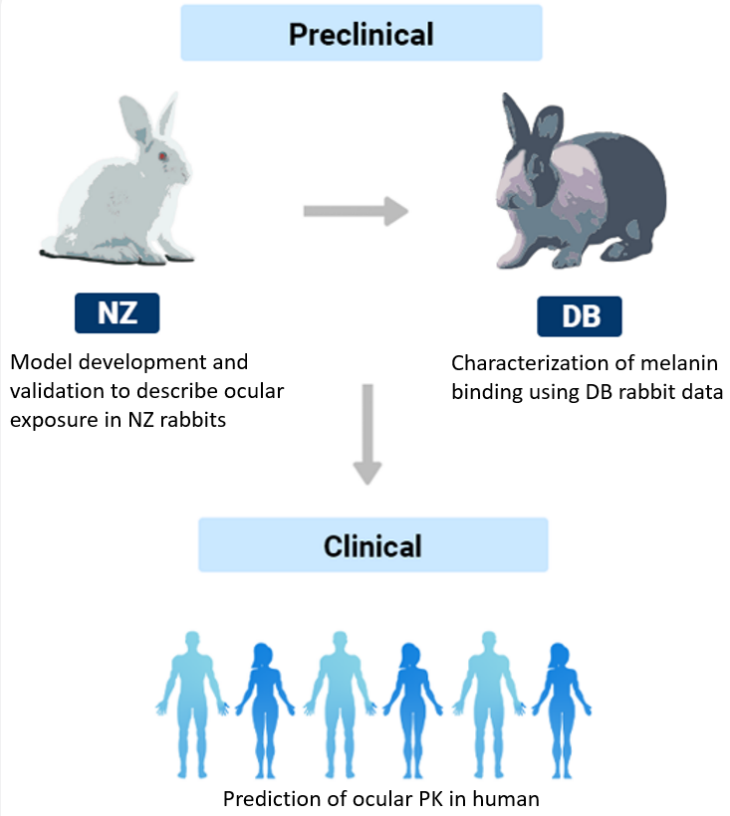

Figure 1. PBPK modeling strategy to perform the preclinical to clinical ophthalmic PK extrapolation using OCAT model. NZ: New Zealand; DB: Dutch Belted. Adapted from Le Merdy, et al 2023.[4]

[4] Le Merdy M, AlQaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2023) 40(2), 431–447. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444

RESEARCH PROJECTS AND COLLABORATIONS

New Grant(s) and Contract(s)

- Contract (75F40123C00072) *A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs* with Carrie German at CFD Research Corporation
- Contract (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina Inc.

Continuing Grant(s) and Contract(s)

- 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 (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* with Zhang Feng at University of Texas at Austin
- Contract (75F40119C10096) *New Analytical Methods for Complex Sameness of Injectable, Long-Acting PLGA Formulations* with Haesun Park at Akina, Inc.
- Contract (75F40119D10024-75F40120F19002) *PK/PD of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Absorption Systems

Completed 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
- Contract (HHSF223201810114C) *In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence* with Xiuling Lu at University of Connecticut

Active FDA Research

- *Development of an Ophthalmic PBPK Modeling Platform*
- *Evaluation of Dexamethasone Intracanalicular Insert to Support Determination of Bioequivalence*
- *Ophthalmic Antimicrobial Kill Rate Study*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

OUTCOMES

Product-Specific Guidances

There were four new PSGs published in FY 2023 related to *Otic and Ophthalmic* products. PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Chloroprocaine Hydrochloride Ophthalmic Gel.* (Aug. 21, 2023) Link to Posting
- *New Draft Guidance for Bimatoprost Ophthalmic Implant.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Triamcinolone Acetonide Suprachoroidal Suspension.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Ketotifen Fumarate Ophthalmic Solution/Drops.* (Nov. 17, 2022) Link to Posting

Articles

- Babiskin A, Wu F, Mousa Y, Tan M-L, Tsakalozou E, Walenga R, Yoon M, Raney S, Polli J, Schwendeman A, Krishnan V, Fang L, and Zhao L. *Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches: a Workshop Overview.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12: 619-623. https://doi.org/10.1002/psp4.12920. PMID: 36631942.
- Belenos A, Wood E, Hu M, Kozak D, Xu X, and Fisher A. *Product Quality Research for Developing and Assessing Regulatory Submissions for Generic Cyclosporine Ophthalmic Emulsions.* The AAPS Journal. (2023) 25: 20. https://doi.org/10.1208/s12248-023-00781-x. PMID: 36702976.
- Beringhs AO, Naageshwaran V, Gum G, Seremak D, Malla S, Vo A, Tan M-L, Babiskin A, Wang Y, Kozak D. *Impact of Variations in Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions on Preclinical Pharmacokinetics and Pharmacodynamics Following Once Daily Topical Instillations.* IOVS: Investigative Ophthalmology & Visual Science. (2023) 64, 2622.
- Costello M, Liu J, Wang Y, Bin Q, Xu X, Li Q, Lynd N, and Zhang F. *Reverse Engineering the Ozurdex Dexamethasone Intravitreal Implant.* International Journal of Pharmaceutics. (2023) 634: 122625. https://doi.org/10.1016/j.ijpharm.2023.122625. PMID: 36690129.
- Costello M, Liu J, Chen B, Wang Y, Qin B, Xu X, Li Q, Lynd N, and Zhang F. *Drug Release Mechanisms of High-Drug-Load, Melt-Extruded Dexamethasone Intravitreal Implants.* European Journal of Pharmaceutics and Biopharmaceutics. (2023) 187: 46-56. https://doi.org/10.1016/j.ejpb.2023.04.003. PMID: 37037387.
- German C, Chen Z, Przekwas A, Walenga R, Babiskin A, Liang Z, Fan J, and Tan M-L. *Computational Model of In Vivo Corneal Pharmacokinetics and Pharmacodynamics of Topically Administered Ophthalmic Drug Products.* Pharmaceutical Research. (2023) 40(4): 961–975. https://doi.org/10.1007/s11095-023-03480-6. PMID: 36959411.
- Nejad HB, Zaman R, Smith W, Wu K-W, Feng X, Beringhs AO, Wang Y, Kozak D, Xu X. *Impact of Material and Manufacturing Process on Performance of an Ophthalmic Implant.* IOVS: Investigative Ophthalmology & Visual Science. (2023) 64: 735.
- Kozak D, Zhu D, Zhang Y, Dong Y, Patel D, and Xu X. *Measuring Drug Partitioning and Release to Support In Vitro Bioequivalence of Generic Ophthalmic Emulsion Drugs.* IOVS: Investigative Ophthalmology & Visual Science. (2023) 64: 1143

OUTCOMES *continued*

- Le Merdy M, Alqaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2023) 40: 961-975. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444.

- Mekjaruskul C, Beringhs AO, Qin B, Wang Y, Chowdhury P, and Lu X. *Impact of Apparatus and Adapter on In Vitro Drug Release of Ophthalmic Semisolid Drug Products.* Pharmaceutical Research. (2023) 40: 2239–2251. https://doi.org/10.1007/s11095-023-03586-x. PMID: 37679656.

- Naageshwaran V, Bigonne H, Gum G, Malla S, Sol C, Bon C, Xu X, Vo A, Smith W, Beringhs AO, Kozak D, Tan M-L, Babiskin A, Babiskin A, Urtti A, Amo E, and Ranta V. *Topical Pharmacokinetics of Brinzolamide Suspensions in Rabbits and Variability Analysis for Sample Size and Design Considerations.* International Journal of Pharmaceutics. (2023) 642(123183). https://doi.org/10.1016/j.ijpharm.2023.123183. PMID: 37369289.

- Tan M-L, Chandran S, Jereb R, Alam K, Bies R, Kozak D, Walenga R, Le Merdy M, and Babiskin A. *Mechanistic Modeling of Ophthalmic, Nasal, Injectable, and Implant Generic Drug Products: a Workshop Summary Report.* CPT Pharmacometrics Systems & Pharmacology. (2023) 12: 631-638. https://doi.org/10.1002/psp4.12952. PMID: 36851886.

Posters

- Das J, Hasan M, Smith W, Graner J, Qin B, Wang Y, Park K, Tian G, and Xu X. *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Mekjaruskul C, Beringhs AO, Meng T, Qin B, Wang Y, Xu Q, Halquist M, Lu X. *Novel In Vitro, Ex Vivo and In Vivo Assessment of Ophthalmic Semi-Solid Drug Products.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Qin B, Wang Y, Zhang Q, Li Q, and Kozak D. *What Do We Know About PLGA Polymers in FDA-approved Drug Products: A Journey of Characterizing PLGA Polymers and Formulations.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Le Merdy M, Lukacova V. *Ocular Exposure Extrapolation Across Multiple Species Using PBPK Modeling and Simulation: Latanoprost Solution Case Study.* Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. La Coruna, Spain. Jun. 28, 2023.

- Beringhs AO, Naageshwaran V, Gum G, Seremak D, Malla S, Vo A, Tan M-L, Babiskin A, Wang Y, Kozak D. *Impact of Variations in Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions on Preclinical Pharmacokinetics and Pharmacodynamics Following Once Daily Topical Instillations.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.

- Zhu D, Zhang Y, Deval P, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: A Novel In Vitro Release Testing Method for Complex Ophthalmic Drug Products.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.

OUTCOMES *continued*

- Beringhs AO, Naageshwaran V, Gum G, Seremak D, Malla S, Vo A, Tan M-L, Babiskin A, Wang Y, Kozak D. *Impact of Variations in Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions on Preclinical Pharmacokinetics and Pharmacodynamics Following Once Daily Topical Instillations.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Kozak D, Zhu D, Zhang Y, Dong Y, Patel D, and Xu X. *Measuring Drug Partitioning and Release to Support In Vitro Bioequivalence of Generic Ophthalmic Emulsion Drugs.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Le Merdy M, AlQaraghuli F, Lukacova V. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Besifloxacin Suspension Case Study.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA. April 23, 2023.
- Naageshwaran V, Gum G, Kumar S, Manza L, Lyulkin M, Cook N, Xu X, Patel D, Qu H, Walenga R, Tan M-L, Babiskin A, Kaisar M, and Kozak D. *Tear Film Thickness (TFT) is the Most Sensitive Measure to Capture Differences in the Critical Quality Attributes of a Formulation Using Anterior Optical Coherence Tomography (AS-OCT).* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Nejad HB, Zaman R, Smith W, Wu K, Feng X, Beringhs AO, Wang Y, Kozak D, Xu X. *Impact of Material and Manufacturing Process on Performance of an Ophthalmic Implant.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Nejad HB, Zaman R, Smith W, Wu K, Feng X, Beringhs AO, Wang Y, Kozak D, Xu X. *Impact of Material and Manufacturing Process on Performance of a Dexamethasone Ophthalmic Implant.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.
- Kumar S, Cook N, Gum G, Manza L, Naageshwaran V, Lyulkin M, Xu X, Patel D, Qu H, Walenga R, Tan M-L, Babiskin A, and Kaisar M. *Impact of Changes in Ophthalmic Emulsion Globule Size Distribution and Viscosity on Tear Film Thickness and Menisci Characteristics.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Qaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, Lukacova V, and Le Merdy M. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Gatifloxacin Solution Case Study.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Zhen Z, Mekjaruskul C, Qin B, Wang Y, and Lu X. *Impact of Apparatus and Adaptor Setups on In Vitro Drug Release of Ophthalmic Semi-Solid Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Zhu D, Zhang Y, Kozak D, Ashraf M, and Xu X. *Automated Adaptive Perfusion: A Novel In Vitro Release Testing System for Complex Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

OUTCOMES *continued*

Presentations

- Fan Q, and Harigaya Y. *Cyclosporine & Difluprednate Ophthalmic Emulsions.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Lu X. *Novel In Vitro, Ex Vivo and In Vivo Assessment of Ophthalmic Semi-Solid Drug Products.* Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Las Vegas, NV, Jul. 27, 2023.
- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2023. North Bethesda, MD, Jun. 04, 2023.
- Xu X. *In Vitro Release Test for Complex Drug Product: What is Your Perspective?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) - Chicagoland Pharmaceutical Discussion Group (CPDG). Chicago, IL, May 19, 2023
- Xu X. *Complex Equilibria and Complex Drug Products: Fundamentals in Advancing Regulatory Science.* Presentation at the University of Connecticut. Virtual Meeting, Nov. 28, 2022.
- Kuehster L. *Stochastic and Deterministic Analysis of Reactivity Ratios in the Partially Reversible Copolymerization of Lactide and Glycolide.* Presentation at The American Institute of Chemical Engineers (AIChE) Annual Meeting. Phoenix, AZ, Nov. 13, 2022.
- Kozak D. *Considerations for Post-Approval Changes to Complex Generic Drug Products.* Presentation at the 2022 Association for Affordable Medicines (AAM): GRx + Biosims Conference. North Bethesda, MD, Nov. 08, 2022.
- Le Merdy M. *Ophthalmic Drug Products: Leveraging M&S Approaches to Perform Inter-Species Predictions and Support Drug Product Development and Approval.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting. Oct. 27, 2022.
- Zhang F. *Melt-Extruded Dexamethasone Ophthalmic Implants: Process, Structure and In Vitro Drug Release.* Presentation at the 4th Annual Formulation and Drug Delivery USA Conference. San Diego, CA, Oct. 11, 2022.

TOPICAL PRODUCTS

Summary of FY 2023 Activities

During FY 2023, FDA's GDUFA-funded research continued to support the development of efficient BE approaches for topically applied drug products (including products administered via the skin, as well as vaginal and rectal routes of administration) as part of an effort to facilitate generic drug development and enhance patient access to these important medicines.

One goal of this research program is to continue the development and implementation of efficient characterization-based BE approaches for prospective generic products when the formulation composition is well matched to that of the reference standard. During FY 2023, data from FDA-funded research studies supported the development of general guidances related to comparative physicochemical and structural (Q3) characterization tests, in vitro release test (IVRT) studies as well as in vitro permeation test (IVPT) studies.[5,6,7] More than 80 new and revised product-specific guidances, with recommendations coordinated in relation to these general guidances, were published with the goal of increasing the efficiency, consistency, and predictability of generic product development approaches for topical products applied to the skin, as well as those that are dosed using the vaginal, rectal, or anal routes of administration.

Additionally, FDA sought to understand the mechanisms that allow prospective generic products and reference standards to be bioequivalent when they do not have the same formulation, but are similar in components, composition, and/or Q3 attributes. To elucidate these mechanisms, in vitro experiments and in silico modeling and simulation were performed through collaborations with the University of South Australia (Grant 1U01FD006496) and the Topical Product Testing LLC (Grant 1U01FD006507). These research collaborations sought to elucidate when compositional changes in inactive ingredients can change the thermodynamic activity of the drug in a topical formulation, and how changes in thermodynamic activity correlate with bioavailability.

Additionally, a research collaboration with the University of Queensland (Grant 1U01FD006700) studied how differences in specific Q3 attributes that can impact sensorial properties of topical products (e.g., a cooling sensation, rheological differences) may be perceived by human subjects. Research at the University of Rhode Island (Grant 1U01FD007656) is ongoing to develop characterization-based BE approaches for complex vaginal and rectal products, such as suppositories and creams, including evaluation of methodologies for assessing local bioavailability for such products. Another goal was to develop efficient PK-based methods to directly monitor the drug's bioavailability at or near its site(s) of action in the skin.

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[5] FDA Draft Guidance for Industry. *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs.* Available at: https://www.fda.gov/media/162471/download

[6] FDA Draft Guidance for Industry. *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs.* Available at: https://www.fda.gov/media/162476/download

[7] FDA Draft Guidance for Industry. *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs.* Available at: https://www.fda.gov/media/162475/download

During FY 2023, FDA and the CRCG hosted a public workshop titled "Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development" on Nov 3, 2022[8]. The practical feasibility and remaining challenges associated with the utilization of dermal open flow microperfusion (dOFM) and dermal microdialysis (dMD) as efficient cutaneous PK-based BE approaches were extensively discussed. As a result, the objectives of the new research initiated with Joanneum Research (Grant 1U01FD007669) and continuing research with Long Island University (Grant 1U01FD006930) were revised to further enhance the clinical study design for cutaneous PK-based BE approaches using these dermal sampling techniques. Independently, research at the University of Bath (Grant 1U01FD006533) and Massachusetts General Hospital/Harvard Medical School (Grant 1U01FD006698) developed sensitive and discriminating non-invasive cutaneous PK-based methods using advanced confocal Raman imaging techniques (see **Research Highlight** below).

To advance the development of in silico tools for skin absorption, the FDA awarded two new grants; Grant 1U01FD007954 was awarded to Certara UK, LTD and Grant 1U01FD007957 was awarded to the University of Bath. These grants focused on rigorously validating model predictions of skin permeation that consider drug product metamorphosis following application upon the skin, and the impact of formulation characteristics on skin permeation. A more detailed description of these collaborative agreements can be found in Chapter 7 "Quantitative Methods & Models", and specifically in the section describing "Locally-Acting Physiologically Based Pharmacokinetic Modeling".

[8] FDA/CRCG Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development (https://www.complexgenerics.org/education-training/formulation-characterization-and-cutaneous-pharmacokinetics-to-facilitate-generic-topical-product-development/)

RESEARCH HIGHLIGHT

The BE of systemically acting drug products is routinely evaluated using PK BE studies; however, it has been historically challenging to evaluate cutaneous PK following the topical application of a drug product to the skin. Over the last few years, FDA has funded research at the University of Bath (Grant 1U01FD006533) and Massachusetts General Hospital/Harvard Medical School (Grant 1U01FD006698) to develop non-invasive cutaneous PK-based methods using advanced microscopy and spectroscopy. Recent research using metronidazole topical formulations at the University of Bath demonstrated that spectroscopy-based methods can be used to characterize the epidermal PK profile of a topically applied drug. Fully saturated metronidazole solutions in 90:10 water/propylene glycol, and 0.75% w/w metronidazole gels (currently marketed by Prasco (reference standard) were assessed ex vivo using abdominal pig skin. Raman spectroscopy signals from metronidazole (at 1192 cm^{-1}) and propylene glycol (at 840 cm^{-1}), an inactive ingredient in all formulations studied, were detected as a function of depth and time following topical application of the products to the skin using a Renishaw RM1000 Raman microscope running v1.2 WIRE software, Renishaw plc, Wotton-Under-Edge, UK. Signals were normalized to account for signal attenuation with depth. The Raman-deduced disposition of metronidazole from the gels appeared to be consistent as a function of time and depth for the within-gel comparison of the reference standard (that was evaluated in duplicate to assess the reproducibility of the method). In contrast, the composition of the solution clearly influenced the epidermal PK of metronidazole, and overall, the results successfully demonstrated the robustness, sensitivity, and discriminatory ability, of the spectroscopy-based approach. Similar datasets were also generated at the Massachusetts General Hospital for tazarotene topical solutions and cream, using ex vivo human skin, and stimulated Raman spectroscopy, further confirming the reproducibility, sensitivity, and discriminatory ability of Raman-based methodologies for the quantification of cutaneous PK. Such characterizations of drug bioavailability and localization in the skin can be useful for the evaluation of BE. Additional research is necessary to evaluate the utility of the methodology in vivo, and to develop strategies for utilizing the methodology as a component of efficient BE approaches for topical products.

RESEARCH HIGHLIGHT *continued*

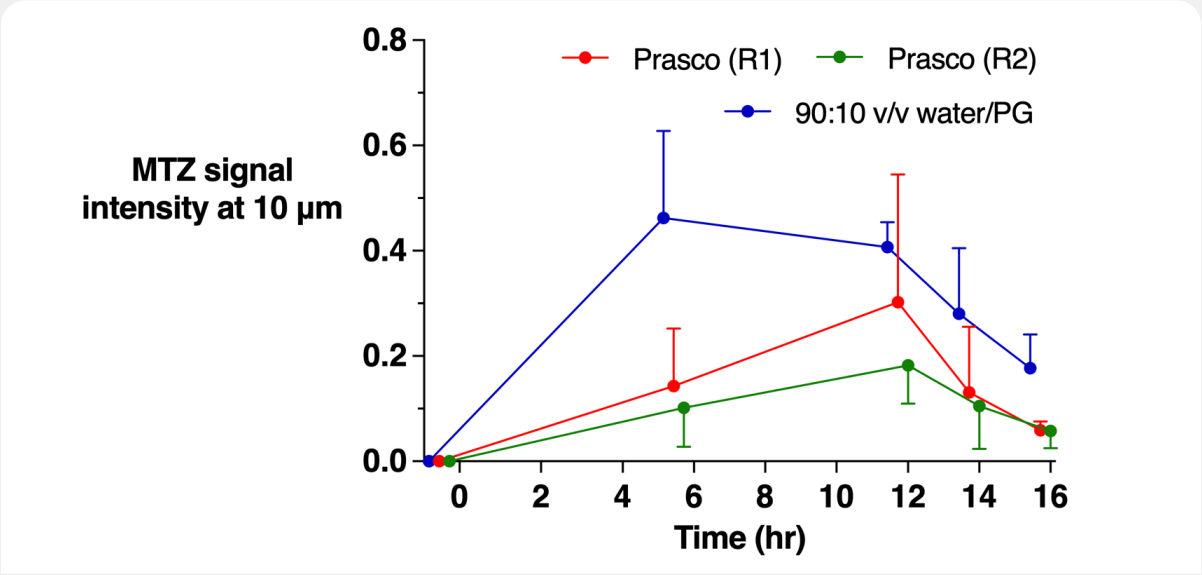

Figure 1: Normalized metronidazole Raman signal intensities at 10µm, as a function of time, after application of the gels and laboratory-made (solution) formulations. Experiments with the reference standards (Prasco 1 and Prasco 2) were duplicated to provide an internal control. Data were shown as mean ± SD (n = 4). PG: propylene glycol.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007957) *Development and Validation of a Multi-Functional, Multi-Purpose Quantitative Tool for Dermal PBPK Modeling* with M. Begona Delgado-Charro at University of Bath
- Grant (1U01FD007954) *Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients* with James Clarke at Certara UK, LTD
- Contract (75F40123C00204) *In Vitro Tests to Support Bioequivalence Determination When Generic Dermatological Formulation has Differences from the Brand Product Formulation* with Ajay Banga at The Corporation of Mercer University
- Contract (75F40123C00213) *Role of Excipients and Excipient Substitution in Topical Semi-Solid Formulations and Their Effect on Product Performance and Quality* with Bozena Michniak-Kohn at Rutgers University

Continuing Grants and Contracts

- Grant (1U01FD006700) *Bioequivalence of Topical Products: Elucidating the Sensorial and Functional Characteristics of Compositionally Different Topical Formulations* with Yousuf Hussain Mohammed at University of Queensland
- 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

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- Grant (1U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Sathyanarayana N Murthy at Topical Product Testing LLC
- Grant (1U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products using Non-Invasive Techniques (U01)* with Richard H. Guy at the University of Bath
- 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 Certara UK, LTD
- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at Simulations Plus, Inc
- Grant (1U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with David Taft at Long Island University, Brooklyn Campus
- Grant (1U01FD007656) *In Vitro Based Approaches to Evaluate the Bioequivalence of Locally-Acting Rectal and Vaginal Semi-Solid Drug Products* with Jie Shen at Northeastern University
- Grant (1U01FD007669) *Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics* with Frank Sinner at Joanneum Research
- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterisation, Release and Permeation Data to the Next Level - PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK Limited

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *Characterization of Topical Gel, Cream, Foam Formulations to Elucidate the Impact of Drug Product Microstructure on Product Performance/Bioavailability to Facilitate the Development of Product Specific Guidances.*

OUTCOMES

General Guidance

- FDA Draft Guidance for Industry. *Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs.* April 2023. Link to Posting
- FDA Draft Guidance for Industry. *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs.* April 2023. Link to Posting
- FDA Draft Guidance for Industry. *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs.* October 2022. Link to Posting
- FDA Draft Guidance for Industry. *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs.* October 2022. Link to Posting
- FDA Draft Guidance for Industry. *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs.* October 2022. Link to Posting
- FDA Draft Guidance for Industry. *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence.* October 2022. Link to Posting

Product-Specific Guidances

There were 19 new and 76 revised PSGs published in FY2023 related to *Topical* products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Abametapir Lotion.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Acyclovir; Hydrocortisone Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Acyclovir Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Adapalene Gel (NDA 020380).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Adapalene Gel (NDA 021753).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Adapalene; Benzoyl Peroxide Gel (NDA 022320).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Adapalene; Benzoyl Peroxide Gel (NDA 207917).* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Ammonium Lactate Cream (NDA 020508).* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Ammonium Lactate Lotion (NDA 019155).* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Benzoyl Peroxide; Clindamycin Phosphate Gel (NDA 050819).* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Benzoyl Peroxide; Clindamycin Phosphate Gel (NDA 050756).* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Benzoyl Peroxide; Clindamycin Phosphate Gel (NDA 050741).* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Benzyl Alcohol Lotion.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Betamethasone Dipropionate; Calcipotriene Suspension.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Betamethasone Dipropionate; Calcipotriene Ointment.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Betamethasone Dipropionate; Calcipotriene Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Bexarotene Gel.* (Oct. 21, 2022) Link to Posting

