CENTER FOR DRUG EVALUATION AND RESEARCH

FY 2024

GDUFA SCIENCE AND RESEARCH REPORT

U.S. FOOD & DRUG ADMINISTRATION

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INTRODUCTION

What is the GDUFA Science & Research Program?

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 pharmaceutical equivalence, bioequivalence (BE), and quality of generic alternatives.

How Does the GDUFA Science & Research Program Protect and Promote Public Health?

In general, 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.

Who are the Collaborators that Advance the GDUFA Science & Research Program?

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, but are not limited to, 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.[1]

What Are the Focus Areas of the GDUFA Science & Research Program?

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) 2024.

How is the FY 2024 GDUFA Science & Research Report Organized?

This FY 2024 GDUFA Science and Research report describes active research projects and outcomes in eight chapters corresponding to those eight priority areas for FY 2024, with a ninth chapter that reports on additional generic drug science and research. 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. Information in each scientific specialty area includes:

[1] As part of FDA's reorganization to create a unified Human Foods Program and to restructure its field operations, starting October 1, 2024, the office formerly known as the Office of Regulatory Affairs became the Office of Inspections and Investigations. For more information please see: https://www.fda.gov/about-fda/fda-organization/fda-modernization-efforts-establishing-unified-human-foods-program-new-model-field-operations-and

- A descriptive summary of research ongoing or completed during FY 2024, typically highlighting one research project
- Lists of new, ongoing, and completed grants and contracts for research
- A list of active FDA research projects
- Lists of research outcomes, including general guidances for industry and product-specific guidances (PSGs), 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).

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. This program 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. GDUFA research outcomes help FDA establish efficient new approaches that can be used by 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 2024, FDA awarded seven new grants and six new contracts during FY 2024 (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 state-of-the-art analytical procedures to characterize product quality and performance. These new or modernized analytical procedures provide manufacturers more efficient approaches for developing generic products. They also help FDA to assess the bioequivalence (BE) and quality of complex generic products more efficiently. 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. In addition, to facilitate the adoption of these novel approaches, FDA routinely publishes peer reviewed scientific literature providing examples of improved techniques for product characterization.

In FY 2024, FDA issued 206 new and revised PSGs (109 of which were for complex products), which provided recommendations for developing generic drugs and generating the evidence to support ANDA approval. This included 147 PSGs for products with no approved ANDAs at the time of PSG publication (including 80 PSGs for complex products). Approximately 31 PSGs provided a more efficient BE approach (including 20 PSGs for complex drug products), and many were supported by the outcomes of GDUFA research. These new and revised PSGs 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.

In addition to informing FDA guidances, GDUFA research also allows FDA to evaluate whether proposed BE approaches in pre-ANDA product development meetings are likely to be suitable. In FY 2024, FDA conducted 72 such product development meetings. 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 and prepares FDA to assess ANDAs once submitted.

For example, on July 1, 2024, FDA approved the first generic bupivacaine liposome injectable suspension, 1.3% (referencing Exparel®) which provides post-surgical non-opioid pain management. This first generic approval is a notable achievement because of how scientifically challenging it was to develop a BE approach for this product, which uses a complex liposomal dosage form. GDUFA-funded research helped to develop recommendations for the physicochemical and structural (Q3) characterization of this product and to relate in vitro product characterizations to in vivo performance. The GDUFA science and research program supported the development of a PSG for this product, and prepared FDA to assess the adequacy of information ultimately submitted in the ANDA for this approved generic product.

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. The program also facilitates continued engagement through pre-ANDA meetings during product development to discuss how insights from GDUFA research can be leveraged. Following ANDA submission, the science and research knowledge gained in the program 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 2024.

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 developers implement scientific insights from GDUFA research outcomes in a manner consistent with FDA's regulatory expectations, the CRCG hosted four scientific workshops during FY 2024. 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 2024 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 major GDUFA science and research priority area during GDUFA III[1] is to develop methods for generics to address impurities such as nitrosamines. The advancement of research in this area focuses on i) 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)), ii) evaluating the risk of human exposure to these impurities, and iii) developing methods for abbreviated new drug application (ANDA) applicants to efficiently address the potential risks. Research during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

Summary of FY 2024 Activities

During FY 2024, FDA's research related to N-nitrosamine impurities in drug products involved two external research Grants and several internal research projects. These works focused on assessing the risk of forming N-nitrosamines including nitrosamine drug substance-related impurities (NDSRIs), developing analytical methods for the quantitation of impurities, understanding 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 (BE) of generic products.

The presence of mutagenic and carcinogenic N-nitrosamine impurities in medicinal products poses a potential safety risk. While incorporating antioxidants in formulations is a potential risk mitigation strategy, concerns arise regarding their potential interference with passive intestinal permeability and/or active transport of drug by inhibiting intestinal drug transporters. The objective of the external research Grant (as part of a financial assistance award U18FD007054) with the University of Maryland was to assess the effect of antioxidants on Biopharmaceutics Classification System (BCS) Class III drug permeability using MDCK-II cell monolayers. The antioxidants in the studies included eight acids [ascorbic, ferulic, fumaric, caffeic, malic, citric, 4-aminobenzoic acid (PABA), and L-cysteine], propyl gallate and maltol. Antioxidant effects were assessed for four BCS Class III drugs containing amines at high-risk of forming NDSRIs: ranitidine hydrochloride, cimetidine, acyclovir, and pirenzepine. The results indicated that at least 10 mg (or 25 mg in some cases) of the tested antioxidant(s) can be incorporated in drug formulations to potentially prevent formation of NDSRIs while not affecting the passive intestinal permeability of low permeable drugs[2]. The external research Grant (U01FD005978) 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 30 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). After evaluating the inhibition potency and estimated concentrations of the two most potent antioxidants, the findings suggest that commonly used antioxidants in oral formulations are unlikely to impede intestinal transporters in clinical studies[3].

As part of an internal FDA research project, scientists have been developing analytical methods using liquid chromatography coupled with high-resolution mass spectrometry (LC–HRMS) techniques for NDSRI analysis in various drug products. Three of the analytical methods developed at FDA were included in the Recommended Acceptable Intake Limits for NDSRI guidance[4], serving as examples for confirmatory testing methods of NDSRIs. An FDA publication[5] described NDSRI analytical methods in a case study to explore the establishment of conditions for the life cycle of analytical procedures. In addition, the developed methods have also been applied to analyze various drug products for NDSRIs, providing insights into the extent of NDSRI contamination, and the findings have informed evidence-based regulatory decisions. Recent findings have revealed that NDSRI contamination can also originate from the related substance (or fragment) of active pharmaceutical

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[2] Chiang Yu Y, Lu D, Rege B, and Polli J. *Lack of Effect of Antioxidants on Biopharmaceutics Classification System (BCS) Class III Drug Permeability.* Journal of Pharmaceutical Sciences. (2024) 113(8): 2215 – 2222. https://doi.org/10.1016/j.xphs.2024.03.005. PMID: 38484875.

[3] Kulkarni CP, Yang J, Koleske ML, Lara G, Alam K, Raw A, Rege B, Zhao L, Lu D, Zhang L, Yu LX, Lionberger R, Giacomini KM, Kroetz DL, and Yee SW. *Effect of Antioxidants in Medicinal Products on Intestinal Drug Transporters.* Pharmaceutics. (2024) 10(16): 647. https://doi.org/10.3390/pharmaceutics16050647. PMID: 38794309.

[4] FDA Guidance for Industry. *Recommended Acceptable Intake (AI) Limits, Implementation Timelines, Emerging Scientific and Technical Issues, and Testing Methods.* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits#testing.

[5] Zhang J, Raghavachari R, Kirkpatrick D, Keire D, Xu X, and Faustino P. *Analytical Procedure Development and Proposed Established Conditions: A Case Study of a Mass Spectrometry Based NDSRI Analytical Procedure.* Journal of Pharmaceutical Sciences. (2024) S0022-3549(24)00266-1. https://doi.org/10.1016/j.xphs.2024.07.022. PMID: 39111548.

ingredients (API). Scientists at FDA analyzed various drug products for this group of NDSRIs and their API fragment precursor. These results helped in estimating the occurrence of API fragment NDSRIs and the likelihood of conversion from the precursors, and thus, provided valuable information in developing regulatory strategies to address this emerging challenge.

In a separate research project, FDA scientists investigated the underlying mechanism of N-nitrosodimethylamine (NDMA) formation in metformin drug products. A comparison of drug product formulations with NDMA formation suggested that a correlation might exist between NDMA formation and the amount of hypromellose excipient in the formulation. This could occur from a possible nitrosating agent in hypromellose reacting with residual dimethylamine (DMA) that was used in the synthesis of the metformin API.

FDA scientists also continued research to explore mitigation strategies to decrease the formation of nitrosamines in drug products. The results from the initial mitigation research project using bumetanide as a first model drug was published as a peer reviewed research paper[6] and referenced in the updated nitrosamine FDA guidance for industry[7] to recommend the use of antioxidants and pH modifiers in mitigating nitrosamine formation in drug products. The scientists from FDA further investigated the effectiveness of different antioxidants and pH modifiers in tablet formulations, and of different manufacturing conditions, to mitigate the formation of NDSRIs, using other secondary amines as a model drug.

To assess the toxicological risk of nitrosamines, CDER scientists are collaborating with scientists at the National Center for Toxicological Research (NCTR) on research projects to determine the best methods for evaluating the mutagenicity of N-nitrosamine drug impurities. A study tested 12 small molecule N-nitrosamines and 17 NDSRIs using various combinations of bacterial tester strains, incubation times, and metabolic activation systems to determine methods that work best for detecting the mutagenicity of nitrosamine drug impurities in the Ames test[8,9]. Collaborative studies are also being conducted to develop in vitro and in vivo methods that can potentially be used to follow-up on and/or confirm Ames test mutagenicity findings for small nitrosamine drug impurities and NDSRIs. The in vitro mammalian cell studies utilize human cells possessing endogenous human metabolic activity (e.g., human lymphoblastoid TK6 cell lines expressing different cytochrome (CYP) P450 enzymes). The in vivo project uses transgenic (Big Blue) rats and measures mutation using the transgene as well as by error-corrected Next Generation Sequencing and assesses clastogenicity and aneugenicity using the liver micronucleus assay.

BE reassessment through clinical studies of reformulated drug products (e.g., by adding antioxidant) poses a risk to healthy subjects due to potential exposure to harmful impurities and adds time and resources to bring reformulated products to the market. To address this, the Office of Research and Standards (ORS) and the Office of Bioequivalence (OB) within the Office of Generic Drugs (OGD) are leading efforts in developing data analytics tools to speed up BCS evaluation to support an alternative BE approach. The BCS evaluation for nitrosamine-impacted drug products, offers a practical solution to managing risks based on BCS and addressing the safety concerns posed by nitrosamine impurities. Leveraging a BCS-based alternative BE approach for these drugs can help expedite the reformulation process and ensure the BE

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[6] Shakleya D, Asmelash B, Alayoubi A, Abrigo N, Mohammad A, Wang J, Zhang J, Yang J, Marzan TA, Li D, Shaklah M, Alsharif FM, Desai S, Faustino PJ, Ashraf M, O' Connor T, Vera M, Raw A, Sayeed VA, 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.

[7] FDA Guidance for Industry. *Control of Nitrosamine Impurities in Human Drugs.* Revision 2 (September 2024) https://www.fda.gov/media/141720/download.

[8] Li X, Le Y, Seo JE, Guo X, Li Y, Chen S, Mittelstaedt RA, Moore N, Guerrero S, Sims A, King ST, Atrakchi AH, McGovern TJ, Davis-Bruno KL, Keire DA, Elespuru RK, Heflich RH, and Mei N. *Revisiting the Mutagenicity and Genotoxicity of N-nitroso Propranolol in Bacterial and Human In Vitro Assays.* Regulatory Toxicology and Pharmacology: RTP. (2023) 141, 105410. https://doi.org/10.1016/j.yrtph.2023.105410. PMID: 37210026.

[9] FDA Guidance for Industry. *Recommended Safety Testing Methods for Nitrosamine Impurities* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits#safety.

of high quality safe and effective generics to patients who are dependent on these drug products. Further research and discussions are ongoing to formalize the BCS information and expand the BCS-based framework for nitrosamine-impacted drug products.

During FY 2024, based in part on GDUFA-funded research, the FDA revised its guidance titled "FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs"[10]. This revised guidance describes two general structural classes of nitrosamine impurities: small-molecule nitrosamine impurities and NDSRIs. The guidance discusses the potential root causes, detection of nitrosamine impurities, and recommendations for risk assessments, testing, and implementation of controls and other appropriate strategies to prevent or reduce the presence of nitrosamine impurities in APIs and drug products. Recommendations for an alternative BE approach, if manufacturers and applicants decide to reformulate their products to mitigate nitrosamine impurities, are also provided in the guidance. This alternative BE approach was supported by FDA sponsored research studies.

[10] FDA Guidance for Industry. *Control of Nitrosamine Impurities in Human Drugs.* Revision 2 (September 2024) https://www.fda.gov/media/141720/download.

RESEARCH HIGHLIGHT

In vitro mutation tests are critical for evaluating the risks associated with nitrosamine impurities. The Ames test has traditionally been used to provide evidence of mutagenicity for these impurities. However, the sensitivity of the standard Ames test may be limited for detecting the mutagenicity of certain nitrosamines, partly due to the reliance on exogenous metabolic activation systems (e.g., liver S9) and species differences, which can affect the accuracy of the mutagenicity assessment of nitrosamine impurities. Therefore, follow-up in vitro mammalian cell mutation assays and in vivo mutation assays are necessary to confirm the findings of the Ames test.

The scientists at NCTR developed a human liver-derived metabolically competent HepaRG cell culture system for in vitro genotoxicity assays. Based on the successful evaluation of the genotoxicity of eight small molecule nitrosamine impurities using both 2D and 3D HepaRG models, the NCTR scientists expanded their research to include mutagenicity endpoints in the HepaRG models using error-corrected next-generation sequencing (ecNGS). Both HepaRG 2D cells and 3D spheroids were exposed to NDMA for 72 hours, followed by an additional incubation to facilitate the fixation of induced mutations. Mutations induced by NDMA were measured using two high-accuracy ecNGS technologies, Duplex Sequencing (DS) and High-Fidelity (HiFi) Sequencing. The 72-hour treatment with NDMA resulted in concentration-dependent increases in cytotoxicity, DNA damage, micronucleus (MN) formation, and mutation frequency in both HepaRG models, with significantly greater responses observed in 3D spheroids compared to 2D cells. The sequencing results revealed that NDMA predominantly induced A:T→G:C transitions, along with a lower frequency of G:C→A:T transitions in both HepaRG models, with much higher mutation frequencies observed in 3D spheroids compared to 2D cells (Figure 1). This indicates that HepaRG models can effectively be used for mutagenesis assessment using ecNGS and 3D spheroids provide more sensitive results in detecting NDMA-induced genotoxicity and mutagenicity than 2D cells, likely due to the higher levels of cytochrome P450 (CYP) gene expression and enzyme activities. Overall, this study introduced a novel strategy for detecting nitrosamine-induced mutations in differentiated HepaRG cells using ecNGS. This in vitro mammalian cell mutation assay can provide a human-based, metabolically competent platform for assessing the mutagenicity of other small nitrosamines and NDSRIs. Additionally, ecNGS data using the 3D HepaRG spheroid model may offer a better prediction for human in vivo responses, potentially minimizing unnecessary animal studies.

RESEARCH HIGHLIGHT *continued*

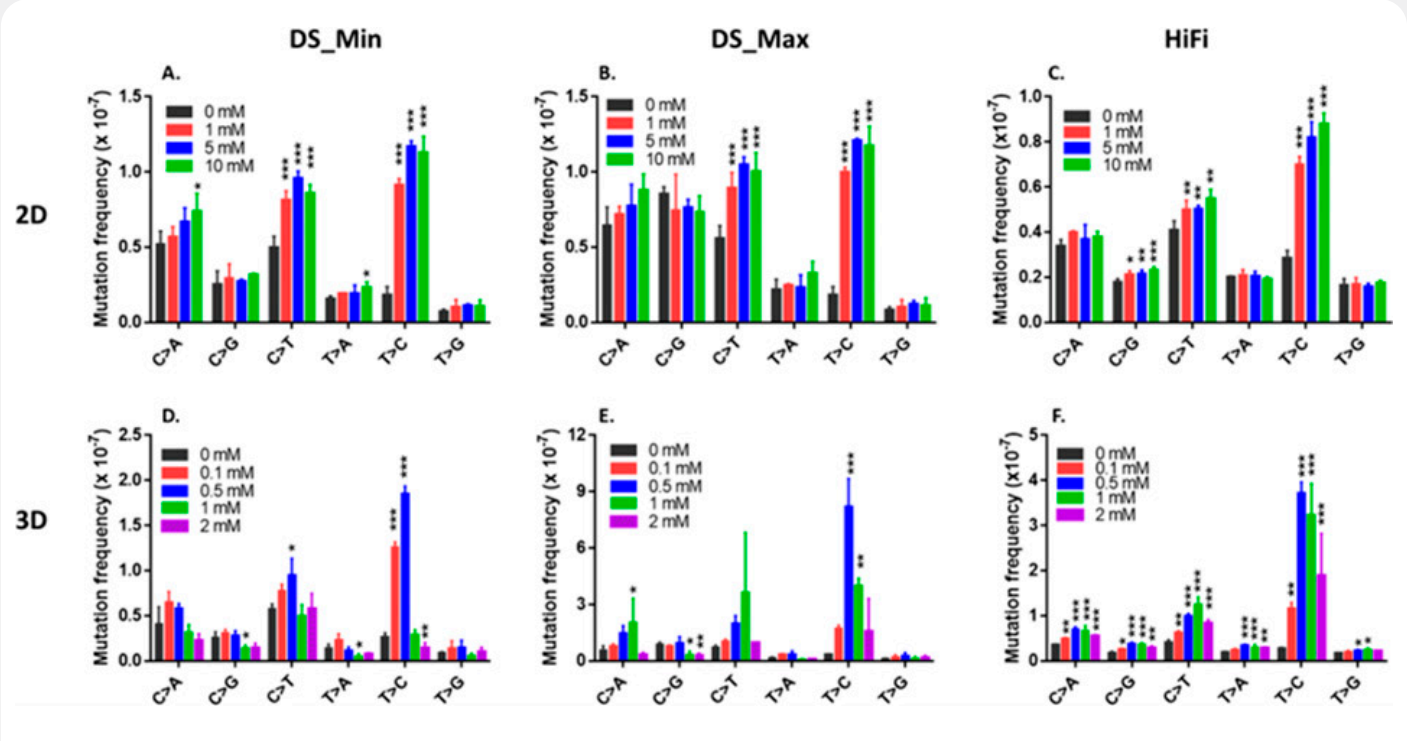

Figure 1. Mutation frequencies of individual base substitution in NDMA-treated 2D and 3D HepaRG cultures. The data are expressed as the mean ± standard deviation (SD) (n = 3). Significant difference was determined by pairwise comparisons between treatment groups and the controls using the glht algorithm with p values adjusted by the Bonferroni correction in RStudio (*p < 0.05, **p < 0.01, and ***p < 0.001 vs. vehicle control). DS, duplex sequencing; HiFi, High-Fidelity sequencing; Min, the minimum mutation counting method; Max, the maximum mutation counting method[11].

[11] Seo J, Le Y, Revollo J, Miranda-Colon J, Xu H, Mckinzie P, Mei N, Chen T, Heflich R, Zhou T, Robinson T, Bonzo J, and Guo X. *Evaluating the Mutagenicity of N-Nitrosodimethylamine in 2D and 3D HepaRG Cell Cultures Using Error-Corrected Next Generation Sequencing.* Archives of Toxicology. (2024) 98(6): 1919 – 1935. https://doi.org/10.1007/s00204-024-03731-4. PMID: 38584193.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Grant (U18FD007054) *Center for Research on Complex Generics* with James Polli, Anna A Shenderova Schwendeman at University of Maryland Baltimore

Completed Grants and Contracts

- Grant (U01FD005978) *Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters* with Dr. Sook Wah Yee at University of California San Francisco

Active FDA Research

- *Assessing the Occurrence and Extension of NDSRI Formed from the Nitrosation of API Related Substances ('Fragment' of API)*
- *Assessing the Prevalence of NDSRI Contamination in Pharmaceutical Products and Gaining Insights into the Contributing Factors for the Contamination: Analytical Method Development and NDSRIs Screening in Various Drug Products*
- *Developing Consensus Approach for Evaluating the Mutagenicity and Cancer Risk of Nitrosamine Drug Impurities and Nitrosated Drug-Substance-Related Impurities (NDSRIs), Using In Vitro Mutagenicity Assays*
- *Endogenous Nitrosamine: Application of Tiny-TIM System as an In-Vitro Tool to Investigate the Nitrosamine Formation under Physiologically Relevant Conditions*
- *Establishment of an In Vivo Mutation Test Pipeline for Evaluating the Mutagenicity of N-Nitrosamines*
- *Evaluating the Strategy of Mitigating NDSRI Formation Through Manufacturing Process (Solid Dispersion) Using Selected Model Drug*
- *IC-MS Method Development to Improve Method Detectability of Nitrite/Nitrate in Drug Product*
- *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, Bumetanide, and Other Model Drug Products*
- *Mutagenicity of NDSRIs in Bacterial and Mammalian Cell Genotoxicity Assays Optimized for Evaluating the Mutagenicity of N-Nitrosamines*
- *Roles of Excipients in the Formation of NDMA in Metformin Drug Products*
- *Managing Bioequivalence Risks for Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances*

OUTCOMES

General Guidance

- FDA Guidance for Industry. *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities.* Update on Recommended Testing Methods for Confirmatory Testing of Certain NDSRIs (February 23, 2024):
  - *Liquid Chromatography-High Resolution Mass Spectrometry (LC-ESI-HRMS) Method for the Determination of N-Nitroso-Bumetanide in Bumetanide Drug Products and Drug Substance* Link to Posting
  - *Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of N-Nitroso-Propranolol in Propranolol Hydrochloride Oral Solution* Link to Posting
  - *Liquid Chromatography-High Resolution Mass Spectrometry (LC-ESI-HRMS) Method for the Determination of Varenicline Nitrosamine Drug Substance-Related Impurity (NDSRI) in Varenicline Drug Product and Drug Substance* Link to Posting
- FDA Guidance for Industry: *Control of Nitrosamine Impurities in Human Drugs.* Revision 2. September 2024. Link to Posting

Articles

- Chiang Yu Y, Lu D, Rege B, and Polli J. *Lack of Effect of Antioxidants on Biopharmaceutics Classification System (BCS) Class III Drug Permeability.* Journal of Pharmaceutical Sciences. (2024) 113(8): 2215 – 2222. https://doi.org/10.1016/j.xphs.2024.03.005. PMID: 38484875.
- Heflich R, Bishop M, Mittelstaedt R, Yan J, Guerrero S, Sims A, Mitchell K, Moore N, Li X, Mei N, Elespuru R, King S, Keire D, Kruhlak N, Dorsam R, Raw A, Davis Bruno K, Mcgovern T, and Atrakchi A. *Optimizing the Detection of N-Nitrosamine Mutagenicity in the Ames Test.* Regulatory Toxicology and Pharmacology: RTP. (2024) 153: 105709. https://doi.org/10.1016/j.yrtph.2024.105709. PMID: 39343352.
- Kulkarni CP, Yang J, Koleske ML, Lara G, Alam K, Raw A, Rege B, Zhao L, Lu D, Zhang L, Yu LX, Lionberger R, Giacomini KM, Kroetz DL, and Yee SW. *Effect of Antioxidants in Medicinal Products on Intestinal Drug Transporters.* Pharmaceutics. (2024) 10(16): 647. https://doi.org/10.3390/pharmaceutics16050647. PMID: 38794309.
- Lu D, Rege B, Rawlings K, Yang J, Alam K, Bode C, Zhao L, Faustino P, Wu F, Shakleya D, Nickum E, Li B, Wang R, Stier E, Miezeiewski B, Patel R, Boam A, Lionberger R, Keire D, and Yu L. *Antioxidants had No Effects on the In-Vitro Permeability of BCS III Model Drug Substances.* Journal of Pharmaceutical Sciences. (2024) 113(9): 2708 – 2714. https://doi.org/10.1016/j.xphs.2024.05.033. PMID: 38862090.
- Seo J, Yu J, Xu H, Li X, Atrakchi A, Mcgovern T, Bruno K, Mei N, Heflich R, and Guo X. *Genotoxicity Assessment of Eight Nitrosamines Using 2D and 3D HepaRG Cell Models.* Archives of Toxicology. (2023) 97(10): 2785 – 2798. https://doi.org/10.1007/s00204-023-03560-x. PMID: 37486449.
- Seo J, Le Y, Revollo J, Miranda-Colon J, Xu H, Mckinzie P, Mei N, Chen T, Heflich R, Zhou T, Robinson T, Bonzo J, and Guo X. *Evaluating the Mutagenicity of N-Nitrosodimethylamine in 2D and 3D HepaRG Cell Cultures Using Error-Corrected Next Generation Sequencing.* Archives of Toxicology. (2024) 98(6): 1919 – 1935. https://doi.org/10.1007/s00204-024-03731-4. PMID: 38584193.

OUTCOMES *continued*

- Zhang J, Raghavachari R, Kirkpatrick D, Keire D, Xu X, and Faustino P. Analytical Procedure Development and Proposed Established Conditions: A Case Study of a Mass Spectrometry Based NDSRI Analytical Procedure. Journal of Pharmaceutical Sciences. (2024). S0022-3549(24)00266-1 https://doi.org/10.1016/j.xphs.2024.07.022. PMID: 39111548.

Posters

- Dobrovolsky V, Pearce M, Chen T, and Yan J. *RBC Pig-a Mutant Frequency in Transgenic Rats Treated with Small-Molecule N-Nitrosamines.* Poster Presentation at the 55th Annual Meeting of the Environmental Mutagenesis and Genomics Society (EMGS). Palm Springs, CA, Sep. 08, 2024.
- Li X, Le Y, Atrakchi AH, McGovern TJ, Keire DA, Davis Bruno KL, Heflich RH, and Mei N. *Mutagenicity and Genotoxicity of Twelve Nitrosamine Drug Substance-Related Impurities in Human TK6 Cells: Correlation with Enhanced Ames Test.* Poster Presentation at the 63rd Annual Meeting of Society of Toxicology (SOT). Salt Lake City, UT, Mar. 11, 2024.
- Mokbel A, Mohammad A, Abrigo N, Faustino P, and Shakleya D. *The Development and Validation of Ion Chromatography Methods for the Evaluation of Nitrosamine Precursors (nitrite, nitrate, and dimethylamine) in Pharmaceutical Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Shakleya D, Mohammad A, Keire D, and Raw A. *Mitigation Strategies to Reduce the Risk of the N-nitrosamine Impurity in Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Chen T, Yan J, Mitchell K, Pearce M, Atrakchi A, Heflich R, and Dobrovolsky V. *Comparison of Duplex Sequencing, Transgenic cII Mutation Assay, and Pig-a assay for Evaluation of Mutagenicity of N-Nitrosodiethylamine in Big Blue Rats.* Presentation at the 55th Annual Meeting of the Environmental Mutagenesis and Genomics Society (EMGS). Palm Springs, CA, Sep. 08, 2024.
- Shakleya D. *Nitrosamine Mitigation in Metformin: NDMA Impurity Formation and its Inhibition in Metformin ER Tablets.* Presentation at the American Chemical Society (ACS) Fall 2024. Hybrid Meeting, Denver, CO, Aug. 19, 2024.
- Yang J. *Navigating the Complexity of LC-MS Method Development for NDSRI Analysis - Case Studies.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2024 Summer Scientific Forum. Kansas City, MO, Jul. 23, 2024.
- Li X. *N-Nitrosamine Drug Impurity Research at FDA/NCTR: Assessing the Mutagenicity of N-Nitrosamines and NDSRIs.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, May 20, 2024.
- Wu F. *Physiologically Based Pharmacokinetic Absorption Modeling to Support BCS Based Waiver of In Vivo BE Studies.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, May 20, 2024.
- Zhang J. *Established Conditions in Analytical Procedure: Overview, Regulatory Examples and an FDA Laboratory Study.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2024. Bethesda, MD, May 03, 2024.