OUTCOMES *continued*

- *Revised Draft Guidance for Butenafine Hydrochloride Cream (NDA 021307).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Butenafine Hydrochloride Cream (NDA 020524).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Calcipotriene Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Calcipotriene Ointment.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Citric Acid; Lactic Acid; Potassium Bitartrate Gel.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Clascoterone Cream.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate Lotion.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Clindamycin Phosphate Gel (NDA 215650).* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate Gel (NDA 050782).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate Gel (NDA 050615).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate; Tretinoin Gel (NDA 050803).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate; Tretinoin Gel (NDA 050802).* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Clobetasol Propionate Lotion.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Crisaborole Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Crotamiton Lotion.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Crotamiton Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Dapsone Gel (NDA 021794).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Dapsone Gel (NDA 207154).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Diclofenac Sodium Gel (NDA 022122).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Diclofenac Sodium Gel (NDA 021005).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Docosanol Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Doxepin Hydrochloride Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Erythromycin Gel.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Fluocinolone Acetonide Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Fluorouracil Cream (NDA 016831).* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Fluorouracil Cream (NDA 022259).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Fluorouracil Cream (NDA 016988).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Gentamicin Sulfate Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Gentamicin Sulfate Cream.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Halobetasol Propionate Lotion.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Hydrocortisone Enema (NDA 016199).* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Hydrocortisone Cream (NDA 009585).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Ivermectin Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Ivermectin Lotion.* (Oct. 21, 2022) Link to Posting

OUTCOMES *continued*

- *Revised Draft Guidance for Ketoconazole Gel.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Ketoconazole Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Lidocaine Ointment.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lidocaine Patch.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Lidocaine Hydrochloride Jelly.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Luliconazole Cream.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Mechlorethamine Hydrochloride Gel.* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Metronidazole Cream (NDA 020531).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Metronidazole Gel (NDA 019737).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Metronidazole Gel (NDA 021789).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Metronidazole Lotion.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Metronidazole Cream (NDA 020743).* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Miconazole Nitrate; Petrolatum, White; Zinc Oxide Ointment.* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Mupirocin Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Mupirocin Calcium Cream.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Nitroglycerin Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Nystatin Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Nystatin Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Nystatin; Triamcinolone Acetonide Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Nystatin; Triamcinolone Acetonide Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Oxymetazoline Hydrochloride Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Ozenoxacin Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Penciclovir Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Pimecrolimus Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Podofilox Gel.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Progesterone Gel.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Ruxolitinib Phosphate Cream.* (Aug. 21, 2023) Link to Posting
- *Revised Draft Guidance for Silver Sulfadiazine Cream.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Sirolimus Gel.* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Spinosad Suspension.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tacrolimus Ointment (NDA 050777, 0.1%).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tacrolimus Ointment (NDA 050777, 0.3%).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tazarotene Cream.* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Tazarotene Lotion.* (Oct. 21, 2022) Link to Posting

OUTCOMES *continued*

- *Revised Draft Guidance for Tazarotene Gel* (NDA 020600, 0.05%). (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tazarotene Gel (NDA 020600, 0.1%).* (Oct. 21, 2022) Link to Posting
- *New Draft Guidance for Tirbanibulin Ointment.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tretinoin Gel (NDA 022070).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tretinoin Gel (NDA 017955).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Tretinoin Gel (NDA 017579).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetonide Ointment (NDA 011600-oin-0.05p).* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetonide Lotion.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetonide Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetonide Ointment (NDA 011600).* (Oct. 21, 2022) Link to Posting

Articles

- Maciel Tabosa MA, Vitry P, Zarmpi P, Bunge AL, Belsey NA, Tsikritsis D, Woodman TJ, White KJ, Delgado-Charro MB, Guy RH. *Quantification of Chemical Uptake into the Skin by Vibrational Spectroscopies and Stratum Corneum Sampling.* Molecular Pharmaceutics. (2023) 20(5):2527-2535. https://doi.org/10.1021/acs.molpharmaceut.2c01109. PMID: 37053523.
- Raney SG, Senemar S, Burke M, Lee C, Shah JR, Li KL, Anand O, Warner KS. *Advances in Product Quality and Performance Tests for Topical and Transdermal Products - View of The USP Expert Panel.* United States Pharmacopeia (49-5). Stimuli PF. (2023) https://doi.org/10.31003/USPNF_S203204_10101_01.
- Senemar S, Kuzma B, Ramezanli T, Ghosh P, Raney S, Rantou E, and Stagni G. *Bioequivalence Evaluation of Topical Metronidazole Products Using Dermal Microdialysis in New Zealand Rabbits.* AAPS PharmSciTech. (2023) 24(7): 204. https://doi.org/10.1208/s12249-023-02660-2. PMID: 37789133.
- Thomas S, Hammell DC, Hassan HE, Stinchcomb AL. *In Vitro-In Vivo Correlation of Buprenorphine Transdermal Systems Under Normal and Elevated Skin Temperature.* Pharmaceutical Research. (2023) 40(5):1249-1258. https://doi.org/10.1007/s11095-023-03487-z. PMID: 37095369.
- Tsakalozou E, Alam K, Ghosh P, Spires J, Polak S, Fang L, Sammeta S, Zhao P, Arora S, and Raney S. *Mechanistic Modeling of Drug Products Applied to the Skin: a Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2022) 12: 575 - 584. https://doi.org/10.1002/psp4.12893. PMID: 36456539.
- Zarmpi P, Maciel-Tabosa M, Vitry P, Bunge A, Belsey N, Tsikritsis D, Woodman T, Delgado-Charro M, and Guy R. *Confocal Raman Spectroscopic Characterization of Dermatopharmacokinetics Ex Vivo.* Molecular Pharmaceutics. (2023) 20(11): 5910-5920. https://doi.org/10.1021/acs.molpharmaceut.3c00755. PMID: 37801410.

Posters

- Bodenlenz M, Augustin T, Teles Barbosa F, Birngruber T, Tiffner K, Raml R, Ramezanli T, Raney S, and Sinner F. *Dermal OFM Indicates Differences in Acyclovir Skin Permeation between Males and Females.* Poster Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 09, 2023.

OUTCOMES *continued*

- Ghosh P, Ramezanli T, and Luke M. *Facilitating Drug Development Through GDUFA Regulatory Science and Research Opportunities for Collaboration with FDA.* Poster Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 09, 2023.
- Kelchen M, Xie L, Luke M, and Ghosh P. *Current Methods for Assessing Bioequivalence of Drug Products Applied to the Skin – a US FDA Perspective.* Poster Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 09, 2023.
- Spires J, Van Osdol B, and Lukacova V. *Development of an In Silico Model of Topical Acyclovir to Explore Formulation Design.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 09, 2023.
- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Belsey N, Woodman T, White K, Ghosh P, Bunge A, Delgado-Charro M, and Guy R. *Assessment of Bio(in)Equivalence of Metronidazole Topical Formulations using Stimulated Raman Scattering Microscopy.* Poster Presentation at the Academy of Pharmaceutical Science (APS) 2023. Virtual Meeting, Aug. 05, 2023.
- Clarke J, Murthy N, Zhang Y, Paterson D, Dancik Y, Djehizian A, Tsakalozou E, Ghosh P, Alam K, and Polak S. *Designing an In Vitro Study to Understand Release of API from the Dispersed Phase of Clobetasol Creams – Verification of the Mechanistic Emulsion Model in the MPML MechDermA.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Niu M, Ghosh P, Ramezanli T, Luke M, and Raney S. *Recommendations Related to In Vitro Permeation Test Studies in Product-Specific Guidances for Topical Drug Products.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
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- Kelchen M, Xie L, Luke M, and Ghosh P. *How Comparative Clinical Endpoint Bioequivalence Studies Facilitate the Development of Generic Topical Drug Products.* Poster Presentation at the International Dermatology Outcome Measures (IDEOM) 2023 Annual Meeting. Washington, DC, Jun. 23, 2023.
- Yang Y, Wang J, Wanasathop A, Zidan A, Niu M, Ghosh P, Faustino P, Ashraf M, and Xu X. *Method Development for the Evaluation of In Vitro Skin Permeation of Clascoterone from Clascoterone Topical Cream, 1%.* Poster Presentation at the American Chemical Society (ACS) Spring 2023: Crossroads of Chemistry. Indianapolis, IN, Mar. 26, 2023.
- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Ghosh P, Belsey N, Woodman T, White K, Bunge A, Delgado-Charro M, and Guy R. *Confocal Raman Spectroscopic Assessment of the Topical Bioavailability of Metronidazole: Comparison of Laboratory-made Formulations and Approved Drug Products.* Poster Presentation at the 3rd Skin@Bath Network Symposium. Bath, United Kingdom, Dec. 14, 2022.
- Ako Adounvo A, Niu M, Ghosh P, Ashraf M, and Zidan A. *Development of an In Vitro Release Method for Mechlorethamine Hydrochloride Topical Gel.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

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- Dick A, Panchal B, Prakash S, Ramezanli T, Ghosh P, Raney S, Roberts M, and Mohammed Y. *Tribological Response of Hydroxyethylcellulose Gels as a Function of Isopropyl Alcohol Concentration and Angular Velocity Profile.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Hamad G, Kelchen M, Ghosh P, Ramezanli T, Raney S, Ashraf M, and Zidan A. *Evaluation of In Vitro Performance Attributes of Imvexxy® (Estradiol) Vaginal Insert.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Iliopoulos F, Pence I, Ghosh P, Raney S, Luke M, and Evans C. *Stimulated Raman Scattering (SRS) Microscopy and Deep Learning: Novel Pharmacokinetic Approach for Evaluation of Topical Bioequivalence.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Kelchen M, Ghosh P, Ramezanli T, and Raney S. *Developing Efficient Bioequivalence Approaches for Generic Vaginal Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Panchal B, Namjoshi S, Ramezanli T, Ghosh P, Raney S, Roberts M, and Mohammed Y. *In Vitro Assessment of Cooling Potential of the Topical Gel System and Influence of Inactive Ingredients.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Rangappa S, Ghosh P, Jiang Y, Raney S, and Murthy S. *Influence of Varying Amount of an Inactive Ingredient on the Microstructure and Performance of Metronidazole Topical Gels.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Senemar S, Ramezanli T, Ghosh P, Raney S, Kuzma B, and Stagni G. *Investigation of the Relationship Between Product-Dose and Dermal Exposure of Lidocaine and Prilocaine from a Topical Cream Product Using Dermal Microdialysis.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
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- Telaprolu K, Arora S, Clarke J, Dancik Y, Tsakalozou E, Ghosh P, Alam K, Roberts M, and Polak S. *Evaluating Influence of Critical Quality Attributes of Metronidazole Topical Gel on Bioequivalence Using the Dermal Virtual Bioequivalence (VBE) Module in Simcyp Simulator.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
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- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Ghosh P, Belsey N, Woodman T, White K, Bunge A, Delgado-Charro M, and Guy R. *Confocal Raman Spectroscopic Assessment of the Topical Bioavailability of Metronidazole: Comparison of Laboratory-Made Formulations and Approved Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

OUTCOMES *continued*

Presentations

- Ramezanli T. *A Case Study to Evaluate the Performance of Dermal Open Flow Microperfusion and Dermal Microdialysis for Assessing the Cutaneous Pharmacokinetics of Topical Lidocaine and Prilocaine Cream.* Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 29, 2023.
- Ghosh P. *Role of Regulatory Science Research Topical Product Development.* Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 28, 2023.
- Ghosh P. *Impact of GDUFA Regulatory Science and Research Program on Topical Product Availability.* Presentation at the Dermatology Innovation Webinar - The Science Behind Innovations in Topical Generic Drug Assessment: Opportunities and Challenges. Virtual Meeting, Sep. 19, 2023.
- Luke M. *Innovation and Topical Generic Drug Science: A Case of Targeted and Planned Innovation.* Presentation at the Dermatology Innovation Webinar - The Science Behind Innovations in Topical Generic Drug Assessment: Opportunities and Challenges. Virtual Meeting, Sep. 19, 2023.
- Ramezanli T. *Translating Science to Regulatory Tools: Novel Approaches for Characterizing and Evaluating the Performance of Topical Drug Products.* Presentation at the Dermatology Innovation Webinar - The Science Behind Innovations in Topical Generic Drug Assessment: Opportunities and Challenges. Virtual Meeting, Sep. 19, 2023.
- Feng, K. *ANDA Challenges Related to Vasoconstrictor Studies.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Ghosh P. *Characterization-Based Bioequivalence Approaches for Topical Products Part 1: Q3 Guidance.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Ghosh P, and Patel H. *General Guidances Related to Characterization-Based Bioequivalence Approaches for Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Kelchen M. *An Overview of the Current Product-Specific Guidances for Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Zidan, A. *How Research Supports Product-Specific Guidances for Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Belsey N. *Visualization of Topical Drug Delivery with Label Free Chemical Imaging.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 10, 2023.
- Evans C. *PK and PD Tomography: Imaging and Quantifying Skin Pharmacology.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023 Waterville Valley, NH, Aug. 10, 2023.
- Bodenlenz M. *Dermal Open-Flow Microperfusion Indicates Differences in Topical Drug Permeation Between Males and Females.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 9, 2023.
- Ramezanli T. *Characterizing In Vivo Cutaneous Pharmacokinetics of Topical Lidocaine Prilocaine Cream using Dermal Open Flow Microperfusion and Dermal Microdialysis.* Presentation at Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 26, 2023.

OUTCOMES *continued*

- Luke M. *FDA Update: FDA and Dermatology DEIA.* Presentation at the 100th Annual Atlantic Derm Conference. Baltimore, MD, May 14, 2023.
- Luke M. *Generic Drugs and Dermatology: Bioequivalence and Access Equity.* Presentation at the Noah Worcester Dermatological Society: 64th Annual Meeting. Napa, CA, May 06, 2023.
- Luke M. *FDA for the Dermatologist - The Basics About FDA and Advances in Science and Regulation of Topical Generic Drugs.* Presentation at the American Academy of Dermatology (AAD) Annual Meeting. New Orleans, LA, Mar. 18, 2023.
- Luke M. *FDA Sponsored Drug Research Towards Generics for Dermatology.* Presentation at the Advancing Innovation in Dermatology 2023. New Orleans, LA, Mar. 16, 2023.
- Evans, C. *Cutaneous Pharmacokinetic and Pharmacodynamic imaging with Coherent Raman Scattering.* Presentation at the SPIE Photonics West: Raman Biomedical Application. San Francisco, CA, Jan. 30, 2023.
- Ghosh P. *GDUFA Science and Research Collaborating with the FDA Research Program.* Presentation at the SPIE Photonics West: FDA Policies and Procedures: What Academic Investigators and Small Business Should Know. San Francisco, CA, Jan. 30, 2023.
- Ghosh P. *Visualizing and Quantifying Drugs Dermal Drug Development.* Presentation at the SPIE Photonics West: Visualizing and Quantifying Drug Distribution in Tissue. San Francisco, CA, Jan. 28, 2023.
- Iliopoulos F, Pence I, Ghosh P, Raney S, Luke M, and Evans C. *Stimulated Raman Scattering (SRS) Microscopy and Deep Learning: Novel Pharmacokinetic Approach for Evaluation of Topical Bioequivalence.* Presentation at the SPIE Photonics West: Raman Biomedical Application. San Francisco, CA, Jan. 28, 2023.
- Raney S. *Revision to U.S. Pharmacopeia General Chapter <1724> Semisolid Drug Products – Performance Tests In Vitro Permeation Test (IVPT).* Presentation at the American Association of Pharmaceutical Scientists Topical and Transdermal Community Roundtable Discussion. Virtual Meeting, Dec. 09, 2022.
- Kelchen M. *General Considerations for the "No Significant Difference" Evaluation of a Proposed Generic Formulation.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Raney S. *Scientific and Regulatory Considerations for Generic Drug Products.* Presentation at the University of Michigan. Virtual Meeting, Nov. 10, 2022.
- Kuzma B, Senemar S, and Stagni G. *A Microdialysis Approach to Assess Dermal Pharmacokinetics of Topical Dermatological Drug Product.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Luke M. *On Understanding the Clinical Relevance of "Formulation" for Topical Drugs Applied to the Skin.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Mohammed A. *Development of Methods for Evaluation of Formulation Differences and their Impact on Therapeutic Equivalence: Broadening the Therapeutic Scope.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.

OUTCOMES *continued*

- Murthy N. *Influence of Progressive Change in the Degree of Saturation of API on the Performance of Topical Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Ramezanli T. *Cutaneous Pharmacokinetics-Based Techniques: Translating Scientific Advances to Regulatory Methods.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Raney S. *A Research Strategy to Develop Efficient BE Approaches for Complex Generic Topical Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Sinner F. *Continuous Skin Sampling Methods for the Assessment of Cutaneous PK-Based Bioequivalence.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development. Virtual Meeting, Nov. 03, 2022.
- Iliopoulos F. *SRS Microscopy and Deep Learning: Novel Approach for Evaluation of Topical Bioequivalence.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Ramezanli T. *Novel Approaches for Evaluating Bioavailability and Bioequivalence (BE) of Topical Drug Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Tsakalozou E. *Physiologically-Based Pharmacokinetic Modeling to Support Bioequivalence and Drug Approval.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Tsakalozou E. *Mechanistic Modeling and Simulation Approaches for Performance Prediction of Locally Acting Complex Drug Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Zidan A. *Advancements in the In Vitro Characterization Methodologies for Alternative BE Approaches of Locally Acting Complex Drug Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Raney S. *Scientific and Regulatory Advances for Complex Generic Topical Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 17, 2022.

CHAPTER 5: DRUG-DEVICE COMBINATION PRODUCTS

A major GDUFA science and research priority is to enhance the efficiency of equivalence approaches for complex drug-device combination products. The advancement of research in this area focuses on evaluating the impact of identified differences in the user interfaces, hardware, software, or propellants between a prospective generic and the reference listed drug on the bioequivalence (BE), therapeutic equivalence, or post-marketing safety of generic drug-device combination products. Research in this area is described below.

Summary of FY 2023 Activities

In FY 2023, research continued to support development of generic drug-device combination products (DDCP). Outcomes of this research will facilitate development of safe, effective, and high-quality generic DDCP.

One goal of this research program was to understand how differences in the design of the user interface of a generic DDCP impact substitutability for a branded product. To develop this scientific knowledge, FDA collaborations with the University of Detroit - Mercy (Grant 1U01FD007360) and the Battelle Memorial Institute (Grant 1U01FD007359) continued progress in FY 2023. The ultimate goal of these grants was to develop alternative methodologies to categorize and evaluate user interface differences of generic DDCP. Grant 1U01FD007359 continued refinement of an alternative methodology that integrates risk management elements and human factor engineering elements to assess and categorize design differences. Two sets of DDCP products, namely dry powder inhalers (DPIs) and autoinjectors, with different use populations, indications, and design were tested in the methodology. Grant 1U01FD007360 continued work on their taxonomy design to organize and create a shared vocabulary for DDCP. This visual taxonomy system utilized principles of task analyses, use error analyses, and risk assessments to link the user interface elements of design to risk. A clinical pilot study also initiated development to test the visual taxonomy. A new contract was awarded (75F40123D00028-75F40123F19001) in FY 2023 to conduct comparative use human factors study investigations to better understand how "other" design differences impact risk of user error when generic substitution occurs. Knowledge from these studies will inform development of new and revised product-specific guidances and enhance review processes for drug-device combination products.

Additionally, FDA sought to understand patient and caregiver perspectives on complex DDCP generic substitution. Contract HHSF223201710072C, with the Imperial College of Science Technology & Medicine (London, UK), continued progress in FY 2023. This contract aimed to develop a standardized questionnaire that can provide a quantitative evaluation of a patient's perception of airflow resistance from a dry powder inhaler (DPI) device. In FY 2023, study results from completed focus groups and cognitive interviews were utilized to generate the latest airflow resistance questionnaire. In addition, the reliability and validity of the questionnaire were further tested in a pilot clinical study. Based on the pilot clinical study results, the questionnaire may be edited and finalized. Ultimately, a pivotal clinical study will be conducted using the finalized questionnaire to analyze and identify the perception on resistance of DPI in chronic obstructive pulmonary disease (COPD) and asthma with different disease severities. Research activities with Contract HHSF223201810113C with the Research Triangle Institute (RTI) International (NC, US), were completed in FY 2023. Data from this contract provided key insights on patient and caregiver perceptions and attitudes toward generic substitution of DPI and autoinjectors. The **Research Highlight** describes key outcomes from two publications authored by FDA and collaborators.

Research was conducted in FY 2023 in FDA laboratories to understand device performance and applicable in vitro BE testing for complex generic DDCPs. FDA laboratories continued to investigate critical material and process parameters of microneedle arrays that affect critical quality attributes (CQAs). This research also utilized Artificial Intelligence (AI) image analysis to evaluate the topographical properties and spatial distribution of the drug in the needles. The knowledge gained through this project is expected to inform FDA's assessment of brand name and generic microneedle products. Another FDA-initiated project was completed during FY 2023 to understand the complexities and aerosolization process of a thermally assisted drug delivery platform for loxapine inhalation powder. Findings from this work supported product-specific guidance (PSG) recommendations published in FY 2023 to facilitate generic development of this product and this research will inform FDA's assessment of brand and generic thermally assisted drug delivery types. Lastly, FDA laboratories initiated a project to understand the impacts of various sources of purified type I collagen on the quality and performances of the bupivacaine collagen implant. The results of the project will fill the knowledge gaps, address the regulatory hurdle to developing a PSG, and ultimately facilitate the timely development of high quality complex generic products.

During FY 2023, FDA and the Center for Research on Complex Generics (CRCG) hosted a public workshop

"Drug-Device Combination Products 101: Identifying, Developing, And Evaluating Drug-Device Combination Products"[1] to facilitate collaborative discussions with industry and the public on scientific perspectives and relevant research, with the aim to support the efficient development of complex generic drug-device combination products.

Lastly, new FDA research was initiated in FY 2023 to increase our understanding of design features and the patent and manufacturing landscape of currently marketed autoinjector and pen injectors. Findings from this research will enable FDA to understand where barriers exist in relation to generic development for these DDCPs.

[1] FDA/CRCG Workshop on DDCP 101 – Identifying, Developing, and Evaluating Generic Drug Device Combination Products (DDCP). https://www.complexgenerics.org/education-training/ddcp-101-identifying-developing-and-evaluating-generic-drug-device-combination-products-ddcp/

RESEARCH HIGHLIGHT

Contract HHSF223201810113C completed in FY 2023, which sought to examine behavioral implications of substituting a generic DDCP for the brand product, to assess how the design and functionality of generic DDCPs affect patient perceptions of product quality, efficacy, and usability, and to explore participants' views on how generic and branded DDCPs compare. To accomplish these objectives, two separate focus group studies were conducted between 2018-2022.

The first study assessed patients' perceptions on DPI generic substitution. RTI International completed 6 in-person focus groups in FY 2021 in 40 patients with asthma and COPD. Participants in this study included adult and adolescent patients experienced with different brands of DPI. Participants completed a journey mapping exercise to assess attitudes and opinions about a scenario where they refill their prescription and unexpectedly receive a generic product instead of brand product. There were overall positive feelings about financial savings with generic substitution, and some anticipatory anxiety about understanding how to use the new device. Most patients desired to participate in discussions and decision making with their healthcare provider about generic substitution of their DPI.

To understand patient perceptions on generic substitution in a different patient population, the second study assessed perceptions related to autoinjector substitution. RTI international completed 8 focus groups between FY 2021 - FY 2022 in 50 participants with autoinjector experience. Participants in this study included adult users of EpiPen, adult caregivers, and adolescent EpiPen users. Participants completed a journey mapping exercise to assess attitudes and opinions about a scenario where they unexpectedly receive a generic epinephrine autoinjector instead of the EpiPen. This study found that participants were interested in cost savings but wanted to be informed about generic substitution prior to this occurring. In terms of differences in design between the brand and generic products, patients thought there were some design features of the generic that were better or equal to brand device.

Research conducted under Contract HHSF223201810113C resulted in two manuscripts (one published and one in press) and provided insights into patient perceptions of generic drug-device substitution in two device types and two different patient populations. Cost saving was found to be an important factor in generic substitution. Future studies could investigate patient perceptions on substitutability of certain design or user interface differences in brand and generic drug-device combination products.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40123D00028-75F40123F19001) *Comparative Use Human Factors Studies to Assess the Impact of Differences Between the User Interfaces of a Generic Drug-Device Combination Product and its Reference Listed Drug* with Jennifer Soosaar at Core Human Factors, Inc

Continuing Grants and Contracts

- Grant (1U01FD007360) *Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA* with Megan O'Meara Conrad at University of Detroit Mercy
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Completed Grants and Contracts

- Grant (1U01FD007359) *Battelle User Interface Design for Generic vs. RLD Combination Products* with Jessica Sanford at Battelle Memorial Institute
- Contract (HHSF223201810113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Monica Scales at RTI International

Active FDA Research

- *Developing Clinically Meaningful Disintegration and Dissolution Methods for Teriparatide Loaded Microneedles*
- *Development of a Biopredictive In Vitro Permeation Test to Evaluate Absorption from Naloxone Nasal Spray*
- *Development of New BE methods for Transdermal Irritation and Sensitization*
- *Evaluation and Comparison of Electronic Components of Three Approved New Drug/Device Combination Inhaler Products Indicated for Treatment of Bronchospasm or Asthma and Implications for Development of Future Generic Versions of Combination Drug/Device Products*
- *Evaluation of Critical Parameters Affecting the Performance of Staccato Drug Delivery System in Support of Development of Guidance for ADASUVE (Staccato Loxapine)*

OUTCOMES

Product-Specific Guidances

There were nine new and three revised PSGs published in FY 2023 related to *Complex Drug-Device Combination Products*. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Afamelanotide Subcutaneous Implant.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Dihydroergotamine Mesylate Metered Nasal Spray.* (Feb. 16, 2023) Link to Posting

OUTCOMES *continued*

- *New Draft Guidance for Donepezil Hydrochloride Transdermal System. (*Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Glucagon Nasal Powder.* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant* (NDA 019726). (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant* (NDA 020578). (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Loxapine Inhalation Powder.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Mometasone Furoate Metered Nasal Spray.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride Intramuscular and Subcutaneous Solution.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Sumatriptan Succinate Subcutaneous Injectable.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Testosterone Metered Nasal Gel.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Varenicline Tartrate Nasal Spray.* (Nov. 17, 2022) Link to Posting

Articles

- Ray S, Boudewyns V, Oguntimein M, Conti D, Malik R, Srivastava I, and Feibus K. *Generic Substitution of Epinephrine Autoinjectors: Patient and Caregiver Perceptions and Attitudes.* Journal of Allergy and Clinical Immunology - Global. (2023) 3(1): 100170. https://doi.org/10.1016/j.jacig.2023.100170. PMID: 37876855.