OUTCOMES *continued*

- Guo X. *Application of 3D HepaRG Spheroids in Genotoxicity Testing.* Presentation at the Annual Genetic Toxicology Association (GAT) Meeting. Newark, DE, Apr. 12, 2024
- Mei N. *In Vitro Genotoxicity Evaluation of Nitrosamine Drug Impurities in Bacterial and Human Cell Assays.* Presentation at the 34th Annual Meeting of Germany Society for Environmental Mutation Research (GUM). Kaiserslautern, Germany, Mar. 20, 2024.
- Heflich RH. *Classifying N-Nitrosamine Drug Impurity Carcinogenic Potency for Risk Assessment.* Presentation at the 63rd Annual Meeting of Society of Toxicology (SOT). Salt Lake City, UT, Mar. 12, 2024.
- Zhang J. *Nitrosamine Analysis Roundtable Discussion.* Presentation at the International Society for Pharmaceutical Engineering (ISPE) QC/ Analytical Community of Practice Webinar. Virtual Meeting, Nov. 09, 2023.
- Shakleya D. *Mitigation Strategies to Reduce the Risk of the N-nitrosamine Impurity in Drug Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, Florida, Oct. 22, 2023.
- Zhao L. *Bioequivalence Risk Assessment for Nitrosamine Reducing Reformulations.* Presentation at the 2023 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 04, 2023.

CHAPTER 2: COMPLEX APIs

A major GDUFA science and research priority area during GDUFA III[1] is to enhance the efficiency of equivalence approaches for complex active pharmaceutical ingredients (APIs), such as peptides and oligonucleotides. 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 during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

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[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

Summary of FY 2024 Activities

In FY 2024, research efforts continued with the development of modern state-of-the-art analytical methods to characterize complex active ingredient products with diverse structures and complex impurities resulting from process differences.

The orphan drug pentosan polysulfate sodium (PPS) is a semi-synthetic polysulfated xylan sourced from the beechwood tree. PPS is mainly composed of a sulfated xylose chain with branched O-methyl-glucuronate (MGA). The inter-lot variation analysis by quantitative nuclear magnetic resonance (qNMR) showed that process-related chemical modifications of aldehyde and pyridine exhibited greater variability than those of MGA or acetylation, indicating consistency in the botanical raw material source but significant variation in process-introduced chemical adducts. This research demonstrated that qNMR is a sensitive tool for measuring fine chemical differences between drug product lots and intrinsic NMR method variation is less than the lot-to-lot variability.

Glatiramer Acetate (GA) is a peptide copolymer with an average molecular weight of 5-9 kDa. A new application of microchip capillary zone electrophoresis coupled to mass spectrometry (CZE-MS) separates peptides based on their electrophoretic mobility, offering an orthogonal separation approach to complement conventional liquid chromatography (LC)-MS. The CZE-MS method was used to analyze enzyme-digested GA peptides and a targeted analysis was performed. The results demonstrated that CZE-MS could be an orthogonal characterization approach for the analysis of digested GA samples.

For recombinantly expressed peptide drugs, the presence of host-cell protein (HCP) impurities has been associated with immunogenicity risks and are a potential concern. An unbiased LC-MS/MS method for the identification and comparative quantification of HCPs in teriparatide drug products was developed and validated in FDA laboratories. The lot-to-lot variability in HCP profiles for approved recombinant teriparatide products was measured, which can now serve as a reference for future follow-on products, or even for the same product after process changes.

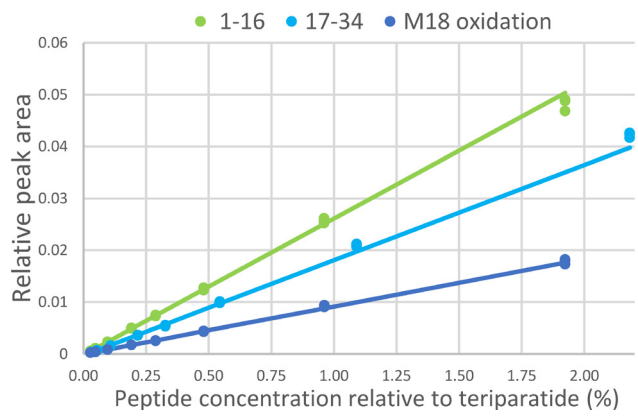
On November 16, 2023, FDA approved the first generic teriparatide product, which helps millions of patients in the United States who suffer from osteoporosis. This is a peptide drug with potential immunogenicity risks, thus it is recommended that proposed generics demonstrate and justify that their immunogenicity risk is not greater than that of the reference listed drug (RLD). To do this, one would need to conduct an impurity comparability study and address any differences through in silico and/or in vitro assays to assess these differences. Therefore, a GDUFA research priority was established to enhance the efficiency of equivalence approaches used for complex APIs such as peptides. The resulting internal and external research collaborations over multiple years systematically advanced scientific insights and improved assays to assess the immunogenicity risks for complex peptide products. One such example of research on teriparatide is described in the **Research Highlight** below.

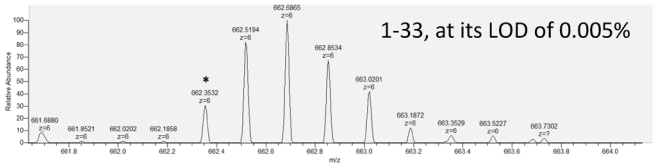
Chemical modifications introduced to improve the drug stability, efficacy and/or safety of synthetic oligonucleotide therapeutics (ONTs) have resulted in molecular complexity, leading to analytical and regulatory challenges for new modality and generic ONTs. High resolution mass spectrometry (HRMS) demonstrates an enhanced analytical capability for decoding the complexity in ONTs, particularly the in-depth assessments of complex ONT impurities. One example is the use of isotopic peak distribution enabled by HRMS to unravel the coeluting isobaric impurities that were previously unresolved by conventional LC-MS analysis. FDA continues to work with external collaborators to develop analytical methods to study oligonucleotide drugs, which includes supporting research on the diastereomeric compositions analysis of phosphorothioate oligonucleotide inotersen (U01FD007651) and analysis of contribution of each diastereomer to the overall biological activity of siRNA inclisiran (U01FD008322) at the University of Maryland, Baltimore.

RESEARCH HIGHLIGHT

Enabled by advances in instrumentation, FDA has begun to receive generic applications for peptide drugs that use LC-HRMS methods for quantification of peptide impurities. The sensitivity and specificity of HRMS compared to LC-UV-based detection make it an attractive analytical method for this purpose, especially given the complex impurity profile of peptide and protein drugs. Given these factors and considering the rising number of such drugs in the development pipeline, the use of these methods in generic applications is expected to continue rising.

To best position the FDA to review data acquired using such cutting-edge methods, an LC-HRMS-based method was developed and validated for quantifying six peptide-related impurities in teriparatide via internal FDA research. Teriparatide, a 34-amino acid peptide, is the API of the RLD FORTEO (Eli Lilly) and generic versions. External calibration curves were constructed with impurity standards of each peptide (Figure 1). The method displayed good specificity, sensitivity, linearity, accuracy, repeatability, intermediate precision, and robustness. The lower limits of quantification were ~0.08-0.14 ng each peptide loaded on the column (equivalent to 0.02% or 0.03% of teriparatide with a column load of 0.5 ug, below the regulatory reporting threshold of 0.10%). It was found that quantification using three isotopic peaks per peptide did not provide a significant benefit over quantification with one isotopic peak. The method was validated successfully without the costly and impractical inclusion of a stable isotope-labeled internal standard of each impurity. Unlike with LC-UV-based detection methods, daily verification of quantification accuracy is important given the complexity and potential day-to-day variability of HRMS instruments. In this method, a limited verification from selected data points across the method's range was incorporated into the daily system suitability check. An alternative approach using a daily regeneration of a minimal (2- or 3-point) calibration curve, was found to be a potentially viable option under certain circumstances.





Peptide	Accuracy (average % recovery ± margin of error at 95% confidence interval, n=4 per concentration level)		
	LOQ	Mid	High
1-16	92 ± 1	93 ± 2	90 ± 1
17-34	103 ± 1	91 ± 1	98 ± 1
1-30	99 ± 1	91 ± 2	102 ± 1
1-33	98 ± 2	90 ± 1	95 ± 2
M18 oxidation	91 ± 2	92 ± 3	98 ± 1
M8, M18 oxidation	102 ± 1	90 ± 1	96 ± 1

Figure 1. The top panel shows the linearity curves obtained over the range of 0.03-2% for three of the six peptide impurities in this study. The bottom panel shows the MS spectrum of the 1-33 peptide impurity at its limit of detection (LOD) of 0.005% (asterisk indicates monoisotopic peak detected), and the accuracy results obtained for all six peptide impurities.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008322) *Comprehensive Assessment of the Diastereomer Composition of LEQVIO (Inclisiran) to Determine how Chemical Synthesis Impacts Biological Activity* with Jace W Jones at University of Maryland Baltimore
- Contract (75F40124C00094) *Developing Universal Control Peptides for T Cell Assays Supporting Immunogenicity Assessments for Regulatory Filings* with Katie Edwards at CUBRC, Inc

Continuing Grants and Contracts

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

Active FDA Research

- *Assessing Feasibility of In Vitro Immunogenicity Assays for Newly Approved Peptide Products*
- *Compare Peptide Structures in Different Formulation*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Higher Order Structure Analysis by NMR*

OUTCOMES

Product-Specific Guidances

There were eight new PSGs published in FY 2024 related to *Complex API* products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Inclisiran Sodium Solution.* (Nov. 21, 2023) Link to Posting
- *New Draft Guidance for Heparin Sodium; Taurolidine Solution.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Liraglutide Solution.* (May 16, 2024) Link to Posting
- *New Draft Guidance for Nedosiran Sodium Solution.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Pegcetacoplan Solution* (NDA 217171). (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Pegcetacoplan Solution* (NDA 215014). (May 16, 2024) Link to Posting
- *New Draft Guidance for Teriparatide Solution.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Tofersen Solution.* (Aug. 28, 2024) Link to Posting

OUTCOMES *continued*

Articles

- Abdullah A, Sommers C, Rodriguez J, Zhang D, Kozak D, Hawes J, Sapru M, and Yang K. *Decoding Complexity in Synthetic Oligonucleotides: Unraveling Coeluting Isobaric Impurity Ions by High Resolution Mass Spectrometry.* Analytical Chemistry. (2024) 96(2): 904 - 909. https://doi.org/10.1021/acs.analchem.3c05016. PMID: 38158374

- Gong Y, Barretto F, Tsong Y, Mousa Y, Ren K, Kozak D, Shen M, Hu M, and Zhao L. *Development of Quantitative Comparative Approaches to Support Complex Generic Drug Development.* The AAPS Journal. (2024) 26: 15. https://doi.org/10.1208/s12248-024-00885-y. PMID: 38267593.

- Menke A, Chen F, and Chen K. *Multinuclear $^{1}H/^{13}C/^{15}N$ Chemical Shift Assignment of Therapeutic Octreotide Acetate Performed at Natural Abundance.* Magnetic Resonance in Chemistry: MRC. (2024) 62(7): 486 - 496. https://doi.org/10.1002/mrc.5436. PMID: 38351244.

- Roberts B, Mattei A, Howard K, Weaver J, Liu H, Lelias S, Martin W, Verthelyi D, Pang E, Edwards K, and De Groot A. *Assessing the Immunogenicity Risk of Salmon Calcitonin Peptide Impurities Using In Silico and In Vitro Methods.* Frontiers in Pharmacology. (2024) 15: 1363139. https://doi.org/10.3389/fphar.2024.1363139. PMID: 39185315.

Posters

- Lee J, Holley C, Dobrovolskaia M, and Pang E. *Innate Immune Response Modulating Impurities Assay for Assessing Synthetic Semaglutide and Liraglutide.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.

- Dieke N, Shipman J, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *High-resolution Ion Mobility Mass Spectrometry (HRIM MS) Empowers Diastereomer Resolution in Synthetic Phosphorothioated Oligonucleotides.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 72nd Conference on Mass Spectrometry and Allied Topics. Anaheim, CA, Jun. 06, 2024.

- Islam M, Abdullah A, Sommers C, Rodriguez J, Zhang D, Kozak D, and Yang K. *A Validated HILIC-HRMS Method for Quantitative Analysis of Synthetic Oligonucleotides.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 72nd Conference on Mass Spectrometry and Allied Topics. Anaheim, CA, Jun. 06, 2024.

- Thawng C, Sommers C, Pang E, Keire D, and Zhu H. *A Spectra Library Assisted Workflow for Host Cell Protein Detection and Quantitation in Recombinant Peptide Drug Products by CapLC-HRMS/MS.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 72nd Conference on Mass Spectrometry and Allied Topics. Anaheim, CA, Jun. 05, 2024.

- Shipman J, Abdullah A, Sommers C, and Rodriguez J. *Rapid Comparative Analysis of Glatiramer Acetate Products with CZE-MS.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 72nd Conference on Mass Spectrometry and Allied Topics. Anaheim, CA, Jun. 04, 2024.

- Thawng C, Sommers C, Pang E, Keire D, and Zhu H. *Semi-Validation of the LC-MS/MS Method for Identification and Comparative Quantification of Host Cell Protein (HCP) Impurities in Teriparatide Drug Products.* Poster Presentation at the American Society for Mass Spectrometry (ASMS) - 72nd Conference on Mass Spectrometry and Allied Topics. Anaheim, CA, Jun. 02, 2024.

OUTCOMES *continued*

- Zhang D, Yang K, Liang L, Zhang L, and Kozak D. *FDA's Efforts in Facilitating Generic Oligonucleotide Drug Development.* Poster presentation at the TIDES USA: Oligonucleotide & Peptide Therapeutics. Boston, MA, May 15, 2024.
- Hawes J, Shi Q, Ren L, Schnackenberg L, and Yang K. *Toxicity of Three Antisense Oligonucleotide Drugs and Eighteen of their Impurities in Primary Human Hepatocytes.* Poster Presentation at the 44th Annual Meeting - American College of Toxicology (ACT). Orlando, FL, Nov. 13, 2023.
- Lee J, Holley C, Dobrovolskaia M, and Pang E. *Innate Immune Response Modulating Impurities Assay for Assessing Synthetic Semaglutide and Liraglutide.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Zhang T, Shamim M, Tower C, Sapkota R, Munson E, Liu D, Chen K, Jiang W, Wang Y, and Zhang D. *Characterization of Intravenous Iron Supplements: Injectafer.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Liang, L. *Emerging Generic Oligonucleotides - Challenges and Progress.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 25, 2024.
- Pang E. *In Vitro, In Silico Immunogenicity Assessments (IVISIA) of Generic Peptide Drug Products.* Presentation at the USP Workshop on Peptide and Oligonucleotide Therapeutics: Regulations and Quality Standards. Rockville, MD, Apr. 10, 2024.
- Yang K. *LC-HRMS-based Multi-attribute Method for Oligonucleotides (MAMO): Characterization and Impurity Profiling.* Presentation at the USP Workshop on Peptide and Oligonucleotide Therapeutics: Regulations and Quality Standards. Rockville, MD, Apr. 09, 2024.
- Chen K. *Direct Assessment of Oligomerization of Chemically Modified Peptides and Proteins in Formulations Using DLS and DOSY-NMR.* Presentation at the USP Bio1-5 Expert Panel Joint Session. Rockville, MD, Apr. 03, 2024.
- Zhang J, Patel P, Shih M, Xu X, and Faustino P. *Recent Advances in Characterization of Peptide and Peptide-Conjugate Drugs: Challenges and Opportunities.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2024. Bethesda, MD, Mar. 04, 2024.
- Zhang D, Bin Q, and Wang Y. *Product-Specific Guidance Development for Patisiran Sodium Intravenous Solution.* Presentation at the IPRP Nanomedicine Working Group. Virtual Meeting, Feb. 01, 2024.
- Kozak D. *Generic Drug User Fee Amendments (GDUFA) Research and the Product-Specific Guidance (PSG) Program for Complex Products: Challenges and Notable Advances.* Presentation at the 2023 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 03, 2023.

CHAPTER 3: COMPLEX DOSAGE FORMS & FORMULATIONS

A major GDUFA science and research priority area during GDUFA III[1] 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 during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below, highlighting LAI products and nanotechnology products independently in separate sub-sections.

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[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

LONG-ACTING INJECTABLE, INSERTABLE, OR IMPLANTABLE PRODUCTS

Summary of FY 2024 Activities

The FDA's multi-year research program on poly(lactic-co-glycolic acid) (PLGA)-based products has enabled FDA to develop and update product-specific guidances (PSGs) and to establish acceptance criteria for abbreviated new drug application (ANDA) assessment, which has led to ANDA approval of such products. It is worth noting that two generic PLGA-based microspheres products were approved in FY 2024 on December 5, 2023, i.e., a generic risperidone long-acting injection referencing Risperdal Consta (reference listed drug (RLD): new drug application (NDA) 021346) and a generic octreotide acetate for injectable suspension referencing Sandostatin LAR (RLD: NDA 021008). Each of these is the first generic product approved referencing each respective RLD.

In FY 2024, FDA continued research to develop new analytical methods for the characterization of complex polymeric excipients in long-acting injectable (LAI) formulations. New analytical methods including double fluorescence probe labeling to acid and alcohol groups of PLGA and a temperature controlled sequential semi-solvent gel permeation chromatography system are being developed. The new methods can alleviate the burden of reverse-engineering and characterizing PLGAs, especially those that are a small component of a product formulation and which may be challenging to characterize.

Advanced imaging techniques were utilized to characterize LAI formulations. An X-ray microscopic image-based true density measurement was developed. The measurement was able to capture a change in the density of microspheres as a result of polymer aging, which was found to be consistent with the change in porosity measured in a single microsphere focused ion beam scanning electron microscopy (FIB SEM) study.

Similarly, an ongoing research project on collagen implants focused on evaluating the qualitative (Q1) sameness of collagen and assessing its physical and chemical properties across various sources compared to the RLD. This evaluation is essential for understanding the possible effects of different collagen sources on CQAs of collagen implants, such as morphology, porosity, drug localization, and performance characteristics, as well as in vitro drug release. Advanced AI image processing and segmentation techniques were employed to accurately measure porosity, drug localization, and drug release from the collagen implants. These findings are expected to help bridge knowledge gaps, support regulatory assessments, facilitate generic development, and provide valuable insights for PSG recommendations.

Progress was also made in the development of in vitro release test (IVRT) methods for PLGA solid implants, biodurable EVA (ethylene-vinyl acetate)-based solid implants, and polydimethylsiloxane (PDMS)-based intrauterine systems (IUSs). A study showed that structurally equivalent dexamethasone PLGA implants exhibited drastically different release profiles in phosphate buffered saline (PBS) despite no difference being observed in normal saline.[2] An ocular pharmacokinetic (PK) study in a rabbit model was conducted to investigate which IVRT condition (normal saline or PBS) was more physiologically relevant. The preliminary results suggested that IVRT in PBS could be overly sensitive. The finding could promote the

[2] Costello MA, Liu J, Kuehster L, Wang Y, Qin B, Xu X, Li Q, Smith WC, Lynd NA, and Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Molecular Pharmaceutics. (2023) 20, 6330-6344. https://doi.org/10.1021/acs.molpharmaceut.3c00742. PMID: 37955890.

development of an IVRT method for dexamethasone implant products for quality control and/or BE purposes.

Another research focus of FY 2024 was to understand the impact of formulation variables on PLGA product performance. Contract 75F40123C00142 was initiated to investigate the impact of active ingredient properties (e.g., particle size and solid state) on the performance of suspension in situ forming implant products and to develop in vitro release methods that allow for the establishment of an in vitro-in vivo correlation (IVIVC). This Contract was an expansion of a previous Contract 75F40120C00021, where the focus was to elucidate the impact of PLGA polymer attributes on product performance. The previous work provided a comprehensive understanding of how slight changes in polymer properties (e.g., molecular weight, lactide to glycolide ratio, blockiness, and end group) affect in vitro and in vivo performance.[3] In addition, factors that contribute to different in vitro and in vivo release profiles were identified, and a level A IVIVC using rabbit model was successfully developed.[4] Contract 75F40123C00196 aims to investigate the impact of formulations parameters on an in situ forming implant product where the drug is fully dissolved in the polymer and solvent. Knowledge gained from these projects will facilitate the development of in vitro characterization based BE approaches for PLGA-based in situ forming implant products.

Two new Grants were awarded in FY 2024 with the aim to develop PBPK model-based mechanistic IVIVCs for long-acting injectable suspensions and implants. One Grant (U01FD008304-01) aims to comprehensively investigate the interplay between the formulation CQAs of an LAI suspension and physiological factors at the local site of administration to accurately predict in vivo drug release using physiologically based pharmacokinetic (PBPK) models. This research represents a significant effort to elucidate the intricate relationships between formulation properties and injection site physiology, providing insight into potential BE approaches for LAI suspensions. The in vitro and in vivo data generated will provide a comprehensive understanding of physicochemical and physiological interactions, allowing the development of robust and reliable PBPK model-based mechanistic IVIVCs for LAIs. Another Grant (U01FD008303-01) aims to develop IVIVCs for a long-acting PLGA-based solid implant using a PBPK modeling approach. This research represents an opportunity to understand how the physicochemical properties of drug molecules/polymers, implant specific properties, critical formulation attributes, and physiology, among other things, influence the in vivo release mechanisms of PLGA implant drug products and their disposition characteristics. Successful execution of the project will entail developing a bio-predictive in-vitro release testing method and determining how critical formulation and physicochemical properties impact the in vitro release of PLGA-based buprenorphine implants; and using a bottom-up PBPK approach to build IVIVCs that predict in vivo PK profiles of PLGA-based implant from in vitro data. A description of this research can also be found in Chapter 7 “Quantitative Methods & Models”, and, specifically in subsection 1 describing “Mechanistic Modeling for Non-Orally Administered Drug Products”.

FDA continued its Contract with University of Connecticut (75F40121C00133) on an LAI suspension, focusing on (1) understanding formulation attributes such as particle agglomeration behavior and their impact on in vitro drug release; 2) developing robust in vitro release testing methods; and 3) building mechanistic PBPK models to understand the in vivo processes and formulations characteristics affecting an LAI product’s in vivo performance. The development of a mechanistic PBPK model of Depo-subQ Provera 104, a medroxyprogesterone acetate (MPA) subcutaneous injectable suspension, enabled the identification of physiological events and product attributes that were critical for the in vivo performance of the tested LAIs[5]. Further investigations were conducted to evaluate the impact of immune cell layer (ICL) as a tissue reaction to the intramuscularly administered LAI. A previously implemented mathematical model describing the temporal changes in the ICL thickness was also improved during this investigation.

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[3] Wang X, Bao Q, Wang R, Kwok O, Maurus K, Wang Y, Qin B, and Burgess DJ. *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.

[4] Wang X, Roy M, Wang R, Kwok O, Wang Y, Wang Y, Qin B, and Burgess DJ. *Towards In Vitro - In Vivo Correlation Models for In Situ Forming Drug Implants.* Journal of Controlled Release. (2024) 372: 648-660. https://doi.org/10.1016/j.jconrel.2024.06.058. PMID: 38936743.

[5] Amaral Silva D, Le Merdy M, Alam KD, Wang Y, Bao Q, Malavia N, Burgess D, and Lukacova V. *Development of Mechanistic In Vitro-In Vivo Extrapolation to Support Bioequivalence Assessment of Long-Acting Injectables.* Pharmaceutics. (2024) 16(4): 552. https://doi.org/10.3390/pharmaceutics16040552. PMID: 38675213.

RESEARCH HIGHLIGHT

The development of a generic IUS product with long period of use (up to 8 years) can be challenging due to the complexity of the formulation and due to uncertainty about how to demonstrate BE. The FDA previously posted a PSG on levonorgestrel IUS[6] to facilitate generic product development. In addition, GDUFA research has been used to address challenges associated with generic IUS development. For example, in previous studies, compositionally equivalent levonorgestrel IUSs were manufactured, characterized, and evaluated using real-time and accelerated release methods to study the impact of formulation attributes on drug release from levonorgestrel IUSs (LNG-IUSs). New BE metrics that enable shortened testing time periods were developed using a modeling approach. In the recent work, the impact of PDMS polymer and additive properties on product performance were investigated.[7] LNG-IUS with a variety of additives and differences in filler content were prepared and then characterized with a scanning electron microscope (SEM) and by differential scanning calorimetry (DSC). In vitro drug release from the IUSs was measured for up to 12 months. The study revealed that the addition of various additives changed the crystallinity of the crosslinking polymer, changed the viscosity and microstructure of the matrix, and exhibited an altered in vitro drug release. A formulation with resins had the fastest drug release among the four formulations evaluated, which may be attributable to the increased solubility of the drug in amorphous polymers. Formulation with diatomaceous earth showed the highest crystallinity in a polymer matrix and the lowest drug release rate (Figure 1). Moreover, the effect of additives and fillers on the mechanical properties of IUSs were studied (Figure 2). Among the formulations tested, silica was found to be the most suitable filler to provide the desired hardness and elasticity for the IUS. The knowledge gained from this work could help support generic drug development with respect to excipient selection.

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[6] *Draft Guidance on Levonorgestrel Intrauterine System.* (Nov. 11, 2024) Link to posting

[7] Fanse, S., Bao, Q., Zou, Y., Wang, Y., and Burgess, D. J. *Tailoring Drug Release from Long-Acting Contraceptive Levonorgestrel Intrauterine Systems.* Journal of Controlled Release. (2024) 370, 124-139. https://doi.org/10.1016/j.jconrel.2024.04.027. PMID: 38648956.