Posters

- Chakma M, Usmani O, Meah S, Biddiscombe M, Bielski E, Feibus K, Natarajan K, Li K, Kinjo M, Illoh O, Han L, Newman B, and Murnane D. *The Importance of Inter-patient Peak Inspiratory Flow Variance in Simplifying DPI Prescribing in COPD: A Meta-Analysis.* Poster Presentation at the European Respiratory Society (ERS) International Congress 2023. Milan, Italy, Sep. 09, 2023.
- Kamal N, Acheampong S, Us Zaman R, Strasinger C, Norman J, Tang Y, Zidan A, and Ashraf M. *Investigation of Formulation Variables Affecting the Performance of Dissolvable Microneedles.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Kamal N, Acheampong S, Us Zaman R, Strasinger C, Norman J, Tang Y, Zidan A, and Ashraf M. *Identification of Formulation Variables Affecting the Performance of Dissolvable Microneedles.* Poster Presentation at the Microneedle Conference 2023. Seattle, WA, May 16, 2023.

Presentations

- Kamal N. *Dermal Drug Delivery via Dissolvable Microneedles: Formulation Variables Affecting CQAs.* Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Kamal N. *Identification of Formulation Variables Affecting the Performance of Dissolvable Microneedles.* Presentation at the Microneedle Conference 2023. Seattle, WA, May 16, 2023.

OUTCOMES *continued*

- Ballard B. *Drug-Device Combination Product Development Simulation.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, And Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Chavan M. *Current Regulatory Perspective for Demonstrating the Quality and Performance of Proposed Generic Versions of Transdermal Systems, Intravaginal Systems, Implants, and Intrauterine Systems.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, And Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Feibus K. *Research Efforts to Broaden Published Data on User Interface Differences & the Impact on User Error to Support Certain Types of User Interface Differences.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, and Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Flint J. *Best Practices for Comparative Use Human Factors Study Design, Execution, and Reporting.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, and Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023. Details
- Hartka K. *Pre-ANDA Program Support of Generic Drug-Device Combination Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, And Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Lee M. *Best Practices for ANDA Submission of Comparative Analyses for Drug-Device Combination Products & the ANDA User Interface Assessment Process.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, and Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Uwemedimo, I, and Lauritsen K. *Definition of a Combination Product and the Complementary and Collaborative Roles of FDA's Office of Combination Products & CDER's Product Jurisdiction Office Have on Classifying Products as Drugs, Devices, or Drug-Device Combination Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, and Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.
- Conrad M. *Insights into the Comparative Use Human Factors Method for FDA Submissions: Results from Interview with Industry Experts.* Presentation at the 12th International Symposium on Human Factors and Ergonomics in Healthcare. Orlando, FL, Mar. 28, 2023.
- Zhao L. *Mechanistic Drug Delivery Models.* Presentation at the Drexel University, Biomedical Seminar Series. Virtual Meeting, Feb. 08, 2023.
- Zhao L. *Mechanistic Drug Delivery Models.* Presentation at the 1st Academic Committee Meeting of Joint R&D Center. Beijing, China, Dec. 31, 2022.
- Zhao L. *Mechanistic Drug Delivery Models.* Presentation at the 2022 Annual Meeting for Professional Committee of Pharmacometrics, Chinese Pharmacological Society. Virtual Meeting, Nov. 25, 2022.
- Zhao L. *Mechanistic Drug Delivery Models.* Presentation at the Pharmacometrics Youth Forum Shanghai 2022. Virtual Meeting, Oct. 09, 2022.

CHAPTER 6: ORAL AND PARENTERAL PRODUCTS

A major GDUFA science and research priority is to enhance the efficiency of bioequivalence (BE) approaches for generic oral and parenteral products. The advancement of research in this area focuses on understanding of how ingredients in oral and parenteral drug products may modulate bioavailability, on improving biorelevant dissolution methods as well as in silico models to support the expansion of biowaivers and global harmonization (e.g., ICH M13A[1]), and on acquiring data needed to support future harmonization for the modified release (MR) oral products. This includes developing evidence to support the feasibility of Biopharmaceutics Classification System (BCS)-based biowaivers for immediate release (IR) oral drug products with differences in formulations larger

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

*than currently recommended in FDA guidance. It also includes exploring the effect of formulation design features on the in vivo pharmacokinetics (PK) of a drug product and investigating the use of in vitro methodologies to support a demonstration of BE when MR oral drug products are administered with soft food (refer to the details in the **Research Highlight**). Additional research priorities relevant to these products encompass the development of approaches to manage potential risks related to subject safety more consistently when developing clinical BE study recommendations and elucidating potential failure modes for BE with specific populations (e.g., pediatric or geriatric patients). A key goal of research in this area is to establish improved tools and methodologies that ensure the equivalence of therapeutic outcomes in diverse populations more efficiently. Research in this area is described below, highlighting BE methods and analyses for oral products and parenteral products independently in two separate subsections.*

BIOEQUIVALENCE METHODS AND ANALYSIS, IR AND MR ORAL PRODUCTS, AND HUMAN SUBJECT SAFETY

Summary of FY 2023 Activities

In FY 2023, FDA continued to invest in advancing BE methods and analysis for oral drug products through four Contracts (75F40121C00132, 75F40121C00020, and 75F40120C00200) and one Grant (3U01FD005978). The scopes of the contracts and grant involve the development of biorelevant and bio-predictive in vitro testing to predict the impact of excipients used in different drug product formulations, as well as the impact of food and other factors, on BE assessment. The desired outcomes of this work include the potential expansion of biowaivers for BCS Class III Drugs (i.e., high solubility, low permeability), establishment of patient centric quality standards, and evaluation of in vitro tools to predict drug product BE outcomes under fed conditions. Additionally, the research performed under Contracts 75F40121C00020 and 75F40120C00200, physiologically based pharmacokinetics (PBPK) modeling was utilized to predict the impact of intrinsic and extrinsic variables (e.g., formulation or food) on BE assessment (research involving PBPK modeling is discussed further in Chapter 7). Additionally, the research performed under Contract 75F40119C10106 developed a large language model to extract information from drug labeling automatically, enhancing product-specific guidance development. Continued from previous research on the impact of excipients on drug absorption, an exploratory human PK study to evaluate the impact of a surfactant excipient, sodium laurel sulfate (SLS), at two levels (3 mg or 30 mg) on the absorption of an immediate release fexofenadine product is planned to proceed into the clinic in FY 2024 (Grant 3U01FD005978). The SLS, is an organic anion transporter protein 2B1 (OATP2B1) inhibitor and fexofenadine, a BCS Class III drug, is a known substrate for the intestinal transporter, OATP2B1. The results from this study are expected to help determine if SLS may impact the transport of a BCS Class III OATP2B1 substrate in vivo, thus affecting its bioavailability, and if so, at what level. If there is no in vivo impact from the excipient, then the data may help support a BCS-based biowaiver for BCS Class III drugs.

The research under Contract 75F40120C00200 sought to establish bio-predictive in vitro dissolution methods for setting patient centric quality specifications using glipizide extended release (ER) tablet as a model drug. The PK study supported by this contract was designed to measure glipizide release rate in different gastrointestinal (GI) tract regions using an incubation tube and a smart pill to record GI physiological relevant parameters (e.g., pH and pressure), complementing data on plasma drug concentrations. The outcome of this research is intended to integrate in vivo drug release rate and drug plasma concentrations. The results are expected to elucidate how in vitro dissolution differences may be associated with variable absorption in vivo.

The ability of a generic drug product to perform the same as a reference listed drug (RLD) when administered under fasting and fed conditions is part of a robust evaluation to demonstrate therapeutic equivalence. Contract 75F40121C00020 explores formulation factors that could potentially impact BE under fed conditions by using an in vitro disintegration test and a dissolution test that can simulate the food induced viscosity, mechanical pressure, and hydrodynamic stress (also refer to Chapter 7 Oral Absorption Models). This project identified critical formulation variables which may affect in vivo BE performance. In addition, the study explored the impact of excipients and formulations on tablet disintegration and dissolution under simulated fed conditions, which is

expected to support the development of bio-predictive in vitro methods.

Ongoing research under Contract 75F40121C00132 sought to identify the conditions that are important when comparing the swallowability of a generic drug product in oral solid dosage forms to that of the RLD. A robotic soft esophagus (RoSE) was used to inform in vitro predictive swallowing of a proposed generic product as compared to its RLD when they differ in size, shape, and other physical attributes. The scope of this research was limited to validating RoSE as a tool to assess the swallowability of model or marketed solid oral dosage form products. Initially, commercially available barium sulfate tablets were studied with RoSE in both supine and inclined positions. The supine position was selected for subsequent experiments due to limitations testing at an inclined position. Round and oval barium sulfate model tablets prepared with the single largest dimensions of 13 mm and 22.25 mm, respectively, of varying thickness were then studied with RoSE placed at a supine position. The swallowability of marketed solid oral dosage form products are currently being explored.

RESEARCH HIGHLIGHT

During FY 2023, an FDA internal research investigating the use of in vitro methodology as a potential BE standard to compare generic products to the RLD when administered with soft food was highlighted on FDA's website.

To facilitate oral administration of drug products in patients who may have difficulty swallowing whole tablets or capsules, a common practice is to sprinkle the drug products on food vehicles before administration. Therefore, it is important that these vehicles do not affect drug products' safety and effectiveness. FDA scientists used pantoprazole sodium delayed release (DR) products as a model drug and studied the in vitro dissolution rate of the drug product after being sprinkled in common food vehicles both approved on the product labeling (e.g., apple juice, applesauce) and not approved on the product labeling (e.g., pudding, yogurt, and milk) to determine if certain food physicochemical properties (e.g., viscosity and pH; **Figure 1**) were associated with differences in pantoprazole release from the dosage form. When pantoprazole sodium DR granules were sprinkled on low pH food with short contact time durations, the dissolution rate didn't change compared with the control group (i.e., without mixing with food vehicles). However, when DR granules were sprinkled on high pH food vehicles with long contact time durations (e.g., 2 h), it caused premature drug release and led to drug degradation, as expected. The results showed that food pH and the interaction between food pH and drug-food contact time were significant factors affecting the in vitro dissolution of pantoprazole sodium DR granules (**Figure 2**). It demonstrated that the in vitro methodology was suitably sensitive to detect differences in product performance in approved versus non-approved labeling conditions.

An in vivo sprinkle BE study is currently recommended to support a demonstration of BE for prospective generic pantoprazole sodium DR products. This research explored the potential utility of in vitro testing to produce consistent sprinkle administration results for food vehicles recommended in the labeling, supported by in vivo data during RLD development. Such an in vitro test may help accelerate generic product development and may help ensure that generic products can be used in accordance with the labeling developed for the RLD product.

RESEARCH HIGHLIGHT *continued*

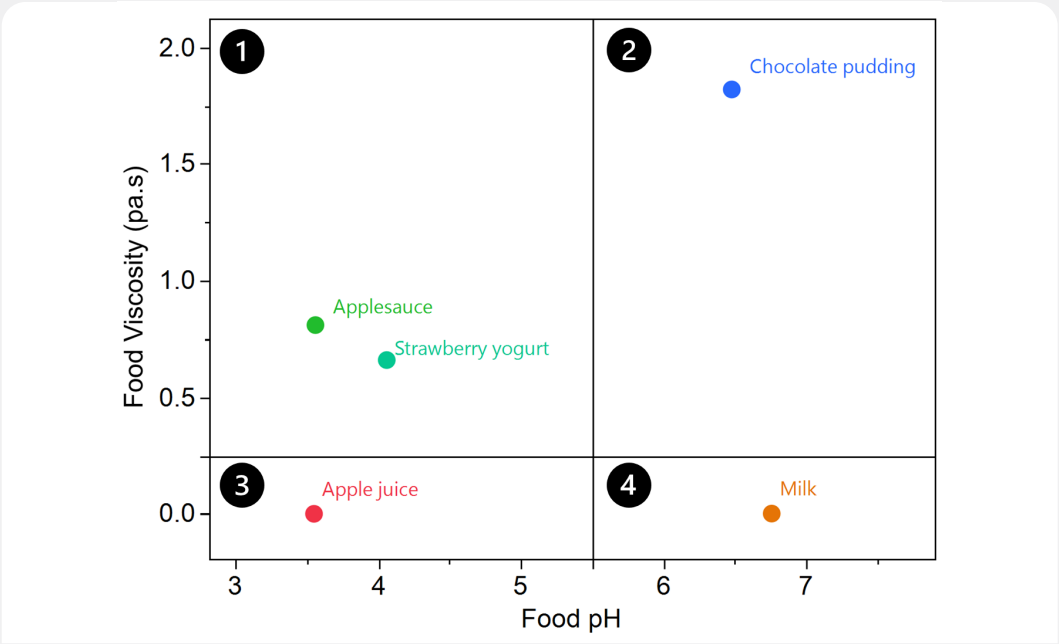

Figure 1. Mean pH and viscosity of food vehicles. Foods with pH higher than pH 5.5 were classified as the high pH group. Foods with viscosities higher than 0.25 Pa.s were classified as the high viscosity group. ❶: low pH and high viscosity group; ❷: high pH and high viscosity group; ❸: low pH and low viscosity group; ❹: high pH and low viscosity group

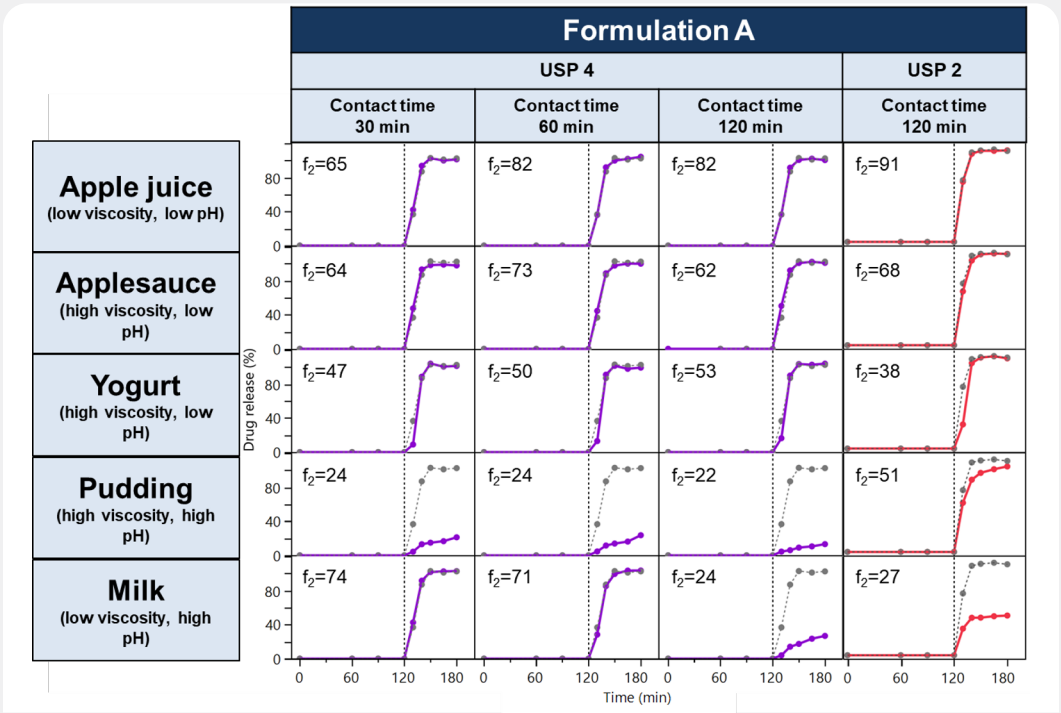

Figure 2. Impact of food pH and contact time on pantoprazole dissolution using USP 4 and USP 2 apparatus (N=6). Purple and red line: the test profile. Grey line: the control profile (without food vehicles).

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007959) *Evaluation of Oral Modified-Release Tablets to Support the Approval of Additional Strengths* with Jie Shen at Northeastern University

Continuing Grants and Contracts

- Grant (3U01FD005978) *The Effect of Sodium Lauryl Sulfate on the Oral Absorption of Fexofenadine in Humans* with Katherine Yang at University of California, San Francisco
- Contract (75F40121C00132) *Applying a Robotic Soft Esophagus (Rose) to Assess the Swallowability of Opioid Drugs* with Peter Xu at The University of Auckland
- Contract (75F40121C00020) *Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on Its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation* with Peter Langguth at Johannes Gutenberg University
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive in Vitro Dissolution-Models* with Duxin Sun, Amit Pai Manjunath at University of Michigan, College of Pharmacy

Completed Grants and Contracts

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

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*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *Evaluation of Formulation Dependence of Drug-Drug Interaction with Proton Pump Inhibitors (PPIs) for Oral Extended-Release Drug Products*
- *Evaluation of the Need for Sprinkle BE Studies*
- *Exploration for Exclusion of Males and Females of Reproductive Potential as a Bioequivalence Study Population in Product-Specific Guidances for Generic Drug Development*
- *Exploration of Food Conditions and Study Populations in Bioequivalence Studies with Pharmacokinetic Endpoints for Antineoplastic Drugs in Generic Drug Development*
- *GDUFA III Product-Specific Guidance Improvement for Oral Products*
- *Identification of Critical Factors for Oral Solution Bioequivalence*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- *Improve BE Analysis for Narrow Therapeutic Index Drugs*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *Prioritization and Optimization of Modified Release BE Guidances*
- *Safety Considerations in Study Subject Selection in Bioequivalence Studies for Generic Drug Development*
- *Swallowability Factors Related to Size, Shape and Material of Generic Tablets*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

OUTCOMES

General Guidance

- FDA Draft Guidance. *ICH M13A Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms.* January 2023. Link to Posting

Product-Specific Guidances

There were one new and five revised PSGs published in FY2023 related to *Oral Absorption and BE Analysis* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance for Calcium Carbonate; Famotidine; Magnesium Hydroxide Oral Tablet, Chewable.* (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet, Extended-Release (NDA 018152)* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet, Extended-Release (NDA 018027)* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet.* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Capsule.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Ranolazine Oral Granules, Extended Release.* (Nov. 17, 2022) Link to Posting

Articles

- Babiskin A, Wu F, Mousa Y, Tan M-L, Tsakalozou E, Walenga R, Yoon M, Raney S, Polli J, Schwendeman A, Krishnan V, Fang L, and Zhao L. *Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches: A Workshop Overview.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12: 619-623. https://doi.org/10.1002/psp4.12920. PMID: 36631942.

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- Coutinho AL, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, Polli JE. *A Robust, Viable, and Resource Sparing HPLC-based LogP Method Applied to Common Drugs.* International Journal of Pharmaceutics. (2023) 644:123325. https://doi.org/10.1016/j.ijpharm.2023.123325. PMID: 37591472.

- Pawar G, Wu F, Zhao L, Fang L, Burckart G, Feng K, Mousa Y, Al Shoyaib A, Jones M, and Batchelor H. *Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study.* (2023) 25(67). https://doi.org/10.1208/s12248-023-00826-1. PMID: 37386339.

- Al Shoyaib A, Riedmaier A, Kumar A, Roy P, Parrott N, Fang L, Tampal N, Yang Y, Jereb R, Zhao L, and Wu F. *Regulatory Utility of Physiologically Based Pharmacokinetic Modeling for Assessing Food Impact in Bioequivalence Studies: A Workshop Summary Report.* CPT: Pharmacometrics Systems Pharmacology. (2023) 12(5): 610-618. https://doi.org/10.1002/psp4.12913. PMID: 36597353.

- Wu F, Mousa Y, Raines K, Bode C, Tsang Y, Cristofoletti R, Zhang H, Heimbach T, Fang L, Kesisoglou F, Mitra A, Polli J, Kim M, Fan J, Zolnik B, Sun D, Zhang Y, and Zhao L. *Regulatory Utility of Physiologically Based Pharmacokinetic Modeling to Support Alternative Bioequivalence Approaches and Risk Assessment: A Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 585-597. https://doi.org/10.1002/psp4.12907. PMID: 36530026.

- Wu K, Zheng K, Tian L, Xia L, Hwang S, Nwakama P, Sun W, Kim M, Tampal N, Xu X, Boyce H, and Feng X. *The Effect of Food Vehicles on In Vitro Performance of Pantoprazole Sodium Delayed Release Sprinkle Formulation.* International Journal of Pharmaceutics. (2023) 635: 122737. https://doi.org/10.1016/j.ijpharm.2023.122737. PMID: 36801362.

- Yoon M, Babiskin A, Hu M, Wu F, Raney S, Fang L, and Zhao L. *Increasing Impact of Quantitative Methods and Modeling in Establishment of Bioequivalence and Characterization of Drug Delivery.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 552-555. https://doi.org/10.1002/psp4.12930. PMID: 36756902.

Posters

- Anno K, Mina M, Zhang Z, Zhang L, and Jiang W. *Survey of Bioequivalence Data of Abbreviated New Drug Applications of Narrow Therapeutic Index Drug Products.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sep. 10, 2023.

- Lim H, Boyce H, Kim M, and Sun W. *Improving Administration Method Consistency of Product-Specific Guidances for Chewable Tablets and Tablet Products with Chewing in Labeling.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sept. 10, 2023.

- McGuire MR, Mostofa A, Frost M, Shon J, Li K. *Swallowability of Solid Oral Drug Products in Regulatory Submissions: Patient-Specific Features, Product Physical Attributes, and Clinical Swallowability Study Designs.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sep. 10, 2023.

- Oh C, Mostofa A, Natarajan K, Sun W, Boyce H, and Kim M. *A Science-based Approach for Recommendation of Antagonist Blockade in the Bioequivalence Studies of Opioid Drug Products.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sep. 10, 2023.

OUTCOMES *continued*

- Ren P, Yang W, Choi S, and Zhang Y. *Impact of Solubility and Dissolution Performance on Bioequivalence Recommendations for Immediate-Release Locally Acting Gastrointestinal Drug Products.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2023 Annual Meeting. Bellevue, WA, Sep. 10, 2023.
- Don R, Lex T, Zhang L, Jiang W, and Gao Z. *In Vitro Drug Disintegration and Dissolution Testing of BCS Class I Drug Midodrine Hydrochloride Under Simulated Food-Induced Viscous Conditions.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Rana M, Wu K, Feng X, Sun W, Xia L, Nwakama P, Kim M, Tampal N, Abdallah I, Boyce H, and Tian L. *In Vitro Evaluation of Morphine Sulfate Extended - Release Formulation Sprinkled on Soft Foods - A Comparison of Two Dosage Strengths of T=0 M and T=6 M Drug Products.* Poster Presentation at the FDA Science Forum 2023. Virtual Meeting, Jun. 14, 2023.
- Paleracio C, Nguyen D, Li K, Tsui C, Frost M, Kim M, and Shon J. *Exploration for Exclusion of Females of Reproductive Potential as a Bioequivalence Study Population in Product-Specific Guidances for Generic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2023 Annual Meeting. Atlanta, GA, Mar. 22, 2023.
- Gao H, Thomas S, and Wu F. *Developing an R Shiny App for Dissolution Profile Similarity Analysis.* Poster Presentation at the FDA Annual Student Scientific Research Day 2023. Virtual Meeting, Aug. 10, 2023.
- Abdallah I, Gabal Y, Boyce H, Zhu J, and Kim M. *A Retrospective Analysis of Pharmacokinetic Variability Between Fasting and Fasting-Sprinkle Bioequivalence Studies of Generic Modified-Release Drug Products: A Case Study on Esomeprazole Magnesium.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Al Shoyaib A, Fang L, Zhao L, and Wu F. *Assessing the Impact of Excipient and Food Intake on Bioequivalence Using PBPK and Virtual Bioequivalence Trial: A Case Example with Acyclovir Immediate Release Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Bode C, Bhoopathy S, Miezeiewski B, Wu F, Ren P, Wang Z, and Zhao L. *In Vitro Comparative Dissolution and Permeation Testing Using the In-vitro Dissolution Absorption System (IDAS) for Expanding Biowaivers to Non Q1/Q2 BCS Class III Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Bode C, Bhoopathy S, Miezeiewski B, Wu F, Ren P, Wang Z, and Zhao L. *Using the In-Vitro Dissolution Absorption System (IDAS) to Evaluate the Effects of Excipients on the Permeation of Putative Biopharmaceutics Classification System Class III Drugs.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Kotsybar J, Zhang L, and Jiang W. *The Impact of Cyclodextrin on Fasting and Fed Bioequivalence Studies in Solid Oral Immediate-Release Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Rana M, Jordan L, Wu K, Feng X, Sun W, Xia L, Hwang S, Nwakama P, Kim M, Tampal N, Boyce H, and Tian L. *Dissolution Rate Increases for Morphine Sulfate Extended-Release Drug Product when Mixed with High pH Soft Food for Long Contact Times.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Wu K, Rana M, Tian L, Sun W, Xia L, Nwakama P, Kim M, Tampal N, Xu X, Boyce H, and Feng X. *A Brief Review of FDA-Approved New Drug Applications Labeled with Sprinkle Administration.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

OUTCOMES *continued*

- Wu K, Rana M, Tian L, Sun W, Xia L, Nwakama P, Kim M, Tampal N, Xu X, Boyce H, and Feng X. *In Vitro Evaluation of an Extended-Release Methylphenidate Hydrochloride Product Sprinkled on Food Vehicles.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Al Ghabeish M. *Q1 and Q2 Recommendations: Sucralfate Oral Suspension.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Dandamudi S. *Non-Q2 Sucralfate Suspension Approval.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Sun W. *Bioequivalence for Oral Locally Acting Gastrointestinal Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Wu F. *OGD Perspectives on PBBM Applications for Generics.* Presentation at the FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling Workshop. Rockville, MD, Aug. 31, 2023.
- Wu F. *Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling to Evaluate the Impact of Excipients on Bioequivalence of BCS Class III Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Zhang L. *Regulatory Science to Support Global Harmonization for Establishing BE for Generic Oral Products.* Presentation at the FY2023 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 11, 2023.
- Wu F, and Tsakalozou E. *A Critical Overview of the Biological Effects of Excipients.* Presentation at the Excipient World Conference & Expo 2023. National Harbor, MD, May 02, 2023.
- Wu F. *How Might Excipients Impact Bioequivalence Assessments of Human Generic Drug Products.* Presentation at the 2023 March AAPS Webinar. Virtual Meeting, MD, Mar. 23, 2023.
- Giacomini K, and Tsakalozou E. *A Critical Overview of the Biological Effects of Excipients (Part I): Impact on Gastrointestinal Absorption.* Presentation at the AAPS Oral PBPK Webinar. Virtual Meeting, Mar. 21, 2023.
- Wu F. *Using PBPK Model to Support Risk Assessment for Oral Products.* Presentation at the Peking University Third Hospital 2023. Virtual Meeting, Jan. 13, 2023.
- Wu F. *Using PBPK Model to Support Risk Assessment for Oral Products, from a Regulatory Perspective.* Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 27, 2022.
- Wu F. *Assessing Food Impact on Bioequivalence Using Physiologically-Based Pharmacokinetic Modeling.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.

INJECTABLE PRODUCTS

Summary of FY 2023 Activities

In FY 2023, research efforts for the development of generic parenteral products without release-controlling excipients focused on 1) developing appropriate analytical methods for characterizing these parenteral products; 2) characterizing the critical quality attributes (CQA) and the impact of manufacturing process on parenteral drug substance suspension and thermodynamically stable microemulsion products; and 3) exploring modeling methods to support BE. Research reports for other parenteral products are covered in the chapter of Complex Dosage Forms & Formulations (Chapter 3).

During FY 2023, a research manuscript was published[2] describing the development of in vitro drug release testing (IVRT) methods for parenteral drug substance suspension products. This research was conducted under the recently completed Contract HHSF223201710135C, in which a USP apparatus 2 with enhancer cells and a USP apparatus 4 with semisolid adapters was developed using medroxyprogesterone acetate (MPA) injectable suspension as a model drug. The methods demonstrated reproducibility and discriminatory ability towards differences in MPA particle size. The release profiles obtained from the developed USP apparatus 4 IVRT method were compared to the PK profiles from rabbits and a level A in vivo-in vitro correlation (IVIVC) was successfully established (see **Research Highlight** below for more information). The study results also provided insights on critical formulation attributes and drug release kinetics which are helpful to further explore in vitro-based BE approaches for drug substance-based injectable suspension products.

FDA continued to collaborate with University of Connecticut (Contract 75F40121C00133) to develop a model-integrated evidence based BE approach for parenteral products. The objective of this research collaboration was to gain understanding of the in vivo behavior of injectable suspension drug products by identifying critical quality attributes of the suspension formulations, establishing a mechanistic (i.e., PBPK model-based) IVIVC model, and narrowing down the knowledge gap in this area.

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[2] Bao Q, Wang X, Wan B, Zou Y, Wang Y, and Burgess D. *Development of In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* International Journal of Pharmaceutics. (2023) 634(122642). https://doi.org/10.1016/j.ijpharm.2023.122642. PMID: 36709013.

RESEARCH HIGHLIGHT

The development of a reproducible and discriminatory IVRT method that elucidates an in vivo-in vitro relationship or IVIVC is desirable for the development and regulatory assessment of parenteral suspension products. In this research project, four IVRT methods were developed and evaluated with respect to the method's reproducibility and ability to discriminate MPA suspensions that are qualitatively (Q1) and quantitatively (Q2) equivalent to the RLD, Depo-SubQ Provera 104®, but have different MPA particle sizes (**Figure 1**). Among the investigated IVRT methods, the USP apparatus 2 with enhancer cells and USP

apparatus 4 with semisolid adapters showed the best discriminatory ability and reproducibility (**Figure 2**). The pharmacokinetics of the RLD product and the four Q1/Q2 equivalent MPA suspensions with different particle size, were studied using rabbit animal model.

The in vitro and in vivo data showed the same rank order, whereby smaller particle sizes were associated with a faster release rate. An exception was observed for formulation F3, which was formulated with the smallest particle size (i.e., 3.67 µm) but showed a slow in vivo release rate. This deviation is attributed to F3's instability after sonication that the particle size of F3 gradually increased over time with the particle size stabilizing at approximately 20 µm on Day 5. The shift of F3's particle size may be due to the Ostwald ripening effect as well as particle aggregation and recrystallization. This observation further demonstrated particle size is a critical quality attribute that impact product performance for drug substance injectable suspensions. A Level A IVIVC was successfully established using the in vitro release profiles obtained with the USP apparatus 4.

- **F1:** API was used as received
- **F2:** The API was recrystallized using acetone-water (1:1) system (water as anti-solvent). Following drying under vacuum at 40° C, the API was passed through a 45 µm sieve. The API was added to the suspending media to achieve suspension F1.
- **F3:** processing based on F1 using probe sonicaton for 5 mins with 10% of pulse. The formulation underwent 10 s sonication, stop 1s.
- **F4:** Same as F1 except using different vendor of PEG3350 (Spectrum Chemical for F1 and BASF for F4)

Formulation	Dv10	Dv50	Dv90	Span
F1	7.21±0.42	13.40±0.54	24.09±0.74	1.26±0.04
F2	8.73±0.31	21.73±0.28	41.08±0.53	1.49±0.04
F3	0.69±0.33	3.67±0.43	10.13±0.99	2.61±0.44
F4	7.00±0.13	13.03±0.23	23.44±0.37	1.26±0.01
RLD	10.37±0.99	18.23±1.36	30.61±1.78	1.11±0.05

Figure 1. Compositionally equivalent MPA suspensions prepared with different particle sizes

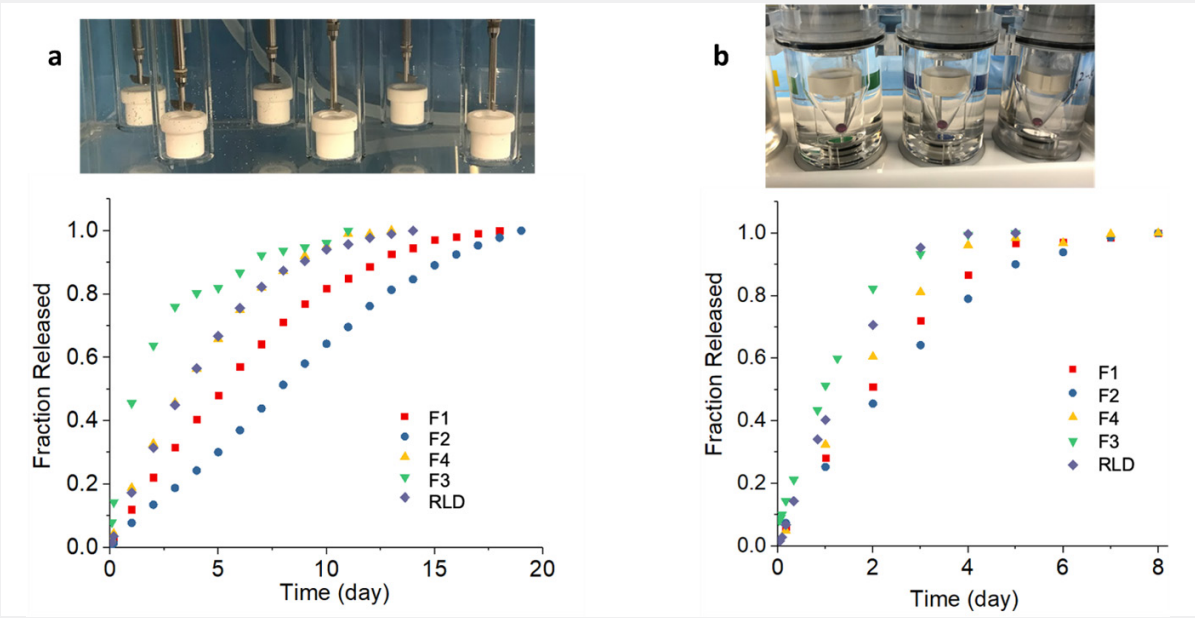


Figure 2. In vitro release profiles of the RLD and Q1/Q2 equivalent suspensions (with different particle sizes) obtained using: a) the USP apparatus 2 with enhancer cells; and b) USP apparatus 4 with semisolid adapters at 37 ± 0.5 °C (mean ± SD, n = 3).

OUTCOMES *continued*

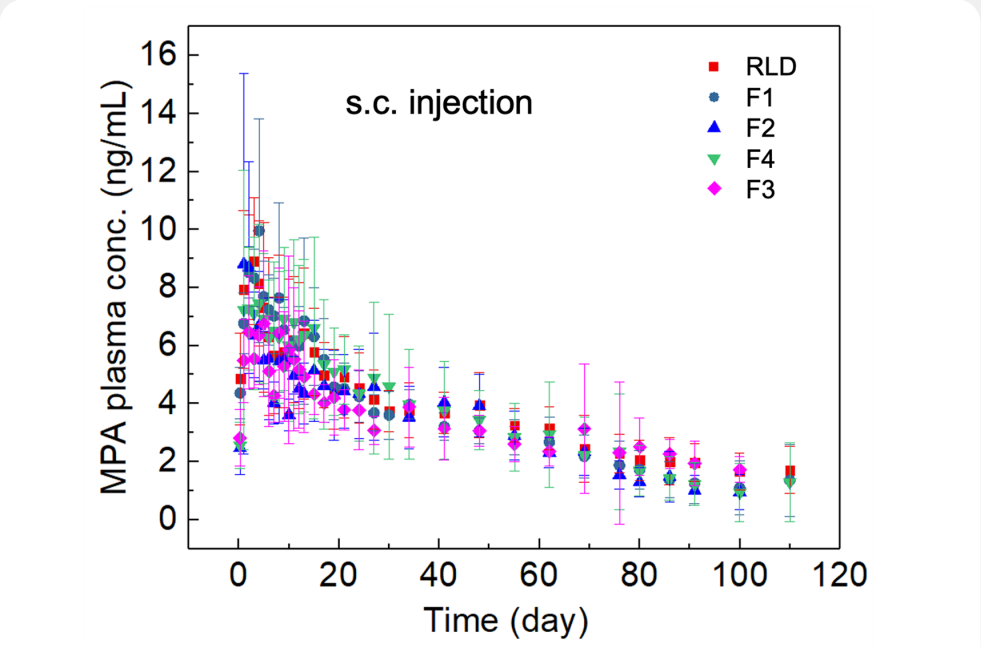


Figure 3. The in vivo release of the prepared suspensions and the RLD Depo-SubQ Provera 104® were investigated in female New Zealand White rabbits (n=6, mean ± SD)

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grant(s) and Contract(s)

- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate Their Generic Development* with Dianne Burgess at University of Connecticut

Completed Grants and Contracts

- Contract (HHSF223201710135C) *In-Vitro In-Vivo Correlation of the Long-Acting Injectable Suspensions Improve Scientific Approaches to Evaluate Generic Drugs* with Diane J Burgess at University of Connecticut

OUTCOMES

Product-Specific Guidances

There were six new PSGs published in FY 2023 related to *Injectable Products*. PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance on Cabotegravir; Rilpivirine Intramuscular Suspension.* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance on Cabotegravir Intramuscular Suspension.* (May 18, 2023) Link to Posting
- *New Draft Guidance for Fosdenopterin Hydrobromide Intravenous Powder.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Melphalan Flufenamide Hydrochloride Intravenous Powder.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance on Triamcinolone Acetonide Intra-Articular for Suspension, Extended Release.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance on Triamcinolone Acetonide Injection Suspension.* (Feb. 16, 2023) Link to Posting

Articles

- Banstola B, Gamage P, Jiang W, and Mudalige T. *Analysis of Phospholipids and Triacylglycerols in Intravenous Lipid Emulsions.* Journal of Pharmaceutical and Biomedical Analysis. (2023) 222. https://doi.org/10.1016/j.jpba.2022.115112. PMID: 36274478.
- Bao Q, Wang X, Wan B, Zou Y, Wang Y, and Burgess D. *Development of In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* International Journal of Pharmaceutics. (2023) 634(122642). https://doi.org/10.1016/j.ijpharm.2023.122642. PMID: 36709013.
- Coutinho A, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, and Polli J. *A Robust, Viable, and Resource Sparing HPLC-based logP Method Applied to Common Drugs.* International Journal of Pharmaceutics. (2023) 644: 123325. https://doi.org/10.1016/j.ijpharm.2023.123325. PMID: 37591472.

OUTCOMES *continued*

Posters

- Smith W, Liu H, Wang Y, Kozak D, and Xu X. *Impact of Formulation Processes on Dosage Form Determination of Phytonadione Injectables.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Zhang Q. *In Vitro Approaches for Injectable Suspension Products: Medroxyprogesterone Acetate & Triamcinolone Acetate.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Smith W. *Phytonadione – Self-Assembled System & Thermodynamics Systems.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2023. North Bethesda, MD, Jun. 04, 2023.
- Jiang W. *Complex Generics Containing Nanomaterials: What's Next in the Pipeline?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) - Chicagoland Pharmaceutical Discussion Group (CPDG). Chicago, IL, May 19, 2023.
- Kozak D. *Considerations for Post-Approval Changes to Complex Generic Drug Products.* Presentation at the 2022 Association for Affordable Medicines (AAM): GRx + Biosims Conference. North Bethesda, MD, Nov. 08, 2022.
- Kozak D. *Development and Characterization of Generic Drug Products Containing Nanomaterials.* Presentation at the FDA NanoDay Symposium 2022. Virtual Meeting, Oct. 11, 2022.

CHAPTER 7: QUANTITATIVE METHODS & MODELS

A major GDUFA science and research priority is to facilitate the utility of model-integrated evidence (MIE) to support demonstrations of bioequivalence (BE). The advancement of research in this area focuses on developing tools and advancing approaches to integrate complementary in silico (modeling), in vivo, and in vitro evidence in ways that collectively mitigate the risk of failure modes for BE and support a framework for virtual BE studies. For example, for long-acting injectable, insertable or implantable (collectively, LAI) products, MIE-based strategies are being actively researched to develop more efficient in vivo pharmacokinetic (PK) BE study designs, such as by reducing the study duration by assessing BE at non-steady-state conditions (also refer to Chapter 3 - LAI Products). In the same product area, research is ongoing and focusing on adequately characterizing the long-term bioavailability of LAI drug

products using in vivo or in vitro methods. Ultimately, the goal is to integrate limited in vivo and in vitro data with physiologically based pharmacokinetics (PBPK) models that generate the remaining evidence needed to support demonstration of BE for these products. Research on Quantitative Methods & Models is described below, highlighting PBPK models, oral absorption models, and quantitative clinical pharmacology independently in separate subsections.

LOCALLY ACTING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

Summary of FY 2023 Activities

In FY 2023, research related to locally acting PBPK modeling was advanced through 20 contracts and grants (that were either active or completed during FY 2023), as well as through internal FDA modeling projects. This work continued the development of mechanistic in silico tools alongside relevant in vitro tests for the prediction of local drug concentrations at the site of administration/action, with the goal that these tools could be developed to support BE demonstration.

Research concerning orally inhaled drug products focused on improving the validation of computational fluid dynamics (CFD) predictions for regional deposition in metered dose inhalers (MDI) and dry powder inhalers (DPI) and further development of an existing lung PBPK model. The focus of nasal drug product research was on improvement of the ability of CFD and PBPK models to accurately predict nose-to-brain drug delivery.

The research related to ophthalmic drug products focused on the further development of preclinical ocular PBPK/pharmacodynamic (PD) models, extrapolation of validated preclinical models to humans, and validation of interspecies model extrapolation. Research on in silico tools describing skin absorption focused on enhancing modeling capabilities in predicting permeation through the skin within the scope of in vitro permeation testing studies and in the clinical setting. Of note, improving model-generated skin absorption predictions impacted by drug product quality attributes were of particular interest. In addition, research conducted in FY 2023 included the development of models of the female reproductive track supported by in vitro and in vivo studies, including an in-silico systems-based multiscale model to predict the target tissue bioavailability of nanoparticles (e.g., liposomal doxorubicin), and a mechanistic PBPK model-based in vivo-in vitro correlation (IVIVC) model for long-acting injectable suspension products.

During FY 2023, to facilitate collaborative discussions with industry and the public on scientific perspectives and relevant research, FDA and the Center for Research on Complex Generics (CRCG) hosted two public workshops that included content relevant to locally acting PBPK modeling. The first was "Best Practices for Utilizing Modeling Approaches to Support Generic Product Development" (October 27-28, 2022)[1] and the second was "Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products" (April 20-21, 2023)[2].

In FY 2023, six new extramural research projects were funded — one grant in the oral inhalation area, two grants in the dermal area, one contract in the ophthalmic area, and two grants in the virtual bioequivalence using mechanistic modeling area.

FDA awarded Grant 1U01FD007987 to Fluidda, Inc. to address challenges with acquiring in vivo regional lung deposition data following orally inhaled drug product administration, where the new grant will explore the use of advanced imaging techniques to collect lung generation level deposition data. For ophthalmic products, a new Contract, 75F40123C00072, was awarded to CFD Research Corporation (in collaboration with a sub-contractor, the University of Eastern Finland). The focus of this contract is on the development of a CFD-PBPK framework for supporting the BE evaluation of ophthalmic drug products supported by in vitro, ex vivo, and rabbit studies. To advance the development of in silico tools for skin absorption, FDA awarded two new grants; Grant 1U01FD007954 was awarded to Certara UK, LTD and Grant 1U01FD007957 was awarded to the University of Bath. These grants focus on rigorously validating model predictions of skin permeation that consider drug product metamorphosis post application, and the impact of formulation characteristics on skin permeation. To explore considerations and reasonable assumptions when performing a virtual bioequivalence assessment with PBPK models, FDA awarded two new grants; Grant 1U01FD007906 was awarded to Simulations Plus, Inc and Grant 1U01FD007904 was awarded to Certara UK, LTD.

In addition, research on in-silico, mechanism-based, tools to describe absorption from the vaginal and rectal routes continued under Grant 1U01FD007656 awarded to University of Rhode Island while semi-mechanistic modeling research to describe cutaneous pharmacokinetics data collected using dermal open flow microperfusion methodology was advanced under Grant 1U01FD007669 awarded to Joanneum Research. A more detailed description of these collaborative agreements can be found in Chapter 4, Complex Routes of Delivery, in the subsection on Topical Products.

[1] FDA/CRCG Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development (https://www.complexgenerics.org/education-training/best-practices-for-utilizing-modeling-approaches-to-support-generic-product-development/)

[2] FDA/CRCG Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products (https://www.complexgenerics.org/education-training/considerations-for-and-alternatives-to-comparative-clinical-endpoint-and-pharmacodynamic-bioequivalence-studies-for-generic-orally-inhaled-drug-products-2/)

RESEARCH HIGHLIGHTS

Modeling and simulation has been proposed to support the development and regulatory assessment of locally acting orally inhaled drug products, by using regional deposition and PBPK modeling to understand the relationships between in vitro metrics, systemic PK, and drug delivery to the site of action[3]. A recent publication by Rajaraman et al.[4], supported by Grant 1U01FD005837 with the University of Iowa, reported a

[3] Walenga R, Butler C, Craven B, Longest W, Mohamed R, Newman B, Olsson B, Hochhaus G, Li B, Luke M, Zhao L, Przekwas A, and Lionberger R. *Mechanistic Modeling of Generic Orally Inhaled Drug Products (OIDPs): A Workshop Summary Report.* CPT Pharmacometrics Systems & Pharmacology. (2022) 12: 560 - 574. https://doi.org/10.1002/psp4.12889 PMID: 36330693

[4] Rajaraman P, Choi J, Babiskin A, Walenga R, and Lin C. *Transport and Deposition of Beclomethasone Dipropionate Drug Aerosols with Varying Ethanol Concentration in Severe Asthmatic Subjects.* International Journal of Pharmaceutics. (2023) 636: 122805. https://doi.org/10.1016/j.ijpharm.2023.122805 PMID: 36898619

RESEARCH HIGHLIGHT *continued*

CFD regional deposition model to investigate the impact of formulation differences and intersubject variability on oral airway and lung deposition for beclomethasone dipropionate inhalation metered aerosol. Four formulations were considered with an ethanol concentration percent by weight (%wt/wt) of 1%, 5%, 10%, and 20% (labeled as A, B, C, and D), and three lung geometries were modeled, including a healthy model and two asthmatic models (labeled as C3 and C4). Results are shown in **Figure 1**, where predictions suggested that there are potentially significant impacts of formulation and lung anatomy on oral airway and lung deposition fraction (DF). Predictions in the C4 lung geometry. Formulations B and C showed the best comparison with available in vivo imaging data from the reference listed drug product.

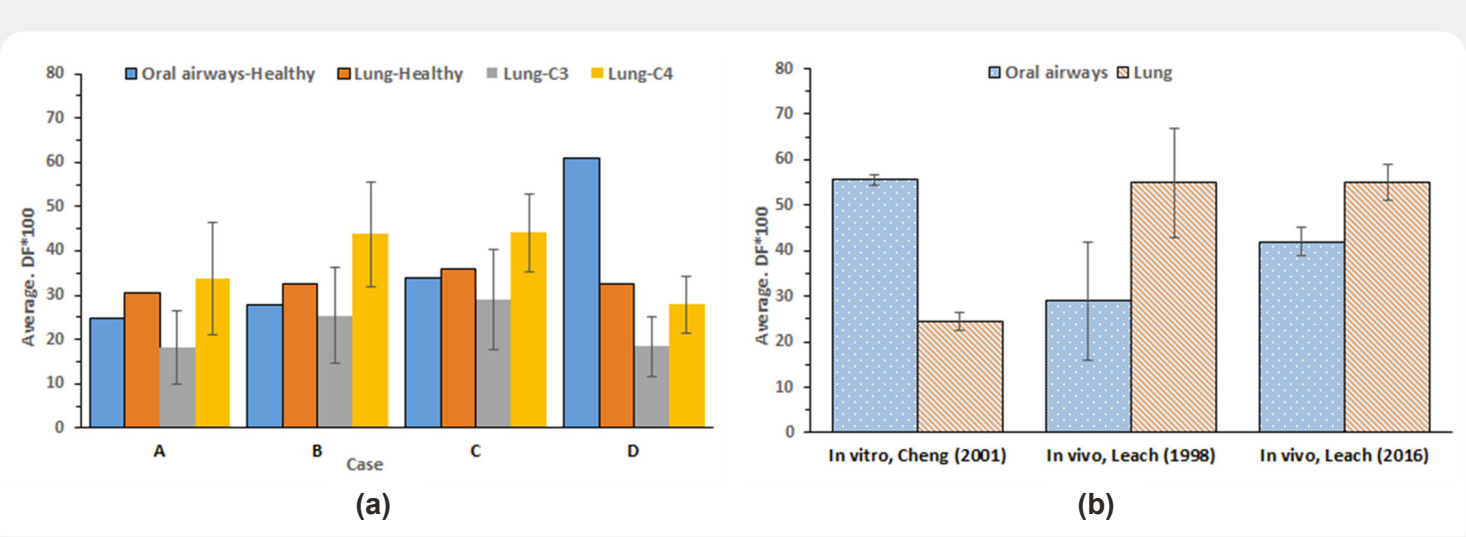


Figure 1. Mean deposition fraction (DF) predictions in the oral airways and lungs a) following administration of four beclomethasone dipropionate inhalation metered aerosol formulations (A, B, C, and D) in computational fluid dynamics (CFD) models of one healthy and asthmatic (i.e., C3 and C4) lungs (n = 3 for each), compared with b) relevant in vitro data from Cheng[5] and in vivo imaging data of oral airway and lung DF from Leach et al.[6] (n = 6) and Leach et al.[7] (n=8). The error bars indicate standard deviation. The figure is reproduced with permission from Elsevier[8].

In the space of mechanistic modeling for ophthalmic drug products, a tear film dynamic model was developed to mimic the dynamic response of the tear film volume to the sudden addition of an eyedrop and volume restoration by changes in tear secretion by the lacrimal gland and drainage through the superior and

[5] Cheng YS, Fu CS, Yazzie D, and Zhou Y. *Respiratory Deposition Patterns of Salbutamol pMDI with CFC and HFA-134a Formulations in a Human Airway Replica.* Journal of Aerosol Medicine. (2001) 14(2): 255-266. https://doi.org/10.1089/08942680152484180 PMID: 11681657

[6] Leach C, Davidson P, and Boudreau R. *Improved Airway Targeting with the CFC-free HFA-Beclomethasone Metered-Dose Inhaler Compared with CFC-Beclomethasone.* European Respiratory Journal. (1998) 12(6): 1346-1353. https://doi.org/10.1183/09031936.98.12061346 PMID: 9877489

[7] Leach CL, Kuehl PJ, Chand R, and McDonald JD. *Respiratory Tract Deposition of HFA–Beclomethasone and HFA–Fluticasone in Asthmatic Patients.* Journal of Aerosol Medicine and Pulmonary Drug Delivery. (2016) 29(2): 127-133. https://doi.org/10.1089/jamp.2014.1199 PMID: 26061801

[8] Rajaraman P, Choi J, Babiskin A, Walenga R, and Lin C. *Transport and Deposition of Beclomethasone Dipropionate Drug Aerosols with Varying Ethanol Concentration in Severe Asthmatic Subjects.* International Journal of Pharmaceutics. (2023) 636: 122805. https://doi.org/10.1016/j.ijpharm.2023.122805 PMID: 36898619

RESEARCH HIGHLIGHT *continued*

inferior lacrimal puncta using CFD approach (**Figure 2**)[9]. This research may be useful in understanding the drug retention time on eye surface and ocular exposure after topical administration.