RESEARCH HIGHLIGHT *continued*

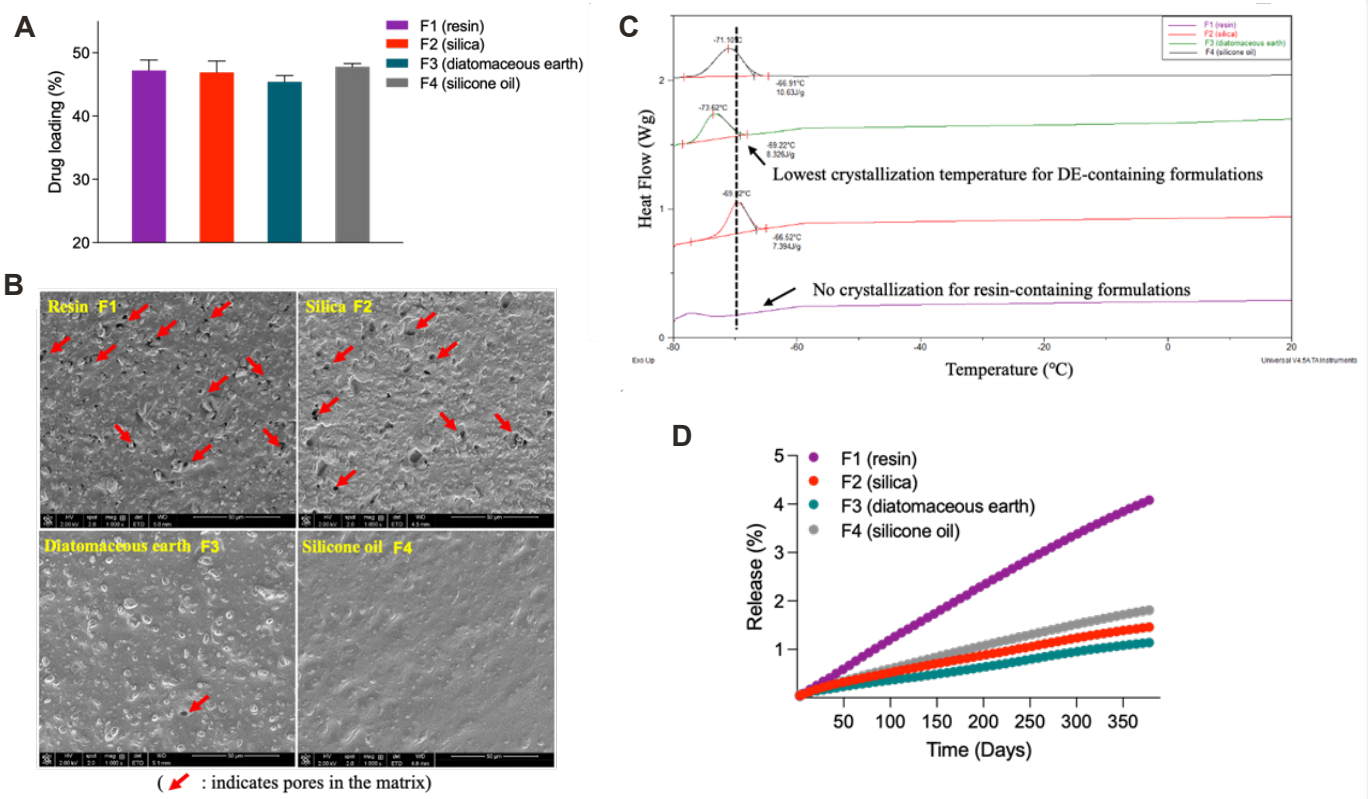


Figure 1. A) Drug loading of LNG-IUSs containing various additives (mean ± SD, n = 3); **B**) representative DSC thermograms of LNG-IUSs containing various additives showing polymer crystallization; **C**) SEM images (500× magnification, scale bar represents 50 µm) of the drug-polymer reservoirs of LNG-IUSs prepared using various additives; and **D**) real-time in vitro drug release profiles of LNG-IUSs containing various additives at 37 ˚C in a water shaker bath at 100 rpm (mean ± SD, n = 3). [Source: Journal of Controlled Release (2024), 370, 124-139. Reproduced with permission from Elsevier]

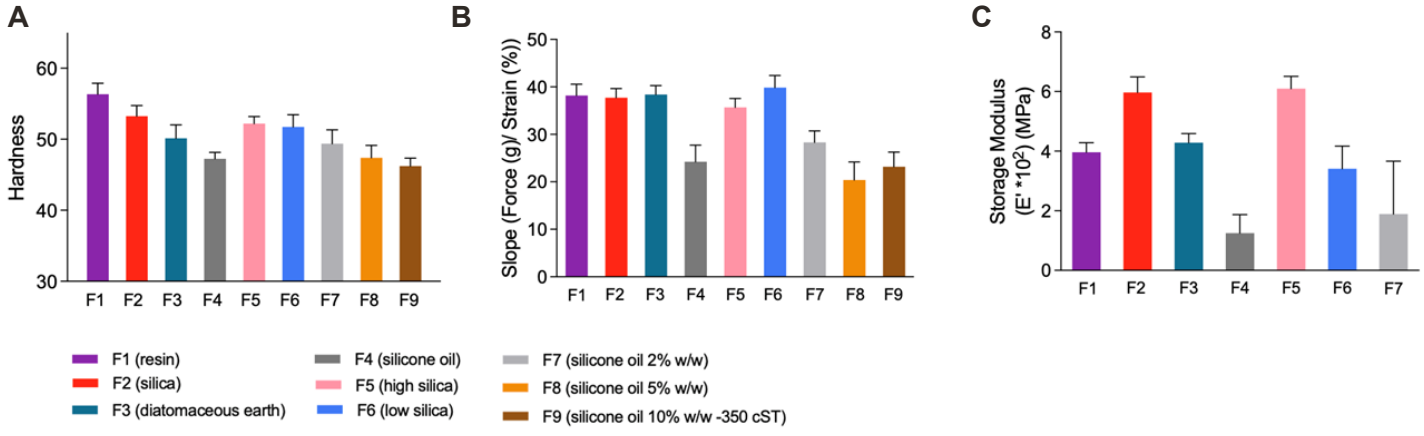


Figure 2. Effect of additives and fillers on mechanical properties of LNG-IUSs: **A**) shore hardness via durometer (mean ± SD, n = 3); **B**) tensile strength (slope of force (g) vs strain (%)) via texture analyzer (mean ± SD, n = 3); and **C**) storage modulus (E', MPa) via dynamic mechanical analyzer (mean ± SD, n = 3). (The formulations were significantly different (*p < 0.1 and **p < 0.05) to the formulation F1). [Source: Journal of Controlled Release (2024), 370, 124-139. Reproduced with permission from Elsevier]

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008303) *Developing PBPK-Model Based Mechanistic IVIVC for PLGA Implants* with Feng Zhang at University of Texas at Austin
- Grant (U01FD008304) *Development of PBPK Model-Based Mechanistic IVIVCs for Long-Acting Injectable Suspensions* with Diane Burgess at University of Connecticut
- Contract (75F40124D00022-75F40124F19001) *3D Microscopy, Artificial Intelligence-based Quantification, and Modeling for Non-Clinical Evaluation and Regulatory Support of Complex Injectable and Insertable Drug Products* with Shawn Zhang at DigiM Solution LLC.

Continuing Grants and Contracts

- Grant (U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane Burgess at University of Connecticut
- Contract (75F40122C00019) *Correlation Between Material Properties, Manufacturing Process, Structural Properties, and Quality Attributes of Long-Acting, Biodurable Implants* 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 (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate their Generic Development* with Diane Burgess at University of Connecticut
- Contract (75F40123C00142) *Impact of API CQAs on In Situ Forming Implants and Understanding In Vitro and In Vivo Performance Differences* with Diane Burgess at University of Connecticut
- Contract (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at Regents of the University of Michigan
- 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 Inc.

Completed Grants and Contracts

- 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 (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

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Active FDA Research

- *Assessing New Analytical Methods for Characterization of Complex Excipients in Long Acting Drug Products*
- *Long-acting injectable (LAI) Product Landscape and Approval Standards by European and the US Regulatory Agencies*
- *Internal Research Identified via SME Triage Process to Support LAI PSG Development*
- *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations*

OUTCOMES

Product-Specific Guidances

There were three new PSGs published in FY 2024 related to *Long-Acting Injectable and Implants* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance on Risperidone for Suspension, Extended Release* (NDA 210655). (Nov. 16, 2023) Link to posting
- *New Draft Guidance on Risperidone for Suspension, Extended Release* (NDA 212849). (Aug. 22, 2024) Link to posting
- *New Draft Guidance for Verteporfin Injectable.* (Aug. 22, 2024) Link to Posting

Articles

- Costello M, Liu J, Wang Y, Qin B, Xu X, Li Q, Smith W, Lynd N, and Zhang F. *Manufacturing Dexamethasone Intravitreal Implants: Process Control and Critical Quality Attributes.* International Journal of Pharmaceutics. (2023) 647:123515. https://doi.org/10.1016/j.ijpharm.2023.123515. PMID: 37844672.
- Costello M, Liu J, Kuehster L, Wang Y, Qin B, Xu X, Li Q, Smith W, Lynd N, and Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Molecular Pharmaceutics. (2023) 20(12): 6330-6344. https://doi.org/10.1021/acs.molpharmaceut.3c00742. PMID: 37955890.
- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Impact of Manufacturing Variables on Product Performance of Contraceptive Levonorgestrel Intrauterine Systems.* International Journal of Pharmaceutics. (2024) 660: 124343. https://doi.org/10.1016/j.ijpharm.2024.124343 PMID: 38880254.
- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Tailoring Drug Release from Long-Acting Contraceptive Levonorgestrel Intrauterine Systems.* Journal of Controlled Release (2024) 370: 124–139. https://doi.org/10.1016/j.jconrel.2024.04.027. PMID: 38648956.
- Ghaffari A, Matter B, Hartman R, Bourne D, Wang Y, Choi S, and Kompella U. *Hot-Melt Extrusion-Based Dexamethasone-PLGA Implants: Physicochemical, Physicomechanical, and Surface Morphological Properties and In Vitro Release Corrected for Drug Degradation.* Pharmaceutics. (2024) 16(7): 895. https://doi.org/0.3390/pharmaceutics16070895. PMID: 39065592.
- Kuehster L, Dai J, Thompson A, Jhon Y, Wang Y, Bin Q, Smith W, Xu X, Zhang F, and Lynd N. *Analysis of Copolymerization with Simultaneous Reversibility and Transesterification by Stochastic Model Regression.* Macromolecules. (2024) 57(9): 4034 - 4044. https://doi.org/10.1021/acs.macromol.4c00037.

OUTCOMES *continued*

- Ren A, Zhong Z, Wang Y, Qin B, Smith W, Xu X, Listro T, and Zhang F. *Manufacture, Characterization, and Elucidation of Drug Release Mechanisms of Etonogestrel Implants based on Ethylene Vinyl Acetate.* Journal of Pharmaceutical Sciences. (2025) S0022: 3549(24)00315-0. https://doi.org/10.1016/j.xphs.2024.08.015. PMID: 39236850.

- Silva D, Le Merdy M, Alam K, Wang Y, Bao Q, Malavia N, Burgess D, and Lukacova V. *Development of Mechanistic In Vitro-In Vivo Extrapolation to Support Bioequivalence Assessment of Long-Acting Injectables.* Pharmaceutics. (2024) 16(4): 552. https://doi.org/10.3390/pharmaceutics16040552. PMID: 38675213.

- Wang X, Roy M, Wang R, Kwok O, Wang Y, Wang Y, Qin B, and Burgess D. *Towards in vitro – In vivo correlation models for in situ forming drug implants.* Journal of Controlled Release. (2024) 372: 648 - 660. https://doi.org/10.1016/j.jconrel.2024.06.058. PMID: 38936743.

- 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.

Posters

- Zhang Q, Cui H, Qin B, Wang Y, and Kozak D. *Current Thinking and Rationale for When an In Vitro Approach to Establish Bioequivalence May be Recommended for an Injectable Suspension.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.

- Madawala C, Srinivasan P, Muhammad A, Youngee S, Korang-Yeboah M, Xu X, Ashraf M, Wang Y, Qin B, Zhang Q, and Kamal N. *Effect of Collagen Sources on the In-Vitro Performance of Collagen Implant.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid meeting, Bethesda, MD, Sep. 24, 2024.

- Annaji M, Sierra Vega NO, Ashraf M, Porter D, Di Prima M, James Coburn J, O'Connor T, and Zidan A. *Optimization of The Process Parameters of Thermoplastic Polyurethane in Droplet Deposition Modeling for Production of Personalized Intravaginal Rings for Menopausal Women.* Poster Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 18, 2024.

- Plavchak C, Smith W, Vandenberg M, Zaman R, Beringhs AO, Wang Y, and Xu X. *Assessing Q1/Q2 Sameness of Polyethylene Glycol Star Polymers as Polymeric Excipients in Ophthalmic Implants Using Size Exclusion Chromatography and Thermal Field-Flow Fractionation.* Poster Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 18, 2024.

- Malavia N, Silva D, Bao Q, Lukacova V, Alam K, Wang Y, and Burgess D. *Formulation Insights into Long-Acting Hormonal Contraceptives for Advancing Generic Product Development.* Poster Presentation at the Controlled Release Society (CRS) 2024 Annual Meeting and Exposition. Bologna, Italy, Jul. 08, 2024.

- Roy M, Wang X, Wang Y, Qin B, Li Q, and Burgess D. *Investigating the Impact of Risperidone CQAs on the In Vitro Release of In Situ Forming Implants.* Poster Presentation at the Controlled Release Society (CRS) 2024 Annual Meeting and Exposition. Bologna, Italy, Jul. 08, 2024.

- Plavchak C, Smith W, Vandenberg M, Zaman R, Beringhs AO, Wang Y, and Xu X. *Assessing Q1/Q2 Sameness of Polyethylene Glycol Star Polymers as Polymeric Excipients in Dexamethasone Ophthalmic Inserts.* Poster Presentation at the 23rd International Symposium on Field- and Flow-based Separations. Nantes, France, Jun. 03, 2024.

OUTCOMES *continued*

- Srinivasan P, Korang-Yeboah M, Xu X, Ashraf M, Wang Y, Qin B, and Kamal N. *Effect of Collagen Source on the In-vitro Performance of Collagen Implant.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.

- Costello M, Liu J, Kuehster L, Wang Y, Qin B, Lynd N, and Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Tailoring Drug Release from Long-Acting Contraceptive Levonorgestrel-Containing Intrauterine Systems.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Lin X, Al Zouabi N, Ward L, Zhen Z, Masese F, Hargrove D, Yuan H, Beringhs A, Kasi R, Bin Q, Wang Y, and Lu X. *Assessing In Situ Forming Implant Formulations Using In Vivo Imaging.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, Florida, Oct. 22, 2023.

- Malavia N, Bao Q, Silva DA, Lukacova V, Alam K, Wang Y, and Burgess D. *Enabling Formulation Development of LAIs Thorough Understanding Critical Formulation Parameters.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, Florida, Oct. 22, 2023.