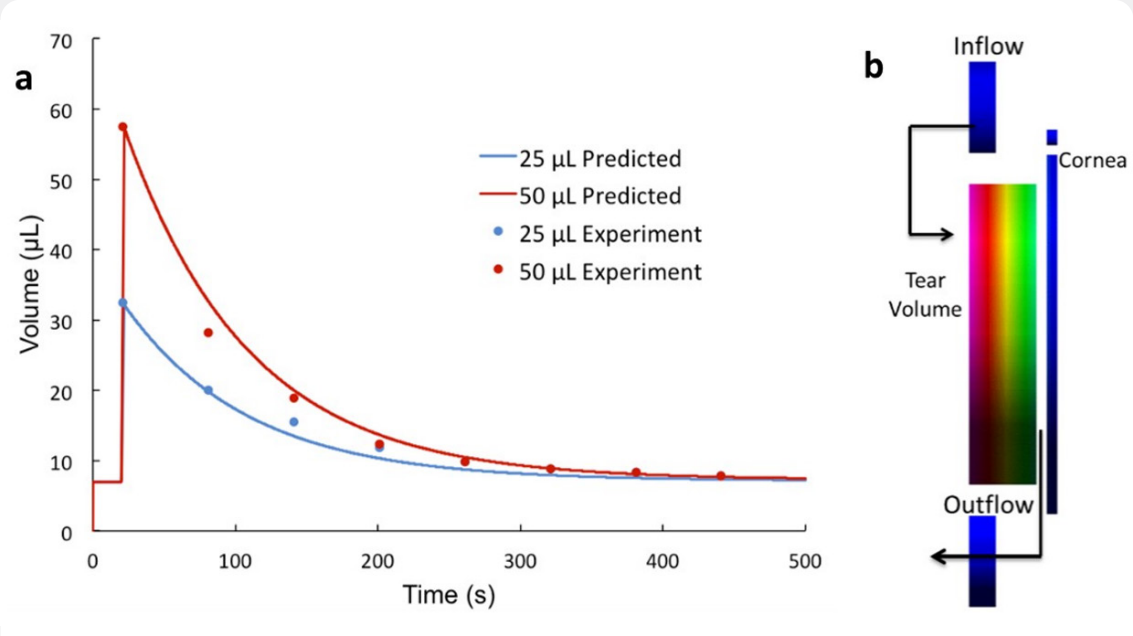


Figure 2. (a) Tear volume changes over time due to instillation of 50 µL and 25 µL drop determined mathematically and from experimental in vivo measurements in rabbit. (b) Virtual wire moving mesh of the tear film with balanced tear hydrodynamics.

[9] German C, Chen Z, Przekwas A, Walenga R, Babiskin A, Liang Z, Fan J, and Tan M-L. *Computational Model of In Vivo Corneal Pharmacokinetics and Pharmacodynamics of Topically Administered Ophthalmic Drug Products.* Pharmaceutical Research. (2023) 40(4): 961–975. https://doi.org/10.1007/s11095-023-03480-6 PMID: 36959411

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007987) *A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods* with Benjamin Lavon at Fluidda, Inc.
- Grant (1U01FD007904) *A State-of-the-Art Virtual Bioequivalence Platform and Case Studies on Complex Formulations, Systemic and Local Concentration-based Bioequivalence* with Frederic Bois at Certara UK, LTD
- Grant (1U01FD007957) *Development and Validation of a Multi-Functional, Multi-Purpose Quantitative Tool for Dermal PBPK Modeling* with M. Begona Delgado-Charro at University of Bath
- Grant (1U01FD007906) *Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies using PBBM-PBPK Models* with Frederico Martins at Simulations Plus, Inc.
- Grant (1U01FD007954) *Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients* with James Clarke at Certara UK, LTD
- Contract (75F40123C00072) *A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs* with Carrie Germain at CFD Research Corporation

Continuing Grants and Contracts

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina at Chapel Hill
- 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 Certara UK, LTD
- Grant (1U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University
- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at Simulations Plus, Inc
- 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 (1U01FD007657) *Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data* with Kayode Ogungbenro at University of Manchester
- Grant (1U01FD007656) *In Vitro Based Approaches to Evaluate the Bioequivalence of Locally-Acting Rectal and Vaginal Semi-Solid Drug Products* with Jie Shen at Northeastern University
- Grant (1U01FD007669) *Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics* with Frank Sinner at Joanneum Research
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterization, Release and Permeation Data to the Next Level - PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK Limited

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- Grant (1U01FD007348) *Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics* with Jill Barber at University of Manchester
- Contract (75F40122C00182) *Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs* with Rodrigo Cristofoletti at University of Florida
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate their Generic Development* with Dianne Burgess at University of Connecticut
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie Au at IQSP - Institute of Quantitative Systems Pharmacology
- Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert Bies at State University of New York at Buffalo

Completed Grants and Contracts

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at the University of Iowa
- 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

Active FDA Research

- *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways*
- *CFD Analysis of Spreadability of Topical Formulations*
- *CFD Models of Soft Mist Inhalers*
- *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*
- *Development of a Nasal PBPK Modeling Platform*
- *Development of an Ophthalmic PBPK Modeling Platform*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

OUTCOMES

Product-Specific Guidances

There were two revised PSGs published in FY 2023 related to *Locally-Acting Physiologically Based Pharmacokinetic Modeling*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *Revised Draft Guidance for Ketoconazole Topical Cream.* (Oct. 21, 2022) Link to Posting
- *Revised Draft Guidance for Clindamycin Phosphate Topical Lotion.* (Oct. 21, 2022) Link to Posting

Articles

- Babiskin A, Wu F, Mousa Y, Tan M-L, Tsakalozou E, Walenga R, Yoon M, Raney S, Polli J, Schwendeman A, Krishnan V, Fang L, and Zhao L. *Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches: A Workshop Overview.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12:619-623. https://doi.org/10.1002/psp4.12920. PMID: 36631942.
- German C, Chen Z, Przekwas A, Walenga R, Babiskin A, Liang Z, Fan J, and Tan M-L. *Computational Model of In Vivo Corneal Pharmacokinetics and Pharmacodynamics of Topically Administered Ophthalmic Drug Products.* Pharmaceutical Research. (2023) 40(4): 961–975. https://doi.org/10.1007/s11095-023-03480-6. PMID: 36959411.
- Kimbell J, Garcia G, Schroeter J, Sheth P, Vallorz-III E, Saluja B, Babiskin A, Tian G, and Walenga R. *Nasal Steroid Spray Simulations Using Measured Spray Characteristics in Healthy and Rhinitic Nasal Passages.* Journal of Aerosol Science. (2023) 174: 106246. https://doi.org/10.1016/j.jaerosci.2023.106246.
- Kolanjiyil A, Walenga R, Babiskin A, Golshahi L, Hindle M, and Longest W. *Establishing Quantitative Relationships Between Changes in Nasal Spray In Vitro Metrics and Drug Delivery to the Posterior Nasal Region.* International Journal of Pharmaceutics. (2023) 635: 122718. https://doi.org/10.1016/j.ijpharm.2023.122718. PMID: 36781083.
- Le Merdy M, Alqaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2023) 40: 961-975. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444.
- Rajaraman P, Choi J, Babiskin A, Walenga R, and Lin C. *Transport and Deposition of Beclomethasone Dipropionate Drug Aerosols with Varying Ethanol Concentration in Severe Asthmatic Subjects.* International Journal of Pharmaceutics. (2023) 636: 122805. https://doi.org/10.1016/j.ijpharm.2023.122805. PMID: 36898619.
- Tan M-L, Chandran S, Jereb R, Alam K, Bies R, Kozak D, Walenga R, Le Merdy M, and Babiskin A. *Mechanistic Modeling of Ophthalmic, Nasal, Injectable, and Implant Generic Drug Products: a Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 631–638. https://doi.org/10.1002/psp4.12952. PMID: 36851886.
- Tang P, Kakhi M, Albariqi A, Behara S, Walenga R, Yang R, and Chan H. *The Role of Capsule Aperture Size on the Dispersion of Carrier-based Formulation at Different Air Flowrates.* International Journal of Phramaceutics. (2023) 642(123152). https://doi.org/10.1016/j.ijpharm.2023.123152. PMID: 37339687.

OUTCOME *continued*

- Tardivon C, Loingeville F, Donnelly M, Feng K, Sun W, Sun G, Grosser S, Zhao L, Fang L, Mentre F, and Bertrand J. *Evaluation of Model-based Bioequivalence Approach for Single Sample Pharmacokinetic Studies.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(7): 904-915. https://doi.org/10.1002/psp4.12960. PMID: 37114321.

- Tsakalozou E, Alam K, Ghosh P, Spires J, Polak S, Fang L, Sammeta S, Zhao P, Arora S, and Raney S. *Mechanistic Modeling of Drug Products Applied to the Skin: A Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12:575-584. https://doi.org/10.1002/psp4.12893. PMID: 36456539.

- Walenga R, Butler C, Craven B, Longest W, Mohamed R, Newman B, Olsson B, Hochhaus G, Li B, Luke M, Zhao L, Przekwas A, and Lionberger R. *Mechanistic Modeling of Generic Orally Inhaled Drug Products (OIDPs): A Workshop Summary Report.* CPT Pharmacometrics Systems & Pharmacology. (2023) 12:560-574. https://doi.org/10.1002/psp4.12889. PMID: 36330693.

- Wu F, Mousa Y, Raines K, Bode C, Tsang Y, Cristofoletti R, Zhang H, Heimbach T, Fang L, Kesisoglou F, Mitra A, Polli J, Kim M, Fan J, Zolnik B, Sun D, Zhang Y, and Zhao L. *Regulatory Utility of Physiologically Based Pharmacokinetic Modeling to Support Alternative Bioequivalence Approaches and Risk Assessment: A Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 585-597. https://doi.org/10.1002/psp4.12907. PMID: 36530026.

- Yoon M, Babiskin A, Hu M, Wu F, Raney S, Fang L, and Zhao L. *Increasing Impact of Quantitative Methods and Modeling in Establishment of Bioequivalence and Characterization of Drug Delivery.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5):552-555. https://doi.org/10.1002/psp4.12930. PMID: 36756902.

Posters

- Spires J, Osdol W, and Lukacova V. *Development of an In Silico Model of Topical Acyclovir to Explore Formulation Design.* Poster Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 09, 2023.

- Clarke J, Murthy N, Zhang Y, Paterson D, Dancik Y, Djehizian A, Tsakalozou E, Ghosh P, Alam K, and Polak S. *Designing an In Vitro Study to Understand Release of API from the Dispersed Phase of Clobetasol Creams – Verification of the Mechanistic Emulsion Model in the MPML MechDermA.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.

- Le Merdy M, and Lukacova V. *Ocular Exposure Extrapolation Across Multiple Species Using PBPK Modeling and Simulation: Latanoprost Solution Case Study.* Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. La Coruna, Spain, Jun. 28, 2023.

- Le Merdy M, Alqaraghuli F, and Lukacova V. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Besifloxacin Suspension Case Study.* Poster Presentation at the 2023 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. New Orleans, LA, Apr. 23, 2023.

OUTCOME *continued*

- Kumar S, Cook N, Gum G, Manza L, Naageshwaran V, Lyulkin M, Xu X, Patel D, Qu H, Walenga R, Tan M-L, Babiskin A, and Kaisar M. *Impact of Changes in Ophthalmic Emulsion Globule Size Distribution and Viscosity on Tear Film Thickness and Menisci Characteristics.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Qaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, Lukacova V, and Le Merdy M. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Gatifloxacin Solution Case Study.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Silva D, Bao Q, Wan B, Malavia N, Burgess D, and Lukacova V. *Establishment of Preclinical Mechanistic In Vitro-In Vivo Correlations for Long-Acting Injectable Suspensions.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Telaprolu K, Arora S, Clarke J, Dancik Y, Tsakalozou E, Ghosh P, Alam K, Roberts M, and Polak S. *Evaluating Influence of Critical Quality Attributes of Metronidazole Topical Gel on Bioequivalence Using the Dermal Virtual Bioequivalence (VBE) Module in Simcyp Simulator.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

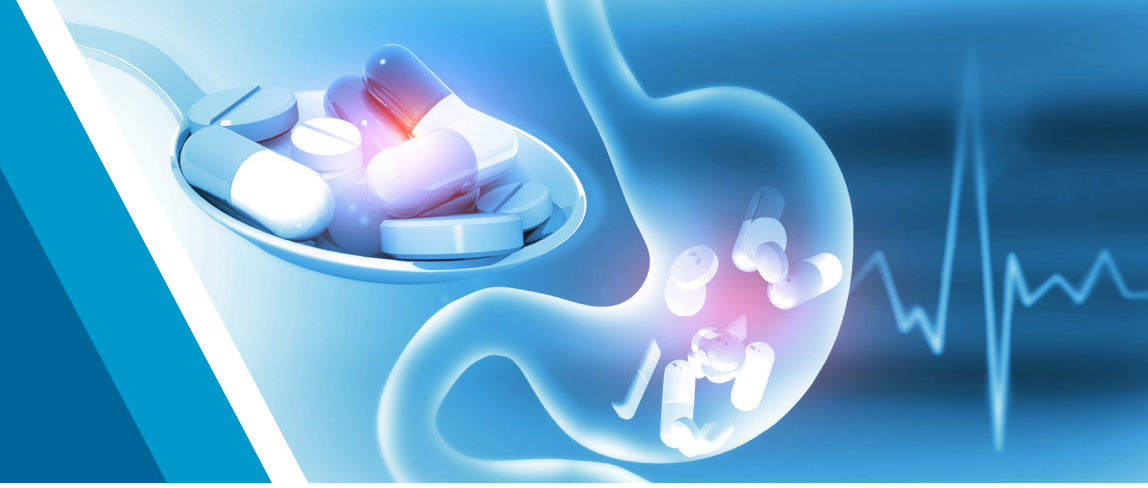
Presentations

- Walenga R. *Modeling and Simulation to Support Development and Approval of Generic Orally Inhaled Drug Products.* Presentation at the Society for Pharmaceutical Dissolution Science (SPDS): In Vitro and In Silico Predictions of Orally Inhaled Drug Product In Vivo Performance. Virtual Meeting, Sep. 15, 2023.
- Chopski S. *Innovative Technology: Particle Image Velocimetry (PIV) and High Speed Imaging to Support Approval of Generic Orally Inhaled Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Workshop, Sep. 14, 2023.
- Walenga R. *Complex Nasal Suspensions: Utilization of In Silico Studies to Support Development and Approval.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Workshop, Sep. 13, 2023.
- Lee J. *In Silico Study of the Effect of Including Lactose Fines in Modeling Dry Powder Inhaler Performance.* Presentation at the FDA 2023 Scientific Computing Days. Virtual Meeting, Sep. 12, 2023.
- Babiskin A. *Considerations for Using Model Master Files.* Presentation at the Physiologically based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives. Rockville, MD, Aug. 30, 2023.
- Bielski E. *Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products.* Presentation at the American Thoracic Society (ATS) International Conference 2023. Washington, DC, May 22, 2023.
- Walenga R. *Utilizing In Vitro and In Silico Methods to Accelerate Product Development for Generic Nasal Drug Products.* Presentation at the Novel Nasal Formulation and Delivery Summit 2023. San Diego, CA, May 18, 2023.
- Lin C. *Cluster-Informed In Silico and In Vivo Regional Deposition Assessments.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.

OUTCOME *continued*

- Walenga R. *Model Purpose and Selection for Supporting Development and Approval of Generic Locally Acting Orally Inhaled Drug Products in the United States.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Babiskin A, and Yoon M. *Regulatory Perspective on Modeling Strategies Across Multiple Submissions.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 27, 2022.
- Le Merdy M. *Ophthalmic Drug Products: Leveraging M&S Approaches to Perform Inter-Species Predictions and Support Drug Product Development and Approval.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting. Oct. 27, 2022.
- Bies R. PBPK *Modeling Approaches to the Female Reproductive Tract.* Presentation at the Gates Grand Challenge, Non-hormonal Discovery Convening. Brussels, Belgium, Oct. 23, 2022.
- Lukacova V. *Application of Modeling and Simulation in Long-Acting Injectable Product Development.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Tsakalozou E. *Physiologically Based Pharmacokinetic Modeling to Support Bioequivalence and Drug Approval.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Tsakalozou E. *Mechanistic Modeling and Simulation Approaches for Performance Prediction of Locally Acting Complex Drug Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.
- Lukacova V. *Current Status and Gaps in Mechanistic In-Silico Modeling for Clinical Translation and Performance.* Presentation at the American Association of Pharmaceutical Scientists (AAPS): Patient-Centric Design of Long-Acting Injectable Drug Products. Virtual Meeting, Oct. 10, 2022.

ORAL ABSORPTION MODELS



Summary of FY 2023 Activities

In FY 2023, external contracts and grants as well as multiple internal research projects focused on the development of biorelevant/biopredictive in vitro testing and PBPK modeling to predict the impact of formulations (including excipients), food, gastric pH, and specific populations (e.g., pediatric) on BE assessment. The extramural and intramural projects related to oral absorption models for BE assessment mainly encompassed three scientific areas including the utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions, potential expansion of biowaivers for Biopharmaceutics Classification System (BCS) Class III Drugs, and enhancement of PBPK absorption modeling capabilities.

Certain research focused on exploring the utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions. Grant 1U01FD007352 focused on the development and validation of a best practices framework for PBPK analysis in support of model-informed biowaivers of fed state BE studies for BCS Class II drugs. In FY 2023, this research demonstrated the feasibility of predicting both positive and negative food effects for amorphous solid dispersion formulations of itraconazole, a BCS Class II weak base drug, and ibuprofen, a BCS Class II weak acid drug (refer to the **Research Highlight** below for more details). Another ongoing Contract 75F40121C00020, sought to identify important product quality attributes by focusing on formulation variables that influence the in vivo performance of such products in fasting and fed states. The generated biorelevant disintegration/dissolution data will be incorporated in PBPK modeling to predict the food impact on BE for BCS Class I or BCS Class III drugs. The above research projects were supporting the draft International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) M13A, Bioequivalence for Immediate-Release Solid Oral Dosage Forms guideline issued in January 2023.

Previously completed research had focused on exploring the potential expansion of biowaivers for BCS Class III Drugs. Specifically, Contract 75F40119C10127 "Expanding BCS Class III Waivers for Generic Drugs to Non-Q1/Q2 Formulations" had previously used the in vitro dissolution absorption system (IDAS) to evaluate the impact of excipients on and permeation of BCS Class III active pharmaceutical ingredients (APIs) including acyclovir, atenolol, hydroxychloroquine, or rasagiline. During FY 2023, data on the measured change of apparent permeability for BCS III drugs by certain excipients were incorporated in PBPK modeling as part of internal FDA research projects to predict the excipient impact on BE and potentially support non Q1/Q2 BCS class III drug product biowaivers. Using acyclovir and ranitidine immediate release products as examples, similar PBPK modeling approaches were used to evaluate the potential impact of an antioxidant on drug exposure from a drug product that may be reformulated to incorporate that antioxidant to mitigate potential risks associated with nitrosamine adducts (for more information, refer to Chapter 1, Impurities). During FY 2023, FDA and the CRCG also hosted a public workshop on "Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics" (June 15, 2023)[10] to discuss the risks of nitrosamine

[10] FDA/CRCG Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics (https://www.complexgenerics.org/education-training/mitigation-strategies-for-nitrosamine-drug-substance-related-impurities-quality-and-bioequivalence-considerations-for-generic-products/)

drug substance related impurities (NDSRIs) formation in certain drug products, strategies to mitigate these risks, and considerations in assessing the safety of NDSRIs. The above research results were presented in this workshop and discussed the potential impacts of reformulations (e.g., adding a suitable antioxidant to the existing formulation) on the bioequivalence of generic products and the strategies to utilize modeling and simulation approaches to assess the bio-inequivalence risks in the event of a reformulation.

Another research focus was on the enhancement of PBPK absorption modeling capabilities. A major goal of the research under Contract 75F40120C00150 was to develop a predictive in silico modeling and simulation platform for drug products delivered via the oral cavity (e.g., buccal tablets, sublingual tablets, etc.). Under this project, permeability of APIs and drug products were measured though the use of a cellular model and these data were used to improve the PBPK modeling platform for oral cavity drug products. The 'dynamic in vitro dissolution and absorption model (DIVDAM)' is currently being employed to understand the potential impact of excipients in the permeation of a drug molecule through buccal/sublingual mucosa. The ultimate goal of this contract is to establish a PBPK model-based IVIVC of oral cavity drug products by taking account of the in vitro dissolution and absorption (an outcome from DIVDAM) and clinical PK data of oral cavity drug products.

A completed Contract HHSF223201810112C focused on understanding the risks associated with the substitution of generic products in pediatric populations when BE studies were conducted in adults. Four narrow therapeutic index (NTI) and low solubility drugs (carbamazepine, phenytoin, tacrolimus, cyclosporine) with BE data reported in both adult and pediatric populations, were used as model drugs to explore biorelevant dissolution methods. In FY 2023, using carbamazepine as an example, the generated dissolution profiles were integrated into PBPK modeling and demonstrated that a dissolution method with 200 mL biorelevant medium provides dissolution profiles that can better predict drug exposure and non-BE risk in pediatric populations.

In addition, based on an earlier FDA/CRCG workshop titled "Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches" held on September 30 and October 1, 2021[11], two workshop reports were published during 2023 that focused on the presentations and discussion points regarding PBPK modeling for risk assessment and evaluating food impact on BE for oral products.

[11] FDA/CRCG Workshop on the Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches (https://www.complexgenerics.org/education-training/regulatory-utility-of-mechanistic-modeling-to-support-alternative-bioequivalence-approaches/)

RESEARCH HIGHLIGHT

The research under Grant 1U01FD007352 sought to develop a best practices model-based framework for integrating drug and drug product data together with gastrointestinal physiology in IVIVE-PBPK models tailored to oral drug administration in order to predict food-formulation interactions and explore the potential for biowaivers of fed state BE studies for BCS class II drugs (**Figure 1**). This was conducted at both the individual and population levels. This research demonstrated the feasibility of predicting both positive and negative food effects for amorphous solid dispersion formulations of itraconazole, a BCS Class II weak base. The generalizability of this approach was demonstrated for ibuprofen, a BCS Class II weak acid, and this project will further assess the external validity of this model-based approach towards anticipating food effect on rivaroxaban and ritonavir formulations.

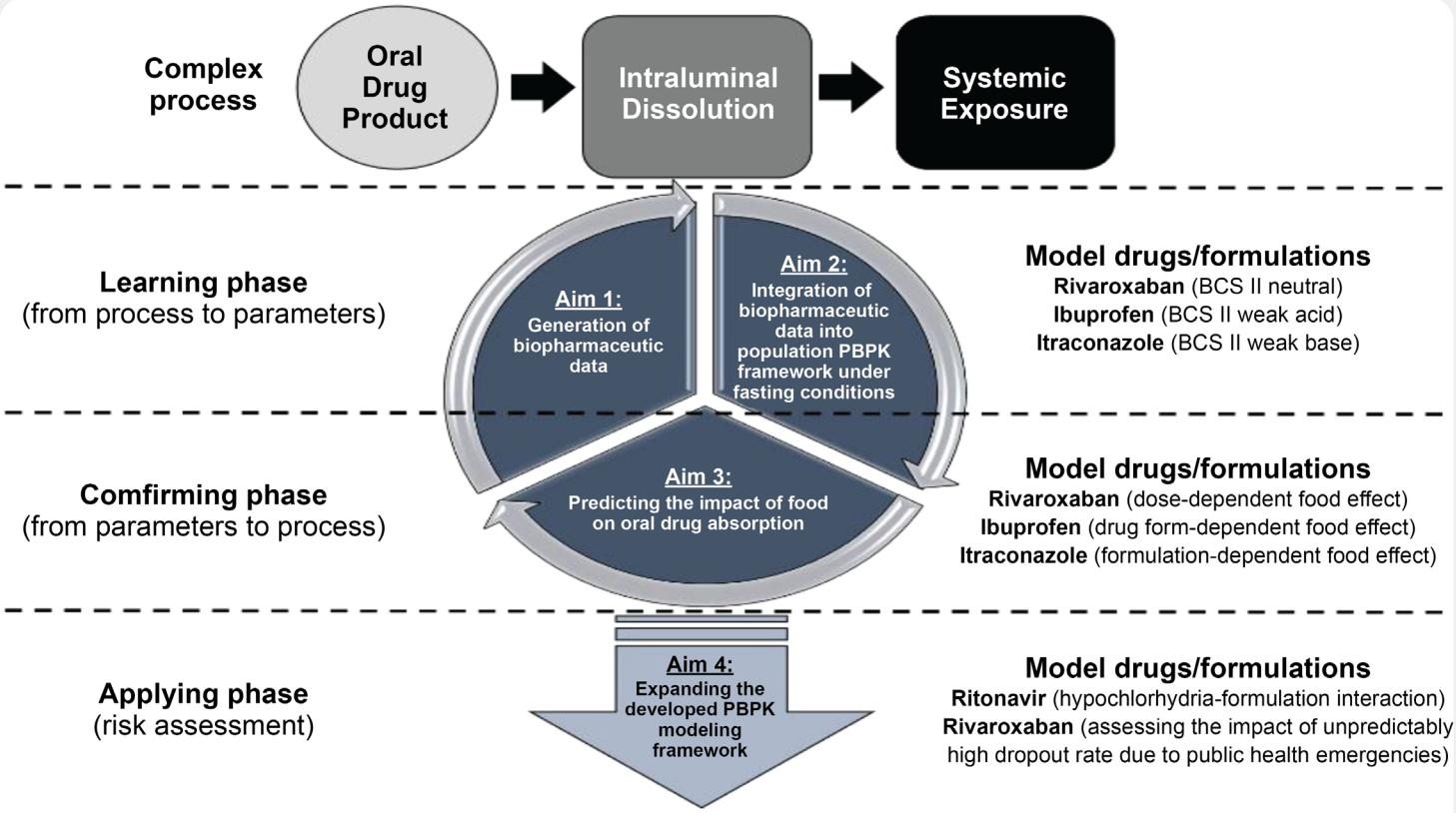


Figure 1. Model-based framework for integrating drug and drug product data together with gastrointestinal physiology in IVIVE-PBPK models to predict the impact of food on oral drug absorption.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007904) *A State-of-the-Art Virtual Bioequivalence Platform and Case Studies on Complex Formulations, Systemic and Local Concentration-based Bioequivalence* with Frederic Bois at Certara UK, LTD
- Grant (1U01FD007906) *Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies using PBBM-PBPK Models* with Frederico Martins at SIMULATIONS PLUS, INC.

Continuing Grant(s) and Contract(s)

- Grant (1U01FD007352) *Development and Validation of a Best Practices Framework for PBPK Analysis for Biopharmaceutic Applications in Support of Model-Informed Biowaivers of Fed State BE Studies for BCS Class II Drugs* with Rodrigo Cristofoletti at University of Florida
- Grant (1U01FD007662) *Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract* with Rodrigo Cristofoletti at University of Florida
- Grant (1U01FD007660) *Development of PBBM Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients* with Nikoletta Fotaki at University of Bath
- Contract (75F40121C00020) *Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation* with Peter Langguth at Johannes Gutenberg University
- 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 University of Health Sciences and Pharmacy in St. Louis
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive in Vitro Dissolution-Models* with Duxin Sun, Amit Pai Manjunath at University of Michigan, College of Pharmacy

Completed Grants and Contracts

- Contract (223201810112C) *Better Understand Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products* with Marie-Christine Jones at University of Birmingham.
- Contract (75F40119C10127) *Expanding BCS Class III Waivers for Generic Drugs to Non-Q1/Q2* with Chris Bode at Absorption Systems.

Active FDA Research

- *Best Practice for Using Physiologically Based Pharmacokinetic (PBPK) Modeling for Orally Absorbed Generic Drug Products*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *GDUFA III Product-Specific Guidance Improvement for Oral Products*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

OUTCOMES

General Guidance

- FDA Draft Guidance. *ICH M13A Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms.* January 2023. Link to Posting

Articles

- Al Shoyaib A, Riedmaier A, Kumar A, Roy P, Parrott N, Fang L, Tampal N, Yang Y, Jereb R, Zhao L, and Wu F. *Regulatory Utility of Physiologically Based Pharmacokinetic Modeling for Assessing Food Impact in Bioequivalence Studies: A Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 610-618. https://doi.org/10.1002/psp4.12913. PMID: 36597353.
- Babiskin A, Wu F, Mousa Y, Tan M-L, Tsakalozou E, Walenga R, Yoon M, Raney S, Polli J, Schwendeman A, Krishnan V, Fang L, and Zhao L. *Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches: A Workshop Overview.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12: 618-623. https://doi.org/10.1002/psp4.12920. PMID: 36631942.
- Coutinho AL, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, Polli JE. *A Robust, Viable, and Resource Sparing HPLC-based LogP Method Applied to Common Drugs.* International Journal of Pharmaceutics. (2023) 644:123325. https://doi.org/10.1016/j.ijpharm.2023.123325. PMID: 37591472.
- Pawar G, Wu F, Zhao L, Fang L, Burckart G, Feng K, Mousa Y, Al Shoyaib A, Jones M, and Batchelor H. *Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study.* The AAPS Journal (2023) 25(4):67. http://doi.org/10.1208/s12248-023-00826-1. PMID: 37386339.
- Wu F, Mousa Y, Raines K, Bode C, Tsang Y, Cristofoletti R, Zhang H, Heimbach T, Fang L, Kesisoglou F, Mitra A, Polli J, Kim M, Fan J, Zolnik B, Sun D, Zhang Y, and Zhao L. *Regulatory Utility of Physiologically Based Pharmacokinetic Modeling to Support Alternative Bioequivalence Approaches and Risk Assessment: A Workshop Summary Report.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 585-597. https://doi.org/10.1002/psp4.12907. PMID: 36530026.
- Yoon M, Babiskin A, Hu M, Wu F, Raney S, Fang L, and Zhao L. *Increasing Impact of Quantitative Methods and Modeling in Establishment of Bioequivalence and Characterization of Drug Delivery.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 552 -555. https://doi.org/10.1002/psp4.12930. PMID: 36756902.

Posters

- Gao H, Thomas S, and Wu F. *Developing an R Shiny App for Dissolution Profile Similarity Analysis.* Poster Presentation at the FDA Annual Student Scientific Research Day 2023. Virtual Meeting, Aug. 10, 2023.
- Al Shoyaib A, Fang L, Zhao L, and Wu F. *Assessing the Impact of Excipient and Food Intake on Bioequivalence Using PBPK and Virtual Bioequivalence Trial: A Case Example with Acyclovir Immediate Release Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

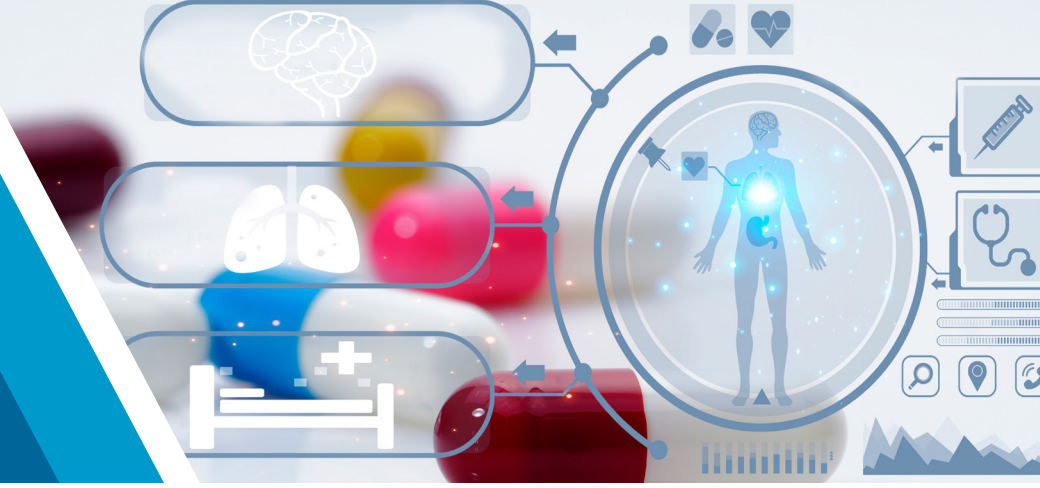
OUTCOME *continued*

- Bode C, Bhoopathy S, Miezeiewski B, Wu F, Ren P, Wang Z, and Zhao L. *In Vitro Comparative Dissolution and Permeation Testing Using the In-vitro Dissolution Absorption System (IDAS) for Expanding Biowaivers to Non Q1/Q2 BCS Class III Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Bode C, Bhoopathy S, Miezeiewski B, Wu F, Ren P, Wang Z, and Zhao L. *Using the In-Vitro Dissolution Absorption System (IDAS) to Evaluate the Effects of Excipients on the Permeation of Putative Biopharmaceutics Classification System Class III Drugs.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Wu F. *OGD Perspectives on PBBM Applications for Generics.* Presentation at the FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling Workshop. Rockville, MD, Aug. 31, 2023.
- Wu F. *Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling to Evaluate the Impact of Excipients on Bioequivalence of BCS Class III Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics. Hybrid Meeting, Rockville, MD, Jun. 15, 2023.
- Wu F, and Tsakalozou E. *A Critical Overview of the Biological Effects of Excipients.* Presentation at the Excipient World Conference & Expo 2023. National Harbor, MD, May 02, 2023.
- Wu F. *Using Physiologically Based Pharmacokinetic Absorption Modeling for Bioequivalence Evaluation in Adult and Pediatric Populations.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2023 Webinar. Virtual Meeting, Apr. 27, 2023.
- Wu F. *How Might Excipients Impact Bioequivalence Assessments of Human Generic Drug Products.* Presentation at the 2023 March AAPS Webinar. Virtual Meeting, Mar. 23, 2023.
- Wu F. *Using PBPK Model to Support Risk Assessment for Oral Products.* Presentation at the Peking University Third Hospital 2023. Virtual Meeting, Jan. 13, 2023.
- Wu F. *Using PBPK Model to Support Risk Assessment for Oral Products, from a Regulatory Perspective.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 27, 2022.
- Wu F. *Assessing Food Impact on Bioequivalence Using Physiologically-Based Pharmacokinetic Modeling.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 18, 2022.

QUANTITATIVE CLINICAL PHARMACOLOGY



Summary of FY 2023 Activities

Quantitative Clinical Pharmacology (QCP), along with MIE, is leveraged by the GDUFA science and research program to develop the most effective in vivo study designs and BE study evaluation approaches. The ultimate aims of these approaches are to facilitate product development and regulatory assessment for generics with complicated in vivo study considerations and to ensure product substitutability.

External research collaborations in FY 2023 continued to advance population PK modeling techniques and methods. The Contract 75F40122C00139 with Uppsala University, aims to enhance the efficiency and accuracy of BE assessment for drugs with high variability and long half-life. It involves proposing and evaluating novel study designs, developing model-integrated methods for reference-scaled average BE, and exploring alternative analysis strategies. The project seeks to address challenges in study duration and power, offering potential benefits to generic drug development. Grant 1U01FD007355 with Certara is dedicated to tackling the challenges associated with model selection in population PK and PD models in model-based BE (MBBE) studies. The grant has demonstrated the limitations of the conventional "one-at-a-time" approach in capturing intricate feature interactions. To address this limitation, the research integrates both local and global search strategies with the explicit aim of facilitating the identification of optimal population PK models.

To aid in the development of alternative BE approaches for orally inhaled drug products (OIDP), in FY 2023, a new grant was awarded to the University of Florida (Grant 1U01FD007936). The research under this grant will use population PK models to assess whether it may be feasible to predict differences in regional lung exposure based on systemic PK concentration data. Through the integration of mechanistic lung models, the project seeks to simulate various scenarios considering factors including but not limited to lung regions, deposition patterns, and absorption rates. The ultimate goal is to provide an alternative approach, supported by PK modeling, to traditional comparative clinical endpoint BE studies, or BE studies with PD endpoints, for establishing the BE of OIDPs.

Internal QCP expertise continues to be leveraged by FDA to develop best practices for pursuing alternative study designs and analysis methods for a wide range of products, including long-acting injectable, insertable, and implantable products (collectively, LAIs), oncology drugs, opioids, and products where only sparse sampling in clinical studies is available. For instance, out of the discussion that took place at the FDA/CRCG workshop on “Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products” held on November 30, 2021[12], FDA has been actively developing a framework for alternative BE study designs to shorten study durations for LAI products by exploring both model-based “in silico” dosing and switch-over study designs where BE could be assessed at non-steady state.

[12] FDA/CRCG Workshop on Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products (https://www.complexgenerics.org/education-training/establishing-the-suitability-of-model-integrated-evidence-to-demonstrate-bioequivalence-for-long-acting-injectable-and-implantable-drug-products/)

RESEARCH HIGHLIGHT

In vivo BE studies with PK endpoints play a key role in the development and approval of many generic drugs. These PK BE studies aim to compare the rate and extent of drug absorption from a test product and the reference standard, traditionally by performing a non-compartmental analysis (NCA) and comparing PK parameters using the two one-sided test (TOST) procedure[13]. Rich PK sampling is important for accurate parameter estimation through NCA, which may not be feasible for certain drug products. Recent research completed under Contracts HHSF223201610110C and 75F40119C10111 had focused on model-based (MB) TOST methods in PK BE studies which have sparse sampling, but challenges remain with the appropriate PK model selection[14,15,16,17].

A published manuscript by Guhl et. al. (based upon work performed under Contract 75F40119C10111) compared the performance of MB-TOST and NCA-TOST for BE assessment in rich and sparse designs.[13] Using non-linear mixed effects modeling (NLMEM), candidate PK models were fit to rich data from a PK study using a parallel design. The best-fit model was a two-compartment model with linear absorption and elimination and treatment effects on all PK model parameters (2cpt_par). Model misspecification was represented by specifying one compartment for distribution (1cpt_par) or treatment effects on the absorption parameter (ka) only with bioavailability (F) fixed to 1 (2cpt_F). PK BE studies were simulated using a parallel design with 24 subjects per arm. Rich and sparse designs included 11 and 5 samples per subject, respectively. Formulation differences were simulated to assess Type I error and power for each method and study design. In MB-TOST, NLMEM was used to estimate treatment effects on AUC (β^{T}_{AUC}) and C_{max} (β^{T}_{Cmax}) from the model parameters[11,12] and the associated standard errors were estimated using three different methods: Asympt, Gallant, and Post[10]. Then, the treatment effects and standard errors were used to calculate TOST statistics.

When the best-fit PK model (2cpt_par) was used to simulate rich designs, Type I errors were close to the nominal value of 5% with MB-TOST Asympt and NCA-TOST, but were inflated with model misspecification (2cpt_F) (**Figure 1a**). When MB-TOST methods were used to evaluate sparse designs, Type I errors were close to the nominal value of 5% using the true model (2cpt_par) but were inflated for C_{max} with model misspecification (1cpt_par) (**Figure 1b**). Study power for MB-TOST and NCA-TOST was generally low due to the parallel design and sample size (**Figure 2**). Thus, MB-TOST showed promise as an alternative BE analysis approach with sparse sampling study designs, provided that the PK model is correctly specified, and additional research is warranted.

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[13] FDA Draft Guidance for Industry. *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*. Available at: https://www.fda.gov/media/87219/download

[14] Loingeville F, Bertrand J, Nguyen TT, Sharan S, Feng K, Sun W, Han J, Grosser S, Zhao L, Fang L, Möllenhoff K, Dette H, Mentré F. *New Model-Based Bioequivalence Statistical Approaches for Pharmacokinetic Studies with Sparse Sampling.* AAPS J. 2020 Oct 30;22(6):141. https://doi.org/10.1208/s12248-020-00507-3. PMID: 33125589.

[15] Möllenhoff K, Loingeville F, Bertrand J, Nguyen TT, Sharan S, Zhao L, Fang L, Sun G, Grosser S, Mentré F, Dette H. *Efficient model-based bioequivalence testing.* Biostatistics. 2022 Jan 13;23(1):314-327. https://doi.org/10.1093/biostatistics/kxaa026. PMID: 32696053.

[16] Tardivon C, Loingeville F, Donnelly M, Feng K, Sun W, Sun G, Grosser S, Zhao L, Fang L, Mentré F, Bertrand J. *Evaluation of Model-Based Bioequivalence Approach for Single Sample Pharmacokinetic Studies.* CPT Pharmacometrics Syst Pharmacol. 2023 Jul;12(7):904-915. https://doi.org/10.1002/psp4.12960. Epub 2023 Apr 27. PMID: 37114321.

[17] Guhl M, Mercier F, Hofmann C, Sharan S, Donnelly M, Feng K, Sun W, Sun G, Grosser S, Zhao L, Fang L, Mentré F, Comets E, Bertrand J. *Impact of Model Misspecification on Model-Based Tests in PK Studies with Parallel Design: Real Case and Simulation Studies.* J Pharmacokinet Pharmacodyn. 2022 Oct;49(5):557-577. https://doi.org/10.1007/s10928-022-09821-z. Epub 2022 Sep 16. PMID: 36112338.

RESEARCH HIGHLIGHT *continued*

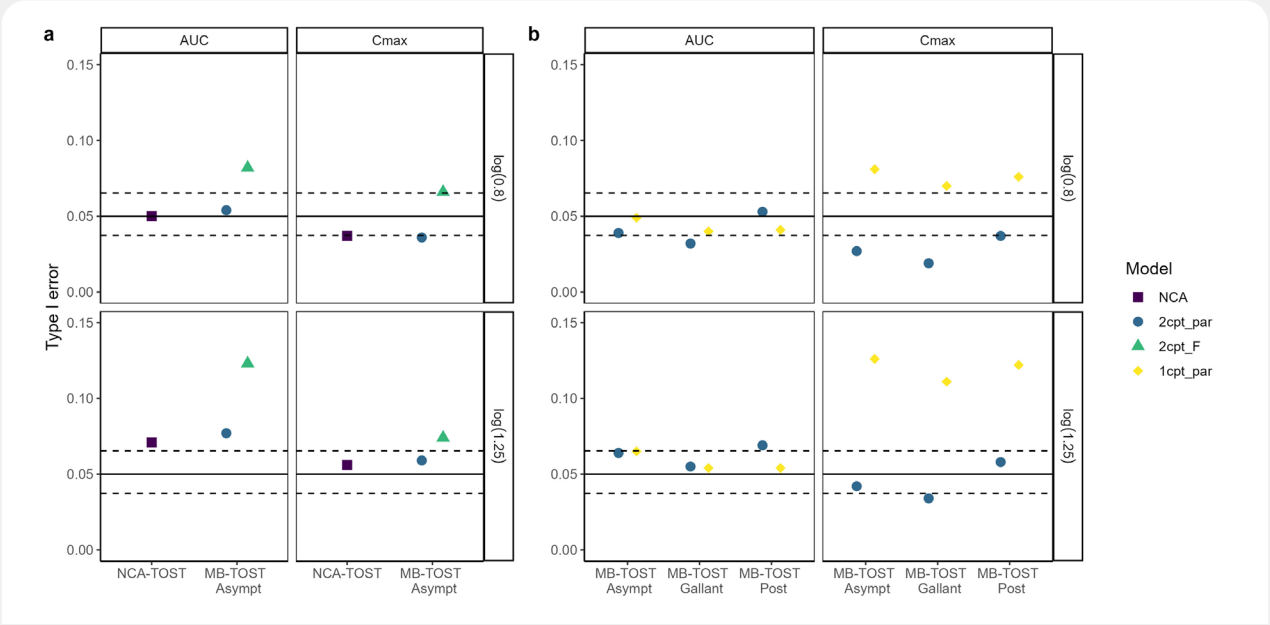

Figure 1. Type I error rate for a simulated geometric mean ratio (GMR) of 0.8 and 1.25 on area under the concentration-time curve (AUC) and maximum concentration (C_{max}) using a) rich design simulations with NCA-TOST and MB-TOST Asympt, and on b) sparse design simulations with MB-TOST Asympt, Gallant and Post.

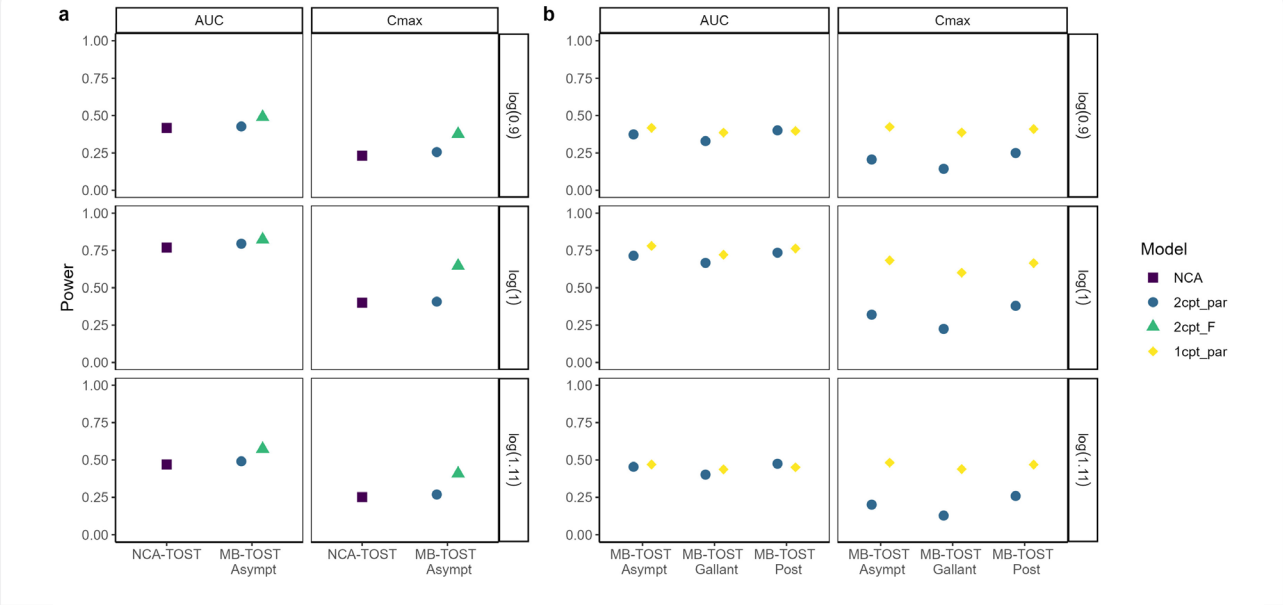

Figure 2. Study power for a simulated geometric mean ratio (GMR) of 0.9, 1.0, and 1.11 on AUC and C_{max} using a) rich design simulations with NCA-TOST and MB-TOST Asympt, and on b) sparse design simulations with MB-TOST Asympt, Gallant and Post.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (1U01FD007936) *Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic Data of Generic OIDPs Via Population Pharmacokinetic Modeling and Non-Compartmental Approaches* with Jürgen Bulitta at University of Florida

Continuing Grant(s) and Contract(s)

- Contract (75F40122C00139) *Model-Integrated Strategies for Bioequivalence Evaluation of Drugs with High Variability and/or Long Half-Life* with Mats O. Karlsson at Uppsala University

Completed Grant(s) and Contract(s)

- Grant (1U01FD007355) *Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis* with Mark Sale at Certara
- 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 (HHSF223201610110C) *Evaluation of Model-Based Bioequivalence Statistical Approaches for Sparse Design PK Studies* with France Mentre at Inst Nat Sante Et La Recherche Medicale (INSERM)

Active FDA Research

- *Clinical Trial Simulation for Clinical Endpoint Bioequivalence Studies*
- *Evaluation and Application of Repeated Crossover Study Design for Bioequivalence Assessment*
- *Evaluation and Development of Model-Integrated Bioequivalence Analysis Strategies*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *Model-based Assessment on Bioequivalence Limits for Anticoagulants*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Pharmacokinetic Data Analysis to Identify Chewing Methods for Opioid Drug*

OUTCOMES

General Guidance

- *FDA Draft Guidance for Industry. Topical Dermatologic Corticosteroids: In Vivo Bioequivalence.* October 2022. Link to Posting
- *FDA Draft Guidance for Industry. Statistical Approaches to Establishing Bioequivalence.* December 2022. Link to Posting

Product-Specific Guidances

There were five new and six revised PSGs published in FY 2023 related to *Quantitative Clinical Pharmacology*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Afamelanotide Subcutaneous Implant* (Feb. 16, 2023) Link to Posting
- *New Draft Guidance for Budesonide Oral Capsule, Delayed Release.* (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Dexmethylphenidate Hydrochloride; Serdexmethylphenidate Chloride Oral Capsule* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant* (NDA 019726) (Nov. 17, 2022) Link to Posting
- *Revised Draft Guidance for Goserelin Acetate Implantation Implant* (NDA 020578) (Nov. 17, 2022) Link to Posting
- *New Draft Guidance for Leuprolide Mesylate Subcutaneous Emulsion* (Feb. 16, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet, Extended-Release (NDA 018152)* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet, Extended-Release (NDA 018027)* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Capsule* (May 18, 2023) Link to Posting
- *Revised Draft Guidance for Lithium Carbonate Oral Tablet* (May 18, 2023) Link to Posting
- *New Draft Guidance for Loxapine Inhalation Powder* (May 18, 2023) Link to Posting

Articles

- Fang L, Li Z, Kinjo M, Lomonaco S, Zheng N, Jiang W, and Zhao L. *Generic Lamotrigine Extended-Release Tablets are Bioequivalent to Innovator Drug in Fully Replicated Crossover Bioequivalence Study.* Epilepsia. (2022) 64(1): 152-161. https://doi.org/10.1111/epi.17438. PMID: 36259141.
- Gong Y, Zhang P, Yoon M, Zhu H, Kohojkar A, Hooker A, Ducharme M, Gobburu J, Celliere G, Gajjar P, Li B, Velagapudi R, Tsang Y, Schwendeman A, Poli J, Fang L, Lionberger R, and Zhao L. *Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products: Summary of Workshop.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12: 624-630. https://doi.org/10.1002/psp4.12931. PMID: 36710372.