- Ren A, Zhong Z, Arbilo L, Wang Y, Smith W, Qin B, Listro T, and Zhang F. *Understanding the Impact of Accelerated Release Testing Conditions on Transport Properties and Release Mechanisms of Drug from Long-acting Ethylene Vinyl Acetate Implants.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Ren A, Zhong Z, Wang Y, Smith W, Qin B, Listro T, and Zhang F. *Manufacturing and Elucidating the Drug Release Mechanisms of Long-acting Ethylene Vinyl Acetate-based Implants.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Silva DA, Malavia N, Burgess D, Alam K, Wang Y, and Lukacova V. *Mechanistic Modeling of Intramuscular Administration of Long-acting Injectable Suspensions Accounting for Fibrosis at the Depot Site.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Tiffner K, Ramezanli T, Birngruber T, Bodenlenz M, Teles F, Raml R, Kainz S, Raney S, and Sinner F. *Investigating the Relationship Between Microstructural Properties and In Vitro Release Characteristics of PLGA Microspheres.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Xia Z, Liu Y, Lu Z, Wang Y, Xu X, and Schwendeman A. *Critical Process Parameters and Their Impacts on the Product Attributes of Bupivacaine Multivesicular Liposomal Formulation (Exparel).* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Zaman R, Smith W, Park J, Liang J, Feng X, Zhang F, Zhong Z, Clark A, Zhaobo F, Zheng J, Ashraf M, Wang Y, and Xu X. *Understanding Release Mechanism and Development of Accelerated Release Tests for Long-term Intrauterine Systems.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Zhong Z, Ren A, Zhang F, Smith W, Wang Y, and Qin B. *Correlation between Material Properties, Extrusion Processing Conditions and Permeability of Etonogestrel in Polyethylene Vinyl Acetate Films Implants.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

OUTCOMES *continued*

Presentations

- Mostofa A. *IVRT Methods for In Situ Depot-Forming Long-Acting Injectable Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Wang Y. *The Journey of First Approvals of Complex Generic Long-acting Injectable Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 25, 2024.
- Struble K. *Regulatory Considerations in Development of Generic LAI Formulations for HIV Treatment and Prevention.* Presentation at the Long-Acting/Extended Release Antiretroviral Research Resource Program Meeting. Virtual Meeting, Sep. 20, 2024.
- Babiskin A. *Regulatory Utility of MMF for Development of Long-Acting Injectable Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Silva DA. *Model Master File in the Context of Long Acting Injectables.* Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Das, J. *Applications of AI in Manufacturing of Pharmaceutical Products: Challenges and Opportunities.* Presentation at the International Forum for Process Analysis & Control. Bethesda, MD, Mar. 03, 2024.
- Zaman, R. *Understanding Drug Release Mechanism in Long-acting Intrauterine Systems.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Lynd A. *Understanding and Characterizing the Sequence Blockiness of Poly(lactide-co-glycolide).* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Park K. *Analysis of PLGAs in Complex Long-Acting Injectable Formulations.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Burgess D. *Understanding In Situ Forming Implants and Development of Appropriate In Vitro Testing Methods.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Schwendeman S. *Exenatide PLGA Microspheres.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.

OUTCOMES *continued*

- Lu X. *Imaging In Situ Forming Implants for Advanced Characterization.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Zhang S. *Image-Based Porosity, Density, and In Silico Modeling for Product Equivalence Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Yilmaz H. *High Resolution Chemical Imaging for Characterization of Intrauterine Systems and Nanomaterial Containing Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Le Merdy M. *PBPK Models of Complex Injectable and Ophthalmic Drug Products: Case Studies.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Das J. *Applications of AI in Manufacturing of Pharmaceutical Products: Challenges and Opportunities.* Presentation at the Small Business and Industry Assistance (SBIA) Pharmaceutical Quality Symposium: Quality, Supply Chain & Advanced Manufacturing. Virtual Meeting, Nov. 01, 2023.
- Qin B. *Long-Acting Injectables: Advances in In Vitro Equivalence Testing.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Wang Y. *Regulatory and Scientific Considerations for Demonstrating Pharmaceutical Equivalence and Bioequivalence of Poly (lactide-co-glycolide) Based Long-Acting Injectable Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.

NANOTECHNOLOGY PRODUCTS

Summary of FY 2024 Activities

In FY 2024, internal and external research projects on nanomaterials continued to 1) enhance the understanding of critical quality attributes (CQAs) that determine lipid nanoparticle (LNP) performance; 2) develop new characterization methods for better understanding of nanomaterial-containing drug products; and 3) support development of more efficient bioequivalence (BE) approaches.

The FDA's ongoing collaboration with Purdue University (Contract 75F40121C00189) and the University of Maryland, Baltimore (Grant U01FD007363) focused on advancing a comprehensive understanding of certain complex iron products. Since their initiation in 2021, these projects have characterized the composition of drug substances and the structure of the iron carbohydrate complex, providing insights into how variations in manufacturing processes and CQAs impact product performance. Based upon the enhanced understanding of iron products, the product-specific guidance (PSG) for ferric carboxymaltose intravenous solution (Injectafer, NDA 203565) was revised in FY 2024, and a new PSG for ferric derisomaltose intravenous solution (Monoferric, NDA 208171) was published in FY 2024.

Ongoing external research projects included studies to understand the impact of siRNA impurities, lipid sources, and manufacturing processes on the performance and quality of siRNA LNP (Contract 75F40123C00118) as well as research to provide insights into the behavior of nanoparticles in various biological environments (Contract IAA-75F40123S30031). Additional ongoing contract research (75F40119C10139) with the Institute of Quantitative Systems Pharmacology (IQSP) evaluated the target site BE of liposomal doxorubicin through in silico system-based multi-scale modeling. This model is intended to account for various biological and physicochemical events that can affect the transport and residence of nanoparticles and their cargo active ingredient. A key outcome of this contract is expected to help link certain nanoparticle attributes with target site bioavailability.

Within the FDA, there are ongoing efforts to enhance characterization methods for liposomal products, focusing on particle size, in vitro drug release, lipid analysis, and lipid-related impurities. Advanced analytical techniques, such as the use of asymmetrical flow field-flow fractionation (AF4), are being developed for precise characterization of nanomaterial subpopulations. The development of AF4 is instrumental in supporting regulatory assessments and ensuring the quality and BE of complex nanomaterial-containing drug products (see **Research Highlight**).

Since the initiation of GDUFA I in 2012, FDA has conducted several Generic Drug User Fee Amendments (GDUFA)-funded research on liposomal products. Extensive GDUFA-funded research has significantly advanced the scientific understanding of the liposome products, including how crucial manufacturing process parameters can affect product performance, the relationship between CQAs and target site bioavailability, and the development of characterization methods for complex liposome structures and drug release from the liposome. These advancements have been used for facilitating the development and supporting assessments of multiple generic liposomal products. To date, there are six approved doxorubicin hydrochloride products and two approved amphotericin B liposome liposomal products. In addition, on July 1, 2024, FDA approved the first generic bupivacaine liposomal product referencing Exparel, NDA 022496. This was a notable achievement considering the challenges associated with developing, manufacturing, and demonstrating BE for multivesicular liposome products.

RESEARCH HIGHLIGHT

The evaluation of nanomaterial-containing products often necessitates the use of sophisticated and new approaches for thorough characterization. For complex drug products containing nanomaterials (e.g., lipid nanoparticles, liposomes, emulsions, iron sucrose injections) identifying unique particle subpopulations may be critical for demonstrating equivalence. Asymmetrical Flow Field-Flow Fractionation (AF4) with multi-detection is one such analytical method that can provide separation and characterization of nanomaterial subpopulations, enabling an assessment of heterogeneity in analyte physicochemical properties including particle size distribution (PSD), molecular weight, apparent density, and morphology. Use of AF4 with multi-detection method has increased in both product development and in supporting regulatory submissions as an orthogonal method to traditional ensemble particle sizing techniques. However, while this technique has gained acceptance, full implementation within the pharmaceutical industry has been slow. A technical understanding of the operating principles is often necessary for the successful application of any emerging technology and its utility in regulatory decision making.

One key parameter when validating, optimizing, and assessing AF4 methodologies is sample recovery. Current guidances and standard test methods suggest an adequate AF4 sample recovery (R) of ≥ 70%. In terms of complex drug products, however, excipients (e.g., preservatives, buffering agents/stabilizers, and surfactant micelles) may convolute recovery calculations due to overlapping concentration signals. These excipients are often removed during separation, reducing the apparent sample recovery (Figure 1). While recovery is important to evaluate, it is critical to consider how to discriminate between recovery for excipients and analytes (e.g., globules, liposomes), and the influences on observed PSD. FDA's internal research examined the relationship between AF4 sample recovery and analyte PSD. The impact of excipients on absolute sample recovery of two model drug products, difluprednate ophthalmic emulsion and doxorubicin hydrochloride liposomal injection, was assessed. Addition or elimination of the excipients prior to AF4 analysis can either decrease or improve absolute sample recovery, respectively. Additionally, multimodal systems can still exhibit some recovery-based variation in PSD due to sample instability driven by compositional effects.

As AF4 is used more frequently, considering the impacts of recovery on PSD may be critical in characterizing samples of mixed analyte composition. Evaluating emerging analytical methods is critical to improving the FDA's readiness in assessing complex drug products. Promoting the development of standards and test methods is critical to the widespread adoption of industrially relevant analytical methodologies. This benefits not only product development but also provides a foundation for assessing methodologies used for the purpose of evaluating drug product quality and demonstrating BE.

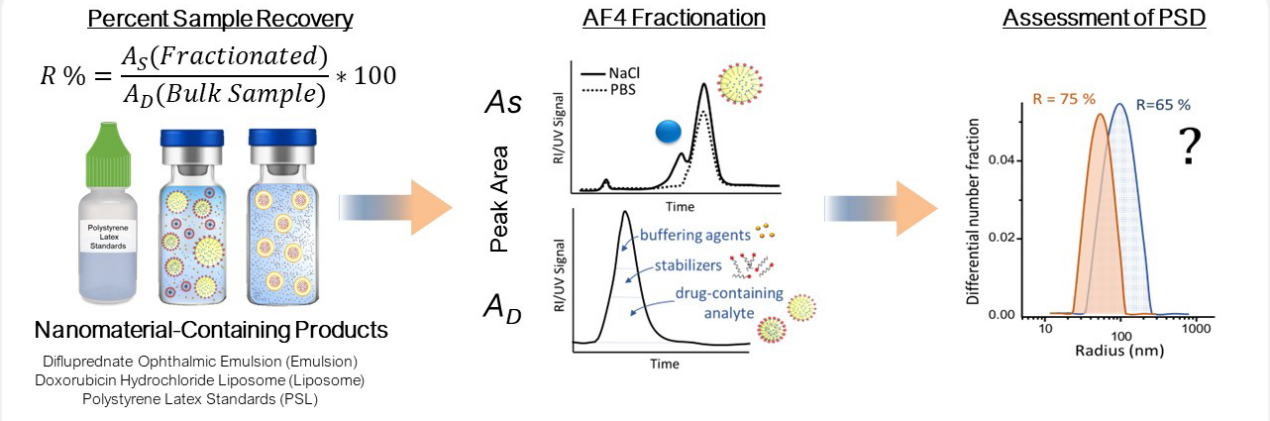


Figure 1. Schematic description of the determination of sample recovery in asymmetrical flow field-flow fractionation.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40124C00132) *Characterizing Albumin-Bound Nanoparticle Drugs Using wNMR* with Yihua Bruce Yu at the University of Maryland, Baltimore

Continuing Grants and Contracts

- Grant (U01FD007363) *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 (IAA-75F40123S30031) *Confinement and Error Model Enhanced Nanoparticle Tracking Analysis (CEMENT)* with Samuel Stavis at the National Institute of Standards & 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
- 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 (U01FD007352) *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 the University of Florida

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*
- *Complex Iron Carbohydrate Drugs: Data Mining and Deficiency Analysis of Pending ANDAs*

OUTCOMES

Product-Specific Guidances

There were two new and two revised PSGs published in FY 2024 related to *Nanotechnology* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *Revised Draft Guidance on Ferric Carboxymaltose Solution.* (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Ferric Derisomaltose Solution.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance on Ferumoxytol Solution.* (Nov. 16, 2023) Link to Posting
- N*ew Draft Guidance for Verteporfin Injectable.* (Aug. 22, 2024) Link to Posting

Articles

- Coutinho A, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, and Polli J. *Relative Performance of Volume of Distribution Prediction Methods for Lipophilic Drugs with Uncertainty in LogP Value.* Pharmaceutical Research. (2024) 41(6): 1121 - 1138. https://doi.org/10.1007/s11095-024-03703-4. PMID: 38720034.
- Duran T, Costa A, Kneski J, Xu X, Burgess D, Mohammadiarani H, and Chaudhuri B. *Manufacturing Process of Liposomal Formation: a Coarse-Grained Molecular Dynamics Simulation.* International Journal of Pharmaceutics. (2024) 659: 124288. https://doi.org/10.1016/j.ijpharm.2024.124288. PMID: 38815641.
- Jayaraj S, Jiang W, and Mudalige T. *An Automated Capillary Electrophoresis Based Method for Drug Release Profiling of Liposomal Doxorubicin.* Journal of Pharmaceutical Sciences. (2024) 113(4): 1088 - 1093. https://doi.org/10.1016/j.xphs.2023.12.017v. PMID: 38135054.
- Niyonshuti I, Jayaraj S, Jiang W, and Mudalige T. *A Robust Chromatographic Method for Drug Release Profiling of Liposomal Doxorubicin HCl.* Journal of Pharmaceutical Sciences. (2024) 13(9): 2837-2842. https://doi.org/10.1016/j.xphs.2024.06.005. PMID: 38857642.
- Siriwardane D, Jiang W, and Mudalige T. *Profiling In-Vitro Release of Verteporfin from VISUDYNE® Liposomal Formulation and Investigating Verteporfin Binding to Human Serum Albumin.* International Journal of Pharmaceutics. (2023) 646: 123449. https://doi.org/10.1016/j.ijpharm.2023.123449. PMID: 37776965.
- Patel R, Cristofoletti R, Wu F, and Al Shoyaib A. *In Vitro Lipolysis Model to Predict Food Effect of Poorly Water-Soluble Drugs Itraconazole, Rivaroxaban, and Ritonavir.* Journal of Pharmaceutical Sciences. (2024) 113(8): 2361 - 2373. https://doi.org/10.1016/j.xphs.2024.04.007. PMID: 38614321.
- Wang C, Gamage P, Jiang W, and Mudalige T. *Excipient-related Impurities in Liposome Drug Products.* International Journal of Pharmaceutics. (2024) 657: 124164. https://doi.org/10.1016/j.ijpharm.2024.124164. PMID: 38688429.
- Wang D, Li J, and Chen K. *Intact NMR Approach Quickly Reveals Synchronized Microstructural Changes in Oil-in-Water Nanoemulsion Formulations.* The AAPS Journal. (2024) 26: 78. https://doi.org/10.1208/s12248-024-00945-3. PMID: 38981948.