OUTCOME *continued*

- Tardivon C, Loingeville F, Donnelly M, Feng K, Sun W, Sun G, Grosser S, Zhao L, Fang L, Mentre F, and Bertrand J. *Evaluation of Model - Based Bioequivalence Approach for Single Pharmacokinetic Studies.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 2(7):904-915 https://doi.org/10.1002/psp4.12960. PMID: 37114321.
- Yoon M, Babiskin A, Hu M, Wu F, Raney S, Fang L, and Zhao L. *Increasing Impact of Quantitative Methods and Modeling in Establishment of Bioequivalence and Characterization of Drug Delivery.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 552-555. https://doi.org/10.1002/psp4.12930. PMID: 36756902.

Presentations

- Feng K. *ANDA Challenges Related to Vasoconstrictor Studies.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 13, 2023.
- Feng K. *Acceptability of Using Alternative PK Metrics from Systemic Pharmacokinetic (PK) Data to Inform Regional Deposition for Orally Inhaled Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 21, 2023.
- Gong Y. *Considerations for FEV1-based Comparative Clinical Endpoint or Pharmacodynamic Bioequivalence Studies for Orally Inhaled Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products. Rockville, MD, Apr. 20, 2023.
- Fang L. *Model Integrated Evidence for Bioequivalence Evaluation to Support Generic Drug Development and Regulatory Approval.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Hooker A. *A Population PK Based Model-Integrated BE Platform.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Zhao L. *Potential Types of Model Master Files.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Babiskin A, and Yoon M. *Regulatory Perspective on Modeling Strategies Across Multiple Submissions.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 27, 2022.
- Fang L. *Partial Area Under Curve (pAUC): Product-Specific Guidance Development.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Webinar. Virtual Meeting, Oct. 25, 2022.

CHAPTER 8: DATA ANALYTICS & ARTIFICIAL INTELLIGENCE

A GDUFA science and research priority is to expand the use of data analytics including artificial intelligence (AI) and machine learning (ML) tools. The advancement of research in this area focuses on building systems and infrastructure that support the functionality of AI/ML tools which FDA can use to improve the efficiency and consistency of scientific assessments and advice. This includes using AI/ML tools such as natural language processing (NLP) that automate the assembly of key information routinely assessed during the development of product-specific guidances (PSGs), or during the assessment of abbreviated new drug applications (ANDAs), as well as AI/ML tools that facilitate planning and resource allocation to support GDUFA commitments. Research in this area is described below.

Summary of FY 2023 Activities

FDA has been developing AI, including ML, large language models (LLMs), etc., to facilitate high-quality and efficient regulatory assessments and decision-making and to promote business intelligence. One example is the development of a user-friendly automation tool to streamline labor-intensive work during the bioequivalence (BE) assessment process, named 'BE Assessment Mate' (BEAM). In FY 2023, the BEAM tool operated entirely in the cloud environment to enhance the tool usage and user experience and served as the data engine integrated with the Office of Generic Drugs (OGD)'s structured assessment tool - Generic Drug Structured Assessment (GDSA) - to facilitate regulatory assessment efficiency in FDA. Another example of the research in this area involves the application of LLMs to promote business intelligence. LLMs, such as ChatGPT, are designed to process and understand natural language text at a scale that was previously not possible with traditional approaches. Currently, LLMs can achieve a wide range of text-related tasks, including text summarization/comparison, language understanding, and text generation, etc. As such, the nature and scope of daily work for FDA assessors is well aligned with, and can be greatly assisted by, ChatGPT-like technologies. Under Contract (75F40119C10106), an LLM tool, namely PharmBERT, was developed to implement automatic information extraction from drug labeling, such as the adverse reaction of the drugs or drug-drug interactions (more details are reported in **Research Highlight** of this chapter).

Another notable ongoing work involved research to develop an ML-assisted tool to improve the quality and assessment of poly(lactic-co-glycolic acid (PLGA) formulations (Chapter 3). The study developed an ML-assisted method to aid the analysis of PLGA-based long-acting injectable formulations and established a correlation between material attributes, processing conditions, and product quality/performance. This approach will help to reduce the traditional iterative approach for optimizing formulation development and can help to improve product quality through an increased ability to predict drug release behavior.

In addition, under Grant U01FD007355, "Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis", a python package "pyDarwin" was developed as a machine learning solution for NONMEM model selection (https://github.com/certara/pyDarwin). Current efforts focus on verifying its usefulness by applying it to develop a pipeline of model-based BE analysis based on real pharmacokinetic (PK) datasets. During FY 2023, data analytics tools also supported regulatory assessments and helped to address regulatory questions regarding in vitro release testing (IVRT), active pharmaceutical ingredient (API) sameness, particle size distribution, sample size estimation, data imputation, etc.

RESEARCH HIGHLIGHT

Drug labeling generally refers to any information provided with prescription drugs that are approved by regulatory agencies, such as the FDA. Drug labeling can contain various topics such as indications, warnings and precautions, and adverse events (side effects). Comprehensive information can be extracted from the drug labeling. For example, by analyzing the drug labeling using NLP techniques, it is possible to automate the process of finding the adverse reaction of the drugs or finding the drug-drug interaction information. As another example, identifying paragraphs with pharmacokinetic information contained in drug labeling can enhance the assessment of pertinent information to support PSG development. NLP techniques, especially recently developed Bidirectional Encoder Representations from Transformers (BERT), have exhibited an exceptional ability for text-based information extraction. A common paradigm in training BERT is to pre-train the model on large unlabeled generic language corpora, so that the model learns the distribution of the words in the language, and then fine-tune on a downstream task. In a study conducted

RESEARCH HIGHLIGHT *continued*

under Contract 75F40119C10106 – "Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency"[1], first, the uniqueness of language used in drug labeling was demonstrated, which cannot otherwise be handled in an optimal manner by other BERT models (**Figure 1**). Then, the developed PharmBERT - a BERT model specifically pre-trained on the drug labeling (publicly available at Hugging Face) was presented. The results showed that PharmBERT outperformed the vanilla BERT, ClinicalBERT, and BioBERT in multiple NLP tasks in the drug labeling domain (**Table 1**). Moreover, how the domain-specific pre-training contributed to the superior performance of PharmBERT was studied by analyzing different layers of PharmBERT, and more insight into how it understands different linguistic aspects of the data were gained.

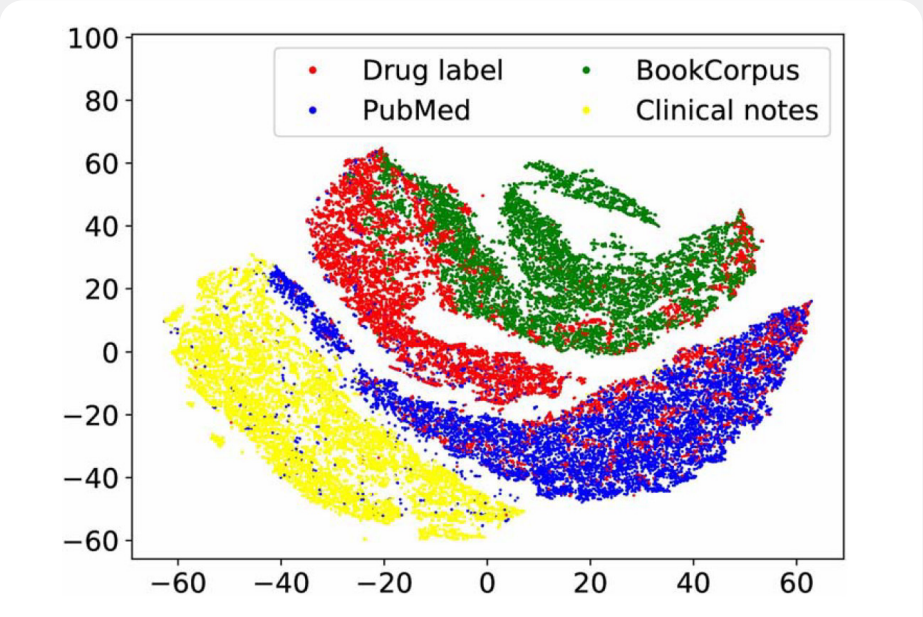

Figure 1. t-SNE representation of BERT-base-cased embeddings for four domains: drug labeling, Book Corpus, clinical notes, and PubMed abstracts. Each task is mainly clustered separately and, therefore, is a different domain. t-SNE referring to "t-distributed stochastic neighbor embedding" is a statistical method for visualizing high-dimensional data by giving each datapoint a location in a two or three-dimensional map based on Stochastic Neighbor Embedding[2].

[1] Valizadehaslani T, Shi Y, Ren P, Wang J, Zhang Y, Hu M, Zhao L, and Liang H. *PharmBERT: A Domain-specific BERT Model for Drug Labels.* Briefings in Bioinformatics. (2023) 24(4). https://doi.org/10.1093/bib/bbad226. PMID: 37317617.

[2] https://en.wikipedia.org/wiki/T-distributed_stochastic_neighbor_embedding

RESEARCH HIGHLIGHT *continued*

Table 1. Fine-tuning results for different BERT models and different experiments. The values are the average F1 over 5 runs. The standard errors are provided in parentheses.

Model	ADR	DDI	ADME
BERT based on uncased texts	0.8769 (0.0016)	0.7814 (0.0027)	0.9025 (0.0029)
BERT based on original texts	0.8700 (0.0017)	0.7772 (0.0072)	0.9021 (0.0033)
ClinicalBERT	0.8760 (0.0029)	0.7672 (0.0030)	0.9033 (0.0035)
BioBERT	0.8897 (0.0009)	0.7905 (0.0036)	0.9116 (0.0019)
PharmBERT based on uncased texts	**0.8923 (0.0012)**	**0.8047 (0.0045)**	0.9132 (0.0026)
PharmBERT based on original texts	0.8845 (0.0007)	0.8005 (0.0050)	**0.9165 (0.0036)**

ADR: Adverse Drug Reaction; DDI: Drug-Drug Interaction; ADME: Absorption, Distribution, Metabolism, Excretion; F1: A model performance metric based on true positives, false positive, and false negatives, and the higher F1 value indicates the better model performance.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (2U01FD005978) *Large Language Models to Support BE Evaluation* with Russ Altman, Percy Liang, and Kathleen Giacomini at CERSI - University of California, San Francisco (UCSF) – Stanford University

Continuing Grant(s) and Contract(s)

- Contract (75F40122C00163) *Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation* with Shawn Zhang at DigiM Solution LLC
- Contract (75F40122C00121) *Machine-Learning-Based Heterogeneous Treatment Effect Models for Informing Product-Specific Guidance Development* with Hualou Liang at Drexel University

Completed Grants and Contracts

- Grant (1U01FD007355) *Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis* with Mark Sale at Certara, Inc.
- Contract (75F40119C10106) *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency* with Hualou Liang at Drexel University

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Active FDA Research

- *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations*
- *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency*
- *Development and Analysis of a Complex Product Database*
- *Development of PK Data Warehouse for BE Analysis*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Machine Learning for Generic Drug Analysis*
- *Postmarketing Surveillance of Generic Drugs Using Sentinel*

OUTCOMES

General Guidance

- FDA Draft Guidance for Industry. *Statistical Approaches to Establishing Bioequivalence*. December 2022 Link to Posting

Articles

- Belenos A, Wood E, Hu M, Kozak D, Xu X, and Fisher A. *Product Quality Research for Developing and Assessing Regulatory Submissions for Generic Cyclosporine Ophthalmic Emulsions.* The AAPS Journal. (2023) 25: 20. https://doi.org/10.1208/s12248-023-00781-x. PMID: 36702976.
- Shi Y, Ren P, Wang J, Han B, Valizadehaslani T, Agbavor F, Zhang Y, Hu M, Zhao L, Liang H. *Leveraging GPT-4 for Food Effect Summarization to Enhance Product-Specific Guidance Development via Iterative Prompting.* arXiv:2306.16275 (2023) https://doi.org/10.48550/arXiv.2306.16275.
- Shi Y, Wang J, Ren P, ValizadehAslani T, Zhang Y, Hu M, Liang H. *Fine-Tuning BERT for Automatic ADME Semantic Labeling in FDA Drug Labeling to Enhance Product-Specific Guidance Assessment.* Journal of Biomedical Informatics 138 (2023) 104285. https://doi.org/10.1016/j.jbi.2023.104285. PMID: 36632860.
- Valizadehaslani T, Shi Y, Ren P, Wang J, Zhang Y, Hu M, Zhao L, and Liang H. *PharmBERT: A Domain-specific BERT Model for Drug Labels.* Briefings in Bioinformatics. (2023) 24(4). https://doi.org/10.1093/bib/bbad226. PMID: 37317617.
- Yoon M, Babiskin A, Hu M, Wu F, Raney S, Fang L, and Zhao L. *Increasing Impact of Quantitative Methods and Modeling in Establishment of Bioequivalence and Characterization of Drug Delivery.* CPT: Pharmacometrics & Systems Pharmacology. (2023) 12(5): 552-555. https://doi.org/10.1002/psp4.12930. PMID: 36756902.

OUTCOME *continued*

Posters

- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Belsey N, Woodman T, White K, Ghosh P, Bunge A, Delgado-Charro M, and Guy R. *Assessment of Bio(in)Equivalence of Metronidazole Topical Formulations using Stimulated Raman Scattering Microscopy.* Poster Presentation at the Academy of Pharmaceutical Science (APS) 2023. Virtual Meeting, Aug. 05, 2023.
- Das J, Hasan M, Smith W, Graner J, Qin B, Wang Y, Park K, Tian G, and Xu X. *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations.* Poster Presentation at the Controlled Release Society (CRS) 2023 Annual Meeting and Exposition. Las Vegas, NV, Jul. 24, 2023.
- Iliopoulos F, Pence I, Ghosh P, Raney S, Luke M, and Evans C. *Stimulated Raman Scattering (SRS) Microscopy and Deep Learning: Novel Pharmacokinetic Approach for Evaluation of Topical Bioequivalence.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

Presentations

- Belsey N. *Visualization of Topical Drug Delivery with Label Free Chemical Imaging.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 10, 2023.
- Evans C. *PK and PD Tomography: Imaging and Quantifying Skin Pharmacology.* Presentation at the Gordon Research Conference (GRC) - Barrier Function of Mammalian Skin 2023. Waterville Valley, NH, Aug. 10, 2023.
- Hu M. *Dose Scale Analysis to Support Bioequivalence Assessment.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: A Deep Dive: FDA Draft Guidance on Statistical Approaches to Establishing Bioequivalence. Virtual Meeting, Mar. 14, 2023.
- Hu M. *Use of Data Analytics Approaches to Support Regulatory Assessment - from FDA Perspective.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.

CHAPTER 9: OTHER GENERIC PRODUCT SCIENCE & RESEARCH

The Generic Drug User Fee Amendments (GDUFA) science and research program advances research in a variety of areas that are complementary to the GDUFA science and research priorities, and which enhance patient access to safe, effective and high-quality generic products. For example, research involving post-approval monitoring of generic products, generic product substitution, and patient perceptions can be important to establish evidence that instills confidence in the therapeutic performance of generic products for patients, caregivers, and prescribers. As another example, research to ensure the availability of generic opioid products can help ensure the availability of medicines that address a major public health need. Research in this area is described below, encompassing research on generic product substitution, opioid products, and other research projects that supported the development and assessment of generic drugs, each in three separate subsections.

PATIENT PERCEPTIONS ABOUT GENERIC PRODUCTS, GENERIC PRODUCT SUBSTITUTION, POST-APPROVAL MONITORING OF GENERIC PRODUCTS

Summary of FY 2023 Activities

As part of the GDUFA science and research program, FDA advanced research to evaluate the substitutability of generic drug products for patients. This included clinical studies evaluating generic substitution in patients, as well as pharmacokinetic (PK) bioequivalence (BE) studies in healthy subjects. FDA research also included analyzing clinical databases on the utilization and substitution of generic drugs, as well as assessing the perceptions of patients and health care providers related to generic substitution.

To evaluate concerns reported about the potential risk of generic drug substitution of lamotrigine extended release (ER) products, a BE study of generic and reference listed drug (RLD) lamotrigine ER products was conducted in a fully replicated BE study design in healthy subjects (Contract HHSF223201210030I). The study demonstrated that the generic lamotrigine ER tablet product was bioequivalent to the RLD, as summarized in the **Research Highlight** below.

A contract with BioPharma Services USA, Inc. (Contract HHSF223201610004I-75F40120F19005) investigated the BE between a generic tacrolimus oral capsule product and its RLD (PROGRAF®) in healthy subjects. FDA evaluated PK parameters and conducted a statistical analysis for the BE assessment. In vitro studies were also performed within FDA laboratories to evaluate the quality of the generic product and of PROGRAF®. The same manufacturing lots of drug products used in the BE study were also tested in these in vitro studies. The data from these in vivo and in vitro studies provided compelling evidence to reassure the public regarding the substitutability of approved generic tacrolimus products in patients[1].

Internal research at FDA was carried out to assess factors that are potentially relevant to generic drug competition in oncology. Information about oncology drugs approved from 1950 to 2021 was collected. A methodology using machine learning was used to assess variables associated with the availability of abbreviated new drug application (ANDA) products (i.e., generic drug availability). The results showed that the RLD age, patent status, product complexity, sales/prescriptions, and a regulatory recommendation for conducting BE studies in patients (as opposed to subjects) were variables that may impact the availability of generic drugs.

Among other internal FDA efforts to monitor post-market products, a cross-disciplinary research team assessed the substitutability of generic mixed amphetamine sulphate (MAS) products for the treatment of attention-deficit/hyperactivity disorder (ADHD). FDA had received reports suggesting a potentially inadequate therapeutic effect when switching from the RLD to generic products, primarily in the adult ADHD population. In response, a research team at FDA worked to investigate this potential issue through a research Contract (75F40121P00621) with Avomeen, LLC to assess whether there may be differences among recently manufactured lots of any of these MAS products, which may have the potential to impact their therapeutic effectiveness. This research is currently ongoing.

[1] Drug Safety and Availability. "FDA is changing the therapeutic equivalence rating for Accord Healthcare Inc.'s generics of Prograf (tacrolimus) oral capsules". September 18, 2023. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-changing-therapeutic-equivalence-rating-accord-healthcare-incs-generics-prograf-tacrolimus-oral

RESEARCH HIGHLIGHT

Lamotrigine extended-release (ER) products are more complex than immediate-release lamotrigine products in terms of both formulation and PK characteristics. To address potential concerns related to the risk of generic-brand substitution of lamotrigine ER products, the FDA sponsored a PK BE study to assess (1) BE of generic and RLD (brand) lamotrigine ER products in healthy subjects and (2) whether additional data (e.g., within-subject variability (WSV) of study products) from a fully replicated study design can enhance BE assessment of generic lamotrigine ER tablet products. The fed PK BE study was a randomized, open-label, single-dose, two-sequence, two-treatment, fully replicated crossover study comparing generic lamotrigine ER tablet (200 mg) to the brand product [Lamictal XR (200 mg)] in 30 healthy subjects (19 males and 11 females). PK profiles were generated based on blood sampling up to 144 hours.

The geometric mean generic-to-brand ratio for peak plasma concentrations (C_{max}), area under the concentration-time curve (AUC) from time zero to the last measurable time point (AUC_{0-t}) and AUC extrapolated to infinity (AUC_{0-inf}) were close to 100% (**Table 1**), and the corresponding 90% confidence intervals for these PK metrics were within the BE limits (80.00%-125.00%), demonstrating BE between the generic and brand lamotrigine ER products. An assessment of WSV for the PK metrics were similar between the two products. Simulated lamotrigine plasma concentrations after repeated dosing (200 mg tablet, once daily) were generated, and the potential PK differences after a brand-to-generic switch were assessed (**Figure 1)**. The simulation predicted equivalent PK measurements of both generic and brand products at steady state. Additionally, the PK measurements were equivalent after a brand-to-generic switch at Day 35, except for the first day upon switching. These results demonstrated that the currently recommended two-way, crossover study design in the product-specific guidance to demonstrate BE and generic-brand substitution of lamotrigine ER products are scientifically sound.

Table 1. Summary of the BE analysis for generic and brand lamotrigine ER tablets.

Metric	WSCV (%) generic	WSCV (%) brand	Geometric LSmeans		Ratio (%)	90% CI (%)
			Generic	Brand		
C_{max} (Ng/ml)[a]	8.2	8.4	2334.2	2229.4	104.70	100.79–108.77
A_{UC0-t} (Ng*h/ml)[b]	5.2	6.3	115252.8	117222.9	98.30	95.98–01.34
$A_{UC0-inf}$ (ng*h/ml)[c]	5.9	6.2	124252.7	124920.4	97.90	94.84–100.95

Abbreviation: WSCV, within-subject coefficient of variation.
[a]Generic *n* = 45, brand *n* = 46.
[b]Generic *n* = 44, brand *n* = 45.
[c]Generic *n* = 43, brand *n* = 44.

RESEARCH HIGHLIGHT *continued*

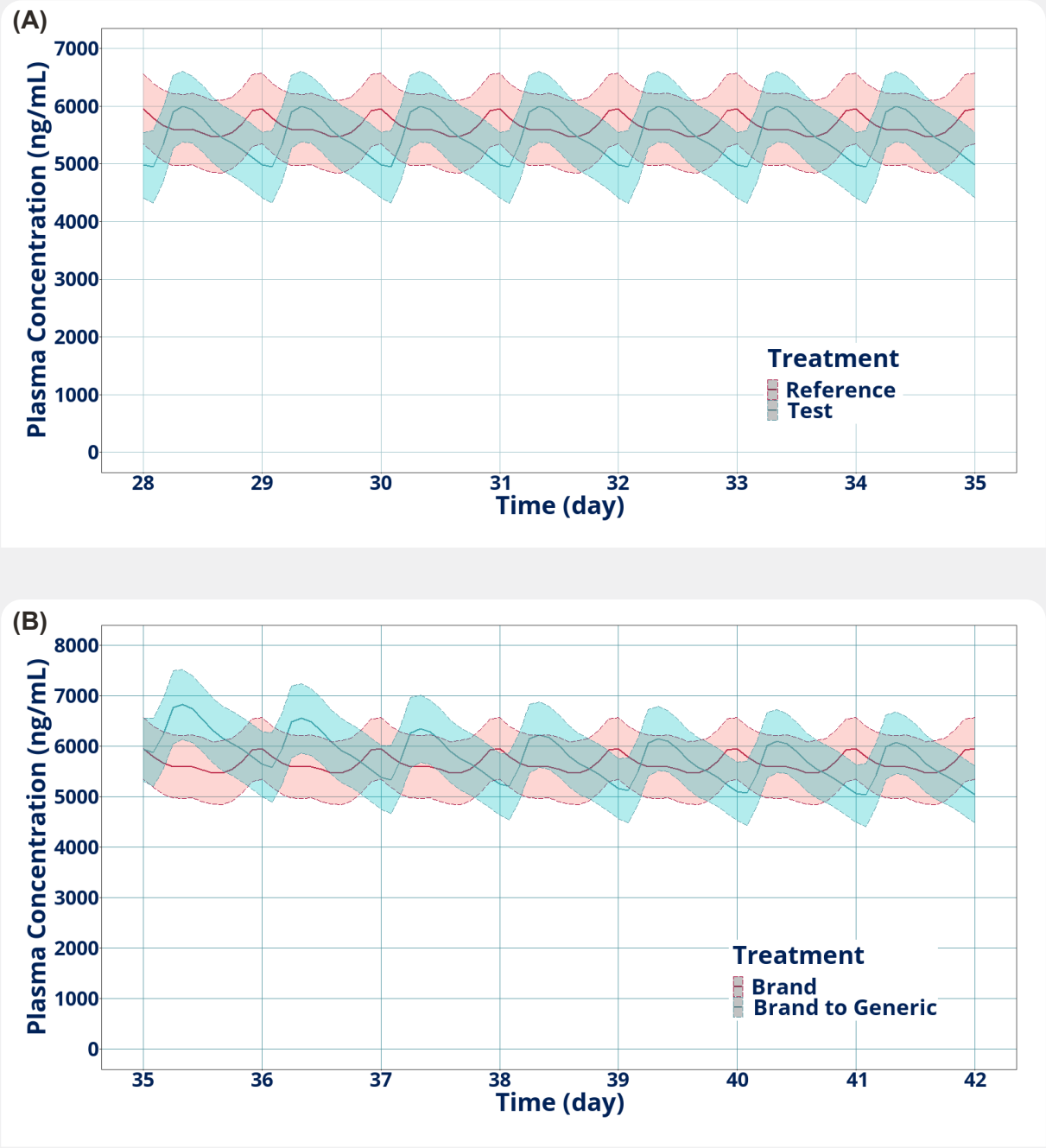

Figure 1. (A) Simulated PK profiles after repeated dosing in the fifth week. Brand (Reference) and generic (Test) are presented in red and blue, respectively. The solid lines are the mean plasma concentrations, whereas the shaded area represent the 95% confidence intervals (Cis) of the simulated plasma concentrations. (B) Simulated PK profiles after a brand-to-generic switch on Day 35. Brand and brand-to-generic switch are presented in red and blue, respectively. The solid lines are the mean plasma concentrations, whereas the shaded area represent the 95% CIs of the simulated plasma concentrations. (Fang et al., 2022)

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Contract (75F40121P00621) *In Vitro Assessment of Mixed Amphetamine Salt (MAS) Products* at Element Materials technology, Ltd.