OUTCOMES *continued*

- Xia Z, Yu M, Liu Y, Yuan W, Wang Y, Xu X, Bae J, and Schwendeman A. *Development of an Accelerated Rotator-based Drug Release Method for the Evaluation of Bupivacaine Multivesicular Liposomes.* Pharmaceutical Research. (2024) 41: 293–303. https://doi.org/10.1007/s11095-023-03651-5. PMID: 38212593.
- Yurtsever F, Jiang W, and Mudalige T. *An Automated Electroanalytical Method for the Drug Release Profiling of Liposomal Doxorubicin HCl Formulations.* Journal of Pharmaceutical Sciences. (2024) 113: 791-797. https://doi.org/10.1016/j.xphs.2023.11.035. PMID: 38072115.

Posters

- Annaji M, Sierra Vega NO, Ashraf M, Porter D, Di Prima M, James Coburn J, O'Connor T, and Zidan A. *Optimization of The Process Parameters of Thermoplastic Polyurethane in Droplet Deposition Modeling for Production of Personalized Intravaginal Rings for Menopausal Women.* Poster Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 18, 2024.
- Chen, K. *Fast Dynamics of Difluprednate in Micelles or Swollen Micelles Revealed by ^{19}F NMR Spin Relaxation Rates.* Poster Presentation at European Magnetic Resonance Congress 2024. Bilbao, Spain, Jun. 30, 2024.
- Zhang T, Shamim M, Tower C, Sapkota R, Munson E, Liu D, Chen K, Jiang W, Wang Y, and Zhang D. *Characterization of Intravenous Iron Supplements: Injectafer.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Gamage P, Jiang W, and Mudalige T. *Qualitative and Quantitative Analysis of Lipids in Exparel® Injectable Liposomal Drug Formulation.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 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 American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Xia Z, Liu Y, Lu Z, Wang Y, Xu X, and Schwendeman A. *Critical Process Parameters and Their Impacts on the Product Attributes of Bupivacaine Multivesicular Liposomal Formulation (Exparel).* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Mudalige T. *Nano-Size Complex Products IVRT.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Plavchak, C. *Understanding the Link between Sample Recovery and Particle Size Distributions for Characterizing Complex Drug Products Using Asymmetrical Flow Field Flow Fractionation (AF4).* Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 18, 2024.
- Qu, H. *Characterization of Complex Drug Product Using Asymmetrical Flow Field Flow Fractionation (AF4): Challenges and Opportunities.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2024 Summer Scientific Forum. Kansas City, MO, Jul. 22, 2024.
- Xu X. *In Vitro Release Test for Complex Drug Products: Thinking Outside the Box.* Presentation at the Disso America 2024. Dissolution Science: Complex Drug Products Conference. Piscataway, NJ, Jun. 11, 2024.

OUTCOMES *continued*

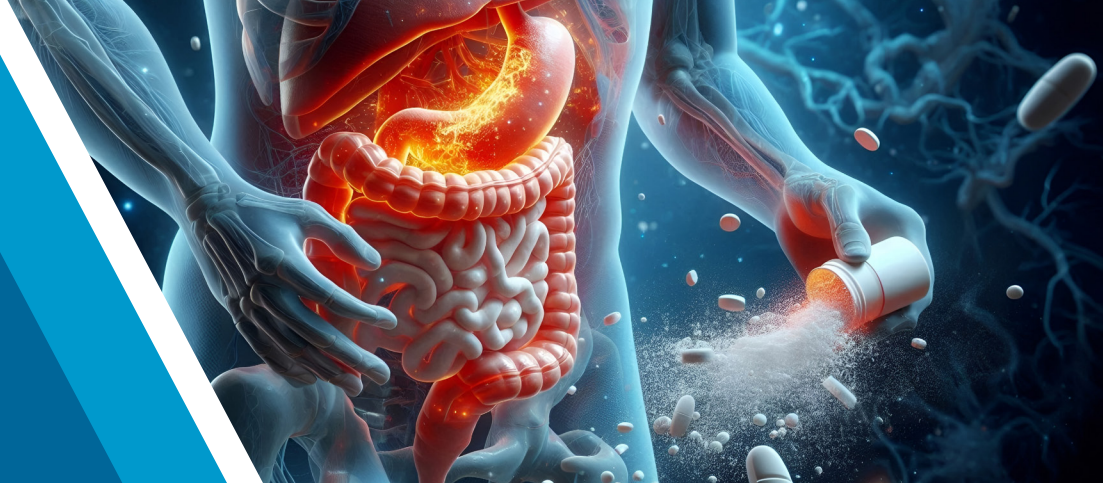
- Xu X. *Perception and Perspective: Fundamentals to Advance Complex Drug Product Development.* Presentation at the AAPS Student Chapter at University of Texas. Austin, TX, Apr. 09, 2024.
- Zhang D, Bin Q, and Wang Y. *Product-Specific Guidance Development for Patisiran Sodium Intravenous Solution.* Presentation at the IPRP Nanomedicine Working Group. Virtual Meeting, Feb. 01, 2024.
- Xu, X. *Innovation through Advanced Manufacturing: Learning from the Future – Accelerating Injectable Product Development and Addressing Drug Shortages.* Presentation at National Institute for Pharmaceutical Technology and Education Pathfinding Workshop – Injectables. Washington, DC, Jan. 11, 2024.
- Smith WC. *Assessing Qualitative Sameness of Polyoxyl Castor Oil in Phytonadione Injectables.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Yilmaz H. *High Resolution Chemical Imaging for Characterization of Intrauterine Systems and Nanomaterial Containing Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Smith WC. *Challenges in the Assessment of Quality for Drug Products Containing Nanomaterials Using AF4-MALS-DLS Methods.* Presentation at the American Society for Testing and Materials International – Committee E56 on Nanotechnology Biannual Meeting. Washington, DC, Nov. 06, 2023.
- Xu, X. *Advancing Nanotechnology Drug Delivery Systems with Novel Assessment Approaches.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Smith W. *Advanced Separations and Detection in Assessment of Quality for Drug Products Containing Nanomaterials.* Presentation at the Small Business and Industry Assistance (SBIA) 2023 NanoDay Symposium: Continuous Manufacturing of Nanomaterials. Virtual Meeting, Oct. 11, 2023.
- Xu X. *Nanotechnology Meets Continuous Manufacturing: Learning from the Future.* Presentation at the Small Business and Industry Assistance (SBIA) 2023 NanoDay Symposium: Continuous Manufacturing of Nanomaterials. Virtual Meeting, Oct. 11, 2023.

CHAPTER 4: COMPLEX ROUTES OF DELIVERY

A major GDUFA science and research priority area during GDUFA III[1] is to enhance the efficiency of bioequivalence (BE) approaches for generic drugs with a complex route of delivery. The advancement of research in this area focuses on understanding how ingredients and other aspects of a formulation influence drug absorption via complex routes of delivery, building in vivo predictive models, and identifying corresponding failure modes for BE. The goal of this research is to support the development of efficient BE approaches for these products. Research during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

LOCALLY ACTING GI PRODUCTS AND BUCCAL/ SUBLINGUAL PRODUCTS



Summary of FY 2024 Activities

In FY 2024, external research involving locally acting gastrointestinal (GI), buccal, and sublingual drug products focused on improving in vitro BE methods and developing biopredictive in silico models.

Work performed during FY 2024 under Grant U01FD007660 aimed to develop a validated physiologically based pharmacokinetic (PBPK) model to provide supportive evidence when evaluating the BE of locally acting GI drug products (e.g., PBPK model-based virtual BE trial simulations). Both in vitro and in silico components were deemed essential for successful model development. Brand and generic locally acting GI drug products available on the market (including budesonide, sulfasalazine, and mesalamine products) were used for in vitro release tests. Such tests were performed under physiologically relevant conditions, by mimicking the gut physiologies of healthy subjects and patients with ulcerative colitis or Crohn's disease (CD). The in vitro release profiles were measured using a biorelevant medium and the results were integrated in the relevant PBPK models. The different methods used for their integration in the PBPK models were then assessed. PBPK models were developed to describe budesonide, sulfasalazine, and mesalamine PK in healthy subjects, and an in vitro to in vivo extrapolation (IVIVE) was established. For budesonide delayed release tablets, in vitro dissolution data were obtained using a USP 4 apparatus with sequential dissolution media change, i.e., Fasted State Simulated Gastric Fluid (FaSSGF), followed by Fasted State Simulated Intestinal Fluid (FaSSIF) and Fasted State Simulated Colon Fluid (FaSSCoF). The PBPK models informed by such dissolution data generally described the corresponding budesonide PK profiles. In addition, to build the sulfasalazine and mesalamine PBPK models, extensive work was done to include the gut microbiome in GastroPlus. This work helps with modeling the biotransformation of sulfasalazine into mesalamine, which is mediated by bacteria in the colon lumen. This new model will predict local and systemic concentrations of active pharmaceutical ingredients (APIs) in patients with ulcerative colitis or CD.

Another Grant (U01FD007662) aimed to test the hypothesis of concordance between systemic and local drug exposures for locally acting drug in the GI tract. During FY 2024, this project used a set of in silico simulations that suggested potential discordances between the local gut and systemic BE metrics of budesonide when considering hypothetical formulations (PMID: 37765205). Subsequently, the research team investigated if using IVIVE-PBPK modeling to simulate local gut BE metrics for three different formulations containing mesalamine (Pentasa, Lialda, and Apriso) would recapitulate the clinical results observed for systemic BE metrics. The research team also measured dissolution profiles for Pentasa, Lialda, and Apriso in biorelevant medium including FaSSGF, FaSSIF, Fed State Simulated Intestinal Fluid (FeSSIF), pH 6.0 phosphate buffer, and FaSSCoF media. The PBPK models were developed and used to predict PK profiles for the three mesalamine products (i.e., Pentasa, Lialda, Apriso) by incorporating dissolution profiles in various media, with the objective being to identify a biopredictive dissolution method. Further verification and validation of the mesalamine PBPK model is ongoing.

Research also continued on buccal and sublingual products. The goal of an ongoing research Contract (75F40120C00150) has been to develop a predictive in silico modeling and simulation platform for drug products delivered via the oral cavity (e.g., buccal and sublingual tablets). During FY 2024, the contractor evaluated the buccal and sublingual permeability

of APIs in marketed oral cavity products (e.g., buprenorphine, fentanyl, sufentanil, and zolpidem) as well as the effect of excipient(s) on API permeability, by using cellular in vitro models. The in vitro permeability data for these APIs was then used to develop a predictive permeability model for oral cavity drug products based on machine learning. Successful completion of this task will allow the model to predict the in vitro mucosal permeation properties of a drug molecule from its molecular structure without the need to conduct in vitro permeation studies. The contractor has further evaluated the dynamic in vitro dissolution of selected model drugs by utilizing a custom engineered 'dynamic in vitro dissolution and absorption model' (DIVDAM). The dynamic in vitro dissolution data along with the clinical PK data of selected model drugs will be used to establish a PBPK model-based IVIVE. Such an IVIVE could potentially be used to support an alternate BE approach for oral cavity drug products.

In addition to external research collaborations during FY 2024, internal FDA research related to GI locally acting products continued, and focused on improving the consistency of in vitro recommendations in PSGs for these products.

RESEARCH HIGHLIGHT

Oral cavity drug delivery has gained significant attention as an alternative to the conventional oral route of administration in order to enhance drug absorption. Moreover, the oral cavity route of administration offers advantages for drug administration in specific populations, including pediatric patients. When a drug is administered within the oral cavity, a fraction of the dose can be directly absorbed through the buccal and sublingual mucosa. In general, the majority of the dose is swallowed, passes through the stomach, and moves along the GI tract where absorption occurs. However, a difference in formulation composition and/or the presence of certain excipient(s) may alter the absorption of a drug from the oral mucosa as well as the GI tract. To stimulate more generic development of oral cavity products, research Contract 75F40120C00150 sought to establish a robust in vitro/in silico model to elucidate the effect of excipients and to predict the plasma PK resulting from both oral cavity and GI absorption. The model development was informed by experimentally determined in vitro permeation data for APIs across human-derived cell culture models of the sublingual (HO-1-u-1) and buccal mucosa (EpiOral). The results from these experiments enabled a quantitative assessment of tissue diffusivity (Figure 1A) and of the dose fraction associated with the tissue barrier (Figure 1B).

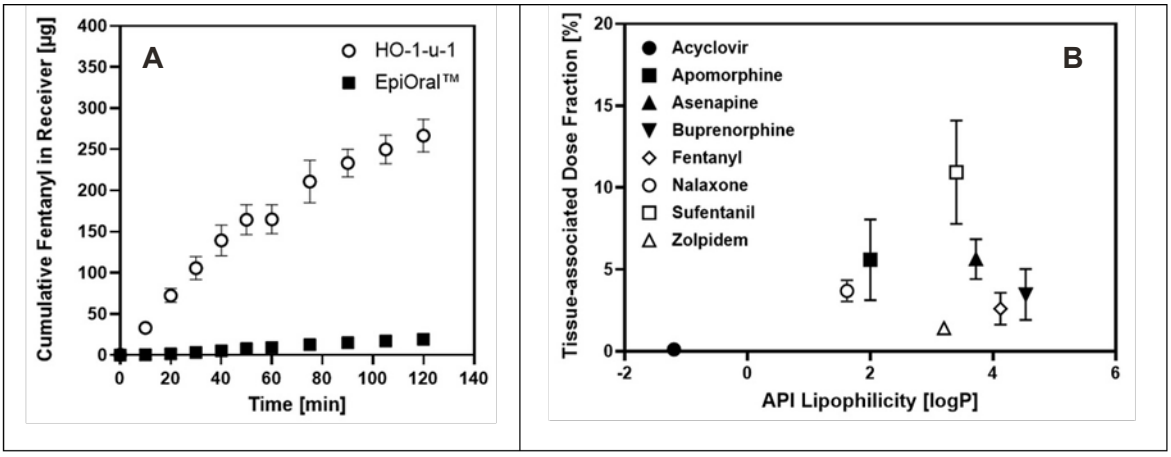


Figure 1. Oral cavity permeability of APIs in vitro. **Panel A**: Transepithelial flux of fentanyl citrate across human-derived cell models of the sublingual (HO-1-u-1) and buccal (EpiOral) mucosal barrier. API dissolved in artificial saliva, pH 6.7, was applied to the donor compartment of a Transwell system at t=0 min. Drug concentrations in the receiver compartment were quantified up to 120 min using reversed-phase HPLC. **Panel B**: Tissue-associated dose fraction recovered for various APIs at the end of the in vitro transport experiment across the buccal EpiOral tissue model. Data are shown as mean ± SD (n=6).