Completed Grants and Contracts

- Grant (1U01FD005271) *Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes Adherence and Immune Responses* with Suphamai Bunnapradist at University of California Los Angeles
- Contract (HHSF223201610004I-75F40120F19005) *A Randomized, Open Label, Two Treatment, Four Period, Single Dose, Fully Replicate, Crossover Bioequivalence (BE) Study of Tacrolimus Capsules 5 mg* at Biopharma

Active FDA Research

- *COVID-19 Generic Drug Utilization*
- *In Vitro Testing for Pharmaceutical Quality of the Brand and Generic Tacrolimus Amorphous Formulations*
- *Postmarketing Surveillance of Generic Drugs Using Sentinel*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

OUTCOMES

Product-Specific Guidances

There was one new PSG published in FY2023 related to this area of generic products. The PSG listed below was directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Budesonide Oral Capsule, Delayed Release.* (Nov. 17, 2022) Link to Posting

Articles

- Fang L, Li Z, Kinjo M, Lomonaco S, Zheng N, Jiang W, and Zhao L. *Generic Lamotrigine Extended-Release Tablets are Bioequivalent to Innovator Drug in Fully Replicated Crossover Bioequivalence Study.* Epilepsia. (2022) 64: 152-161. https://doi.org/10.1111/epi.17438. PMID: 36259141.

Presentations

- Clerman A. *Post-Approval Impact of Generic Fluticasone Propionate & Salmeterol Inhalation Powder (RLD: Advair Diskus).* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Feibus K. *Generic Drug-Device Combination Product Research – Focus on Comparative Device User Interface Assessment and Understanding How Differences Impact Users.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Drug-Device Combination Products 101: Identifying, Developing, And Evaluating Drug-Device Combination Products. Hybrid Meeting. Rockville, MD, May 10, 2023.

OPIOID DRUG PRODUCTS

Summary of FY 2023 Activities

In FY 2023, FDA continued to conduct research related to opioid products with abuse-deterrent formulations (ADFs) and products designed to prevent relapse to opioid dependence or reverse an overdose. The four areas of focus were:

1. Evaluating the safety risk (i.e., hemolytic and thrombotic potential) associated with misuse of opioid drug products via non-intended routes

2. Comparative abuse-deterrent assessments of ADFs when chewed or nasally insufflated

3. Use of modeling and simulation to predict the pharmacokinetics (PK) of nasally insufflated opioid products

4. Studying the impact of formulation factors on the nasal bioavailability of naloxone nasal spray for overdose reversal

Among FDA's research related to ADF products, microfluidic model was developed to assess the hemolytic and thrombotic potential of injected polyethylene oxide (PEO), a polymer used in ADF products. This setup involved using a simple needle model to generate PEO dose response curves, assess the effect of PEO molecular weight on blood element damage, and determine how shear stress levels contribute to hemolysis. The development of a theoretical approach to understand the viscoelastic properties of PEO solutions helped inform test conditions for both in vitro microfluidics and in vivo animal studies. A correlation between free plasma hemoglobin (AUC, (mg/mL·h)) in an animal model after intravenous dosing and the PEO critical overlap concentration, as determined via rheology, indicated that cell damage may increase as the polymer concentration approaches the concentration where polymer chains may begin to interact and entangle.

A notable outcome during FY 2023 of GDUFA funded research on products to address opioid dependence was that FDA approved the first generic naltrexone extended-release injectable suspension (referencing Vivitrol®) to treat alcohol dependence and prevent relapse to opioid dependence. This is an important drug product that addresses two major public health needs affecting millions of individuals in the United States. This first generic approval is a notable achievement because of how scientifically challenging it was to develop, manufacture, and demonstrate bioequivalence. This generic product uses a long-acting injectable (LAI) biodegradable poly(lactide-co-glycolide) (PLGA) polymer microsphere technology. The PLGA formulation confers the product with a sustained effect that only necessitates patients to be dosed once a month. This was the first naltrexone extended-release injectable suspension generic product to be approved, and also the first generic PLGA product to be approved.

FDA began GDUFA-funded research on PLGA-based LAI products in 2013, and ongoing research during the last decade has systematically advanced scientific insights and developed new tools that could support an efficient demonstration of BE for complex generic LAI products like this one. The research focused on developing analytical methods that would ultimately facilitate the reverse engineering, characterization, and selection of suitable PLGA polymers - a critical first step for generic product development. The GDUFA-funded research also focused on developing suitable in vitro drug release testing methods that ultimately elucidated how a drug is released from such a formulation and

how different manufacturing processes and polymer characteristics can influence that drug release. FDA published BE recommendations for this product in a PSG and established criteria by which to assess the BE of a generic LAI PLGA product submitted in an ANDA. The GDUFA-funded research on polymer and formulation characterization thus helped to establish a viable scientific approach and regulatory pathway for generic PLGA-based products, directly supported generic product development, and prepared FDA to assess PLGA-based products when submitted in ANDAs.

During FY 2023, GDUFA funded research under Contract 75F40121C00178 investigated the use of robotics to conduct comparative in vitro assessments of an ADFs' resistance to chewing. The study was designed to investigate the impact of critical human chewing variables (e.g., chewing frequency, chewing direction, and saliva flow rate) on drug dissolution performance of chewed ADFs (i.e., oxycodone hydrochloride [HCl] extended release [ER] capsules, oxycodone HCl ER tablets, and hydrocodone bitartrate ER tablets). The results of this study may help support the modeling and simulation efforts and the development of in vitro-in vivo relationships (IVIVR). Another contract, HHSF223201610004I-75F40119F19004, advanced an in vivo study designed to investigate the effect of chewing time on the pharmacokinetics of hydrocodone bitartrate ER tablets (see **Research Highlight**).

Also during FY 2023, GDUFA funded research under contract HHSF223201610004I-HHSF22301002T included an in vitro characterization study and a pharmacokinetic (PK)/pharmacodynamic (PD) nasal study with oxycodone HCl; naloxone HCl ER tablets. The in vitro study supported the selection of a manipulation method that yielded a low fraction of fine particles (<106µm, 2.8% ± 0.34%), a high yield percent (93.3% ± 1%), drug content ± 5% of the labeled dose (oxycodone HCl: 95.6% ± 1%, naloxone HCl: 96.2% ± 1.2%), and a 2:1 ratio of oxycodone to naloxone across the different particle size fractions. An 11-month stability study on the manipulated products showed product quality (i.e., drug content and purity) to be maintained throughout the duration of the PK/PD study. The aim of the PK/PD study was to investigate the impact of particle size of manipulated tablets on the PK and PD of oxycodone and naloxone following nasal insufflation. Thirty-nine of the 352 subjects who were screened completed the study and received all study treatments.

Other internal FDA research projects continued to investigate experimental elements of nasally insufflated opioid drug products. One project focused on the development of a computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) model to predict PK following nasal insufflation of manipulated oxycodone HCl and naloxone HCl ER tablets. Another project focused on quantifying the regional deposition of nasally insufflated powders, which is thought to impact bioavailability due to poor absorption in the nasal vestibule region and the possibility of direct nose-to-brain drug delivery. Sumatriptan succinate nasal powder was used as a model drug because in vivo imaging data were available from literature to facilitate the validation of the in vitro nasal model results for that drug product, with subsequent plans to use the model to evaluate the deposition patterns of manipulated ADFs. Other internal FDA research focused on the evaluation of nasal bioavailability for different naloxone nasal spray formulations and delivery device systems, which are used for the emergency treatment of opioid overdose reversal.

RESEARCH HIGHLIGHT

HYSINGLA ER (NDA 206627; hydrocodone bitartrate ER tablets) is an ADF with physicochemical properties that are expected to reduce oral abuse when chewed. Contract HHSF223201610004I-75F40119F19004 investigated the impact of the chewing time (0 min or intact tablet, 2 min, 7 min, and 10 min) on PK parameters [i.e., maximum plasma concentration (C_{max}), area under the curve from time zero to 48 hours or the last measurable concentration (AUC_{0-t}), AUC_{inf}, $AUC_{0-3\ hours}$, $AUC_{0-4\ hours}$, and time to maximum observed plasma concentration (T_{max})] of HYSINGLA ER. In addition, this study evaluated intra-subject variability of chewing by repeating the 2 min chewing time treatment. The study design involved a single-dose, randomized, open-label, five-period, five-sequence, four-treatment, partial-replicate, crossover using HYSINGLA ER 60 mg in 67 healthy subjects (including 45 males and 22 females) under fasting conditions. The mean concentration-time profile and PK parameters for hydrocodone of each treatment are shown in **Figure 1** and **Table 1**, respectively. The preliminary results showed that the C_{max} was 63.17 ng/mL, 71.34 ng/mL, 102.85 ng/mL, and 105.29 ng/mL, while the median T_{max} was 14.01 hours, 12.04 hours, 4.00 hours, and 3.00 hours for intact tablet, 2 min, 7 min, and 10 min chewing, respectively.

In comparison, the 7 min and 10 min chewing provided similar median T_{max} and comparable C_{max} [i.e., 90% confidence interval (CI) was within 80.00% - 125.00%], which suggested HYSINGLA ER was chewed completely within 7 min. For the comparison of intact tablet, 2 min, and 7 min chewing, the longer chewing time resulted in higher C_{max} (i.e., 7 min > 2 min > intact tablet) and shorter Tmax (i.e., 7 min < 2 min < intact tablet). In addition, the results showed that $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$ were sensitive to detect the differences between all treatments. However, all treatments were determined to be bioequivalent to each other with respect to AUC_{0-t} and AUC_{0-inf} indicating that these parameters may not be sufficiently sensitive to detect PK differences in a chewing study. When a tablet was chewed for 2 min, $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$ showed high intra-subject variability (i.e., ≥ 0.294), while C_{max}, AUC_{0-t} and AUC_{0-inf} exhibited low intra-subject variability (i.e., < 0.294; **Table 2**). This research established a foundation for understanding the impact of chewing time on PK parameters, which can assist in the development of prospective generic drug products with an abuse-deterrent function against chewing.

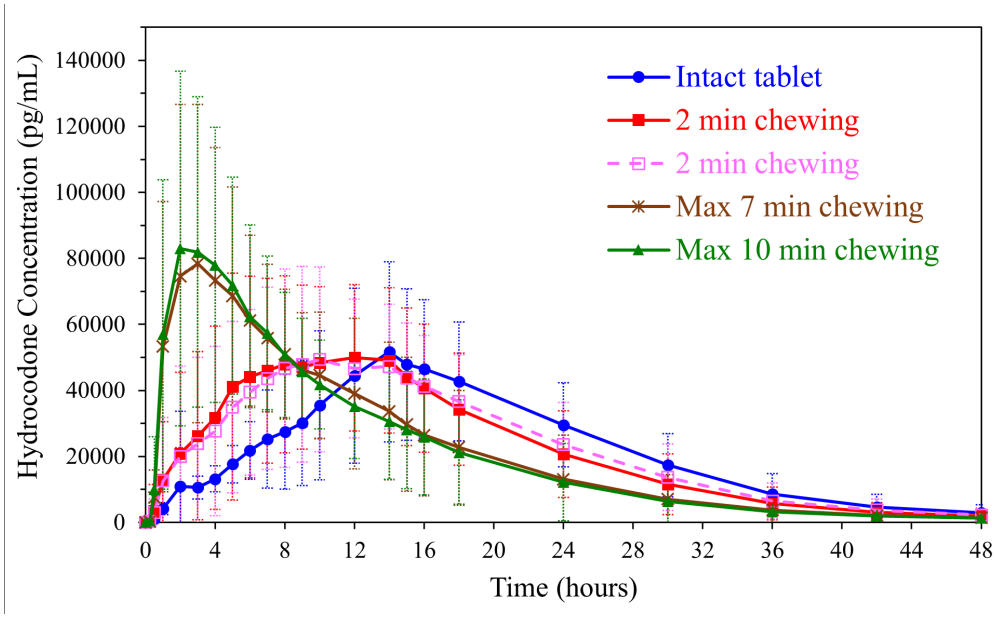

Figure 1. Mean (± SD) concentration-time profile for hydrocodone for all treatments (N=53 for intact tablet, N=46 for 10 min chewing, N=47 for 7 min chewing, N=47 and N=48 for two 2 min chewing, respectively).

RESEARCH HIGHLIGHT *continued*

Table 1. PK parameters of intact tablet, and tablets chewed for 2 min, 7 mins, and 10 min.

	Intact tablet (0 minutes chewing) N=53	2 minutes chewing N=95 (i.e., 48 and 47)	7 minutes chewing N=47	10 minutes chewing N=46
Cmax* (ng/mL)	63.17 (30.94)	71.34 (27.61)	102.85 (35.09)	105.29 (38.21)
$AUC_{0\text{-}3\ hours*}$ (ng·h/mL)	19.73 (23.01)	44.12 (54.53)	156.68 (104.13)	170.55 (110.81)
$AUC_{0\text{-}4\ hours*}$ (ng·h/mL)	31.57 (23.89)	71.277 (79.37)	232.82 (146.26)	250.64(151.82)
$AUC_{0\text{-}48\ hours*}$ (ng·h/mL)	1036.47 (366.89)	1064.75 (314.98)	1064.97 (302.47)	1047.11 (272.87)
$AUC_{0\text{-}inf*}$ (ng·h/mL)	1061.95 (385.48)	1089.99 (332.742)	1082.65 (316.46)	1063.75 (282.99)
Tmax^ (hours)	14.01 (2.00 - 30.00)	12.04 (2.00 - 24.00)	4.00 (1.00 - 24.00)	3.00 (1.00 - 16.00)

* Reported as mean (standard deviation)
^ Reported as median (range)

Table 2. Intra-subject variability of 2 min chewing.

PK parameters	lnC_{max}	$lnAUC_{0\text{-}3\ hours}$	$lnAUC_{0\text{-}4\ hours}$	$lnAUC_{0\text{-}48\ hours}$	$lnAUC_{inf}$
Intra-subject variability	0.260	0.402	0.378	0.165	0.166

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Contract (75F40121C00178) *In-Vitro Tools to Simulate Chewing of Pharmaceutical Opioid Drug Products* with Peter Xu, Feng Zhang at University of Auckland
- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Artan Markollari at Biopharma

Completed Grants and Contracts

- Grant (3U01FD004275-07S1) *Formulation of Hydrocodone Bitartrate Opioid Tablet* with National Institute for Pharmaceutical Technology & Education (NIPTE)
- Contract (HHSF223201610004I-75F40119F19004) Pharmacokinetic (PK) *Study of Opioid Drug Products Following Oral Ingestion of Chewed Products* with Artan Markollari at Biopharma Services USA Inc.

OUTCOMES

Active FDA Research

- *Development of In Vitro Methods for Nasal ADF Opioids*
- *In Vitro Approach for Assessment of Bioavailability and Bioequivalence of Naloxone Nasal Sprays*
- *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists*
- *To Evaluate the Emerging Safety Concerns Associated with the Abuse of Abuse-deterrent Oral Formulations of Opioids via the IV Route and Develop In Vitro Predictive Models to Assess the Safety of Oral Excipients Through Non-intended Routes of Delivery*

Articles

- Feng X, Wu K, Balajee V, Leissa J, Ashraf M, and Xu X. *Understanding Syringeability and Injectability of High Molecular Weight PEO Solution through Time-Dependent Force-Distance Profiles.* International Journal of Pharmaceutics. (2023) (631): 122486. https://doi.org/10.1016/j.ijpharm.2022.122486. PMID: 36521635.
- Qu H, Smith W, Feng X, Wang J, Pinto J, Xu X, and Faustino P. *Asymmetrical Flow Field Flow Fractionation for Molar Mass Characterization of Polyethylene Oxide in Abuse-Deterrent Formulations.* Journal of Chromatography. A. (2023) 1705: 464186. https://doi.org/10.1016/j.chroma.2023.464186. PMID: 37453175.
- Smith W, Qu H, Zheng K, Baek J, Gao Y, Buehler P, Feng X, and Xu X. *Determining Critical Overlap Concentration of Polyethylene Oxide to Support Excipient Safety Assessment of Opioid Products.* International Journal of Pharmaceutics. (2023) 632: 122557. https://doi.org/10.1016/j.ijpharm.2022.122557. PMID: 36584863.

Posters

- Ibrahim A, Wang F, Hollenbeck G, Mostofa A, Sun W, Boyce H, Al Ghabeish M, and Hoag S. *Strategies for Correcting Peak Fronting of Oxycodone Hydrochloride, Naloxone Hydrochloride and Related Substances Observed in Reversed - Phase Liquid Chromatography.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.
- Smith W, Feng X, Qu H, Zheng K, and Xu X. *Determining Critical Overlap Concentration of Polyethylene Oxide (PEO) to Support Excipient Safety Assessment for Opioid Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2022. Boston, MA, Oct. 16, 2022.

OTHER GENERIC DRUG RESEARCH

Summary of FY 2023 Activities

In FY 2023, FDA continued to conduct and collaborate on various other research projects that supported the development and assessment of generic drugs. The outcomes of these diverse initiatives are reported below.

OUTCOMES

Articles

- Kumar V, Wang F, Hu M, Kluetz P, and Liang Z. *Landscape Analysis of Generic Availability for Oncologic Drugs.* Therapeutic Innovation & Regulatory Science. (2023) 57(6): 1279-1286. https://doi.org/10.1007/s43441-023-00562-w PMID: 37561261.

Posters

- Bae J, Tran T, Shon J, Kim M, and Li K. *Exploration of Food Conditions and Study Population in Bioequivalence Studies with Pharmacokinetic Endpoints for Oral Antineoplastic Drugs in Generic Drug Development.* Poster Presentation at the FDA Annual Student Scientific Research Day 2023. Virtual Meeting, Aug. 10, 2023.
- Park S, Nguyen D, Tran T, Li K, Kim M, and Shon J. *Exploration for Exclusion of Males of Reproductive Potential as a Bioequivalence Study Population in Product-Specific Guidances for Generic Drug Development.* Poster Presentation at the FDA Annual Student Scientific Research Day 2023. Virtual Meeting, Aug. 10, 2023.
- Xin E, Babiskin A, and Al Shoyaib A. *Ensuring Therapeutic Equivalence for Drugs to be Used in Pregnant Patients: A Literature Review and Modeling Exercise to Extrapolate BE Results from Non-pregnant Individuals to Pregnant Individuals.* Poster Presentation at the FDA Annual Student Scientific Research Day 2023. Virtual Meeting, Aug. 10, 2023.

Presentations

- Zhang L. *FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.
- Zhao L. *Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants.* Presentation at Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2023. Virtual Meeting, Sep. 14, 2023.

OUTCOME *continued*

- Zhao L. *Applying Modeling & Simulation to Support Drug Lifecycle Management.* Presentation at the AAPS Webinar. Virtual Meeting, Aug. 15, 2023.
- Bengtson K. *GDUFA III Redesigned Pre-Submission (PSUB) Meetings.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar - A Deep Dive: GDUFA III Scientific Meetings. Virtual Meeting, May 15, 2023.
- Sarago C. *GDUFA III Product-Specific Guidance (PSG) Teleconferences.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar - A Deep Dive: GDUFA III Scientific Meetings. Virtual Meeting, May 15, 2023.
- Zhang L. *Introduction to GDUFA III Meetings.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar - A Deep Dive: GDUFA III Scientific Meetings. Virtual Meeting, May 15, 2023.
- Zhang L, Tampal N, and Kim M. *Navigating the First ICH Generic Drug Draft Guideline "M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms".* Presentation at the Small Business and Industry Assistance (SBIA) Webinar - Navigating the First ICH Generic Drug Draft Guideline “M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms”. Virtual Meeting, May 02, 2023.
- Le C. *An Overview of the FDA Product-Specific Guidance (PSG) Program Under GDUFA III.* Presentation at the Small Business and Industry Assistance (SBIA) - Generic Drugs Forum (GDF) 2023: Celebrating 10 Years of the GDF. Virtual Meeting, Apr. 12, 2023.
- Nigam S. *Overview of Pre-ANDA Meetings Under GDUFA III.* Presentation at the Small Business and Industry Assistance (SBIA) - Generic Drugs Forum (GDF) 2023: Celebrating 10 Years of the GDF. Virtual Meeting, Apr. 12, 2023.
- Zhao L. *Introduction: Statistical Approaches to establishing Bioequivalence.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: A Deep Dive: FDA Draft Guidance on Statistical Approaches to Establishing Bioequivalence. Virtual Meeting, Mar. 14, 2023.
- Agarwal S. *Excipient Safety Assessment in Generic Drug Formulations: An Overview.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Ghosh A. *General Approach to the Safety Review of Pediatric Excipients.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Kim E. *Best Practices for Submitting Formulation Assessment Requests and Avoiding Information Requests: Tips for Submitting a Proposed Formulation Table.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Kim T. *Formulation Considerations for Selecting an Appropriate RLD or RS.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Li X. *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use - Guidance Implementation in Q1/Q2 Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.

OUTCOME *continued*

- Mannion M. *FDA Responses to Questions on Q1/Q2 Sameness.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Mannion M. *Requirements and Recommendations Related to Inactive Ingredients.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Phung T. *Pathways for Receiving FDA's Feedback on Formulations.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Raney S. *Generic Drug Science & Research Priorities for Fiscal Year (FY) 2023.* Presentation at the FDA Broad Agency Announcement Day 2022. Virtual Meeting, Dec. 06, 2022.
- Wang Y. *Considerations for the Qualitative Sameness Evaluation of a Proposed Generic Formulation.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Zuk S. *Inactive Ingredient Database (IID) Overview.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned. Virtual Meeting, Dec. 06, 2022.
- Lionberger R. *Complex Generics 2022 Update.* Presentation at the 2022 Association for Affordable Medicines (AAM): GRx + Biosims Conference. North Bethesda, MD, Nov. 09, 2022.
- Zhang L. *GDUFA III Teleconferences and Meetings.* Presentation at the Generics + Biosimilars Conference 2022. North Bethesda, MD, Nov. 07, 2022.
- Mousa Y. *Evaluation of Dissolution Profile Similarity for Bioequivalence Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Tsong Y. *Statistical Experience and Challenges in Assessing Similarity of Dissolution Profiles, Particle Size Distributions and API Sameness.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 28, 2022.
- Batchelor H. *Oral PBPK to Support BE Evaluation for Pediatric Drugs.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Virtual Meeting, Oct. 27, 2022.

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Lead Writers for Summary and Research Highlight

Andre O'Reilly Beringhs, PhD, ORS/OGD
Andrew Babiskin, PhD, ORS/OGD
Anna Wokovich, PhD, OPQR/OPQ
Bin Qin, PhD, ORS/OGD
Deyi Zhang, PhD, ORS/OGD
Eleftheria Tsakalozou, PhD, ORS/OGD
Diaa Shakleya, PhD, OPQR/OPQ
Fang Wu, PhD, ORS/OGD
Haiou Qu, PhD, OPQR/OPQ
Hye Lim Lim, PharmD, ORS/OGD
Ilan Geerlof-Vidavsky, PhD, OPQR/OPQ
Jayanti Das, PhD, OPQR/OPQ
Jingyue (Jan) Yang, PhD, OPQR/OPQ
Karen Li, PharmD, ORS/OGD
Katherine Feibus, MD, ORS/OGD
Kathryn Hartka, PharmaD, PhD, ORS/OGD
Khondoker Alam, PhD, ORS/OGD
Manar Al-Ghabeish, PhD, ORS/OGD
Megan Kelchen, PhD, ORS/OGD
Meng Hu, PhD, ORS/OGD
Ming-Liang Tan, PhD, ORS/OGD
Nahid Kamal, PhD, OPQR/OPQ
Nathan Reed, PhD, OPQR/OPQ
Nicholas Holtgrewe, PhD, OPQR/OPQ
Ping Ren, PhD, ORS/OGD
Priyanka Ghosh, PhD, ORS/OGD
Qiangnan Zhang, PharmD, ORS/OGD
Ross Walenga, PhD, ORS/OGD
Sam Raney, PhD, ORS/OGD
Susan Boc, PhD, ORS/OGD
Wei-Jhe Sun, PhD, ORS/OGD
Wenlei Jiang, PhD, ORS/OGD
William Smith, PhD, OPQR/OPQ
Yan Wang, PhD, ORS/OGD
Yang Yang, PhD, OPQR/OPQ
Yuging Gong, PhD, ORS/OGD

Contributing Reviewers

Adam Fisher, PhD, OQA/OPQ
Ahmed Zidan, PhD, OPQR/OPQ
Alicia Hoover, PhD, OPQR/OPQ
Andrew Clerman, MD, PhD, ORS/OGD
Barbara Kass, CS/OGD
Changning Guo, PhD, OPQR/OPQ
Connie Ruzicka, PhD, OPQR/OPQ
Darby Kozak, PhD, ORS/OGD
David Keire, PhD, OPQR/OPQ
Fang Wu, PhD, ORS/OGD
Geng (Michael) Tian, PhD, OPQR/OPQ
Heather Boyce, PhD, ORS/OGD
Iilun Murphy, MD, OGD
Janel Whitehart, OGDP/OGD
Jihong Shon, MD, PhD, ORS/OGD
Katherine Schreck, OGDP/OGD
Lanyan (Lucy) Fang, PhD, ORS/OGD
Lei Zhang, PhD, ORS/OGD
Liang Zhao, PhD, ORS/OGD
Lisa Bercu, JD, OGDP/OGD
Markham Luke, MD, PhD, ORS/OGD
Robert Lionberger, PhD, ORS/OGD
Ross Walenga, PhD, ORS/OGD
Sarah Rogstad, PhD, OPQR/OPQ
Susan Levine, JD, OGDP/OGD
Tawni Schwemer, OGD
Thomas O'Connor, PhD, OPQR/OPQ
Xiaoming Xu, PhD, OPQR/OPQ
Yi Zhang, PhD, ORS/OGD

Contributors to Data for Collaborations and Outcomes

Christina Hall, ORS/OGD
Eileen Lim, ORS/OGD
Jeny Shah, ORS/OGD
Prachi Verma, ORS/OGD
Rangeeta Kumari, OPQR/OPQ
Sarah Kim, ORS/OGD

Contributors to Report Designing and Editing

Colleen Dermody, CS/OGD
Heather Lilley, OEMS/OO
Jessie Floura, ORS/OGD
Sara Lomonaco, PhD, ORS/OGD