RESEARCH HIGHLIGHT *continued*

In addition to generating data delineating the effects of formulation excipients on barrier properties that restrict API permeation across these mucosal barriers as well as dissolution within the oral cavity, stomach, and small intestine, the key goal of this research Contract is to establish a PBPK model-based in vitro-in vivo correlation (IVIVC) that enables formulators to predict the impact of different compositions on pharmacokinetic (PK) performance in vivo. This may help to facilitate the development of generic drug products intended for oral cavity administration. To achieve this goal, a mechanistic in silico model, describing the in vitro EpiOral model, was developed in MembranePlus to determine API properties (including drug diffusivity (D_m) and unbound fraction in epithelium tissue (f_{ut})) within the oral mucosal barrier in vitro [Figure 2; depicted as A]. In parallel, baseline PBPK models were developed using GastroPlus to describe the absorption, distribution, metabolism, and excretion (ADME) of sufentanil, fentanyl, buprenorphine, zolpidem, and rizatriptan following their intravenous and oral administrations using published data. The baseline models were then used to describe the systemic exposure of these APIs and drug products following their administration as buccal films or orally disintegrating tablets or sublingual solutions. The API absorption from the oral cavity in vivo was estimated using in vitro D_m and f_{ut} values [Figure 2; depicted as C]. For the five compounds evaluated, a consistent scaling factor was used to enhance clinical PK predictions, validating the IVIVE method. The next step will include a measurement of in vitro dissolution profiles for the drug products [Figure 2; depicted as B] and the development of IVIVE for each drug product. These PBPK models will thus enable the prediction of in vivo buccal absorption of the drug products administered into the oral cavity [Figure 2.; depicted as D]. Upon successful completion of this research, the novel PBPK-based IVIVE method with the consistent scale factor may predict the clinical PK of multiple APIs and drug products following oral cavity administration, and may support the development of new and generic oral cavity drug products.

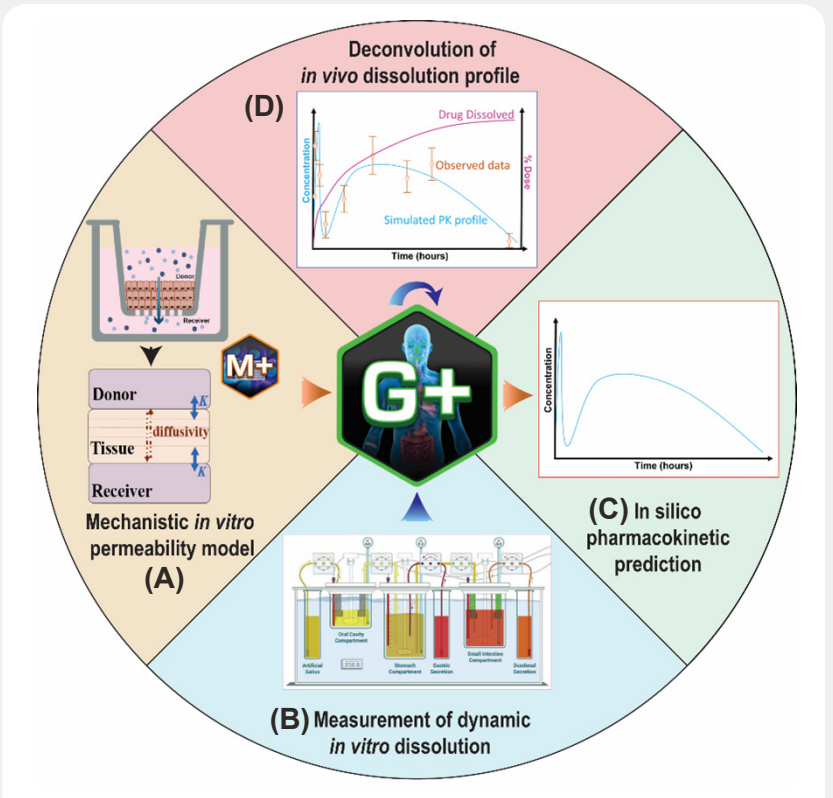


Figure 2. Schematic overview of the mechanistic in vitro model built in MembranePlus for the organotypic EpiOral model (**A**). The IVIVE method is used to predict the in silico in vivo pharmacokinetics of oral cavity dose forms (**C**). The measurements of in vitro dissolution (**B**) are integrated to the PBPK model (**D**) to enable in vivo buccal absorption of oral cavity drug products.

RESEARCH HIGHLIGHT *continued*

To elaborate further on the extent of work as described in Figure 2A, the in vitro EpiOral™ permeability data of five APIs (in pure form) was deconvoluted to obtain their respective D_m and f_{ut} values. The in silico mechanistic model (developed in MembranePlus) describing the in vitro EpiOral™ permeability assay was further used to predict the observed data for the APIs and their corresponding drug products by informing the model with their D_m and f_{ut} values (Figure 3). Four drugs showed no excipient effect, as the D_m and f_{ut} values obtained from pure API permeability data were able to describe the permeation of API from the corresponding drug product. Only fentanyl citrate drug product (Fentora), which indicated an excipient impact on permeability, was modelled as time-dependent Dm in MembranePlus (Figure 3).

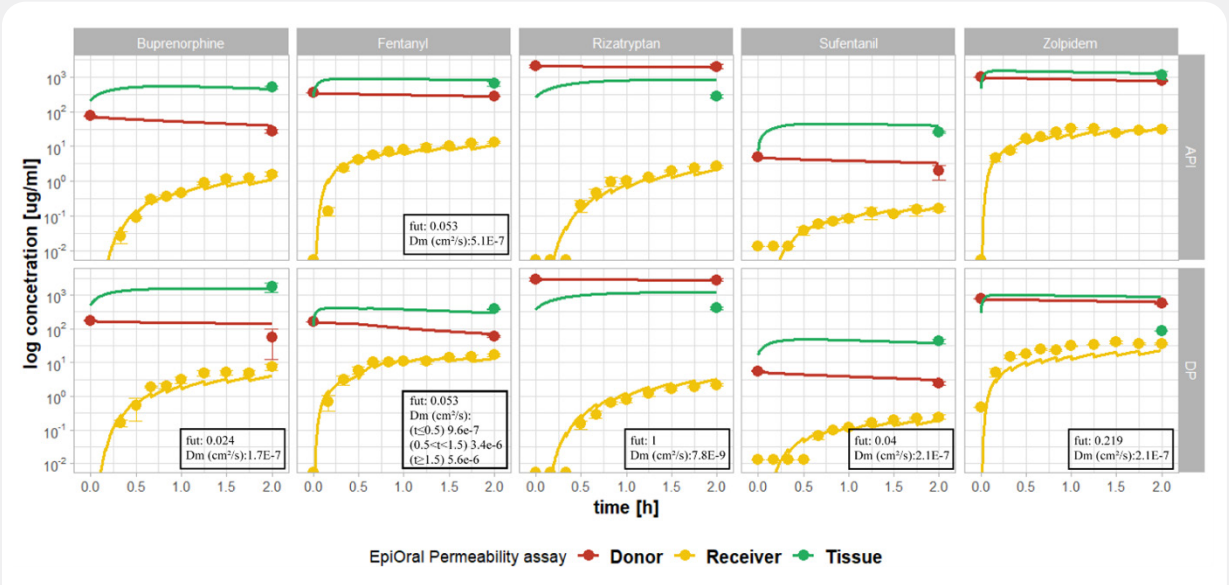


Figure 3. In silico time course concentration profile of five APIs and drug products (DPs) describing the in vitro EpiOral tissue model tissue following their administration in the donor compartment. Lines represent model simulations and dots are observed mean data (n=3) for donor (Red), buccal tissue (Green), and receiver (Yellow) compartments.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008305) *Factors Related to Drug and Formulation Affecting Alcohol Dose Dumping in Modified Release Oral Drug Products* with Mansoor A. Khan at Texas A&M University Health System Science Center

Continuing Grants and Contracts

- Grant (U01FD007660) *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
- Grant (U01FD007662) *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
- 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

- *GDUFA III Product Specific Guidance Improvement for Oral Product*

OUTCOMES

Posters

- Thomas S, Wu F, Zhao L, and Fang L. *Application of Physiologically Based Pharmacokinetic Modeling to Support Bioequivalence Evaluation of Mesalamine Delayed Release Tablets.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Kalra P, Le Merdy M, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Pauletti G, and Zhou H. *Physiologically Based Pharmacokinetic (PBPK) Oral Absorption Model to Predict Mucosal Permeability of Oral Cavity Drug Products.* Poster presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.
- Dwivedi P, Alam K, Tsakalozou E, and Pauletti G. *Oral Cavity Permeability Assessment Using Sublingual and Buccal In Vitro Tissue Models.* Poster presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.

OUTCOMES *continued*

Presentations

- Wu F. *Totality of Evidence Including PBPK Modeling to Support BE Assessment and Approval of Mesalamine Delayed Release Tablets (Part II).* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 25, 2024.
- Thomas S. *Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products: PART I.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Rockville, MD, Oct. 12, 2023.
- Fotaki N. *Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products: PART II.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Rockville, MD, Oct. 12, 2023.

INHALATION AND NASAL PRODUCTS

Summary of FY 2024 Activities

In FY 2024, research continued to support FDA's evaluation of potential alternatives to the conduct of in vivo bioequivalence (BE) studies currently recommended in FDA product-specific guidances (PSGs) for orally inhaled and nasal drug products (OINDPs).

Research relevant to dry powder inhaler (DPI) products conducted by the University of Sydney (Contracts 75F40122C00182 and 75F40122C00202) explored alternative analytical techniques to better understand aerosol plume dynamics as well as to determine the morphology, chemical composition, and distribution of active pharmaceutical ingredients in deposited powder blends. Research including both DPI and metered dose inhaler (MDI) drug products was concentrated in two areas. One area explored the development of more clinically relevant dissolution methods (Contract 75F40123C00201 with Inhalation Sciences Sweden AB). A second area, conducted as part of internal FDA research, explored the critical quality attributes of spray-dried phospholipid porous particles (PPPs) by studying the effects of formulation and manufacturing process on in vitro performance. The results from this research helped to inform the development of several PSGs for inhalation drug products, as discussed in the **Research Highlight** section below.

FDA also prioritized research related to understanding the complexities and challenges associated with the

upcoming transition to low global warming potential (LGWP) propellants (Contract 75F40123C00186). This research focuses on the comparison of in vitro performance characteristics of two commercially available MDIs with model formulations manufactured with LGWP propellants (HFA-152a and HFO-1234ze) and similar container closure systems. Alternative BE characterization methods are being developed to sensitively detect performance differences between HFA-134a and LGWP propellant-based formulations.

For nasal products, research was completed with Virginia Commonwealth University on the evaluation of in vitro regional nasal deposition with nasal sprays using the developed anatomical pediatric nasal models (Contract 75F40120C00172). The Contract also included development of a combined computational fluid dynamics (CFD) and pharmacokinetics (PK) modeling approach that facilitated further exploration of the impact of in vitro metrics on in vivo drug delivery. These studies focused on two commercial nasal spray suspensions (Flonase Sensimist and Nasacort) and two pediatric age groups (2-6 and 7-11 years old). The results suggested that smaller droplets and wider plumes may result in higher posterior drug delivery in vitro. In addition, the comparison of in vitro posterior deposition in children and adults (based on previous data generated by the same researchers) revealed that intranasal drug delivery may be more consistent and efficient in children.

Other ongoing research involving OINDPs include grants and contracts focused on quantitative methods and modeling, which explored refining existing models as well as developing new methods to support model validation. Specifics related to the research on locally acting physiologically based PK (PBPK), CFD, and population PK are discussed in detail in the "Mechanistic Modeling for Non-Orally Administered Drug Products" and "Quantitative Clinical Pharmacology" subsections, respectively, found in Chapter 7. Notably, outcomes from the locally acting PBPK and CFD research contributed to the first recommendations for use of mechanistic modeling to support BE in several PSGs on inhalation drug products (for more detail, please see the Research Highlight in the "Mechanistic Modeling for Non-Orally Administered Drug Products" subsection, Chapter 7).

RESEARCH HIGHLIGHT

Spray-dried PPPs are lipid-based microparticles with ultra-low density attributed to their nanosized porous structure. PPPs are increasingly used in orally inhaled drug products (OIDPs) as they enable higher drug loading, dose consistency, and lung deposition efficiency compared to traditional drug-excipient mixtures. With increasing numbers of approved OIDPs using the PPP platform, a series of FDA draft PSGs[2,3,4] were published in FY 2024 based on support from internal FDA studies. Physicochemical- and morphology-based assessments were conducted on commercial MDI and DPI formulations while manufacturing process and formulation variables were evaluated using in-house PPP formulations. Scanning electron microscopy (SEM) was employed to examine the morphological features of PPPs (Figure 1). A machine learning (ML) approach was used to analyze the particle size and pore size distributions using SEM images of the drug products (Figure 1). A series of analytical methods including cascade impaction, laser diffraction (LD), and morphologically directed Raman spectroscopy (MDRS) are also being utilized to compare aerodynamic particle size distribution (APSD) results to the results from other particle size distribution measurement techniques. Collectively, these studies identified a set of characterization techniques for comprehensive morphological, physicochemical, and aerodynamic particle size evaluations of PPP-based OIDPs, which may provide a foundation for establishing a regulatory framework for quality assessment of PPP-based OIDPs.

[2] *New Draft Guidance for Budesonide; Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting

[3] *New Draft Guidance for Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting

[4] *New Draft Guidance for Tobramycin Powder.* (May 16, 2024) Link to Posting

RESEARCH HIGHLIGHT *continued*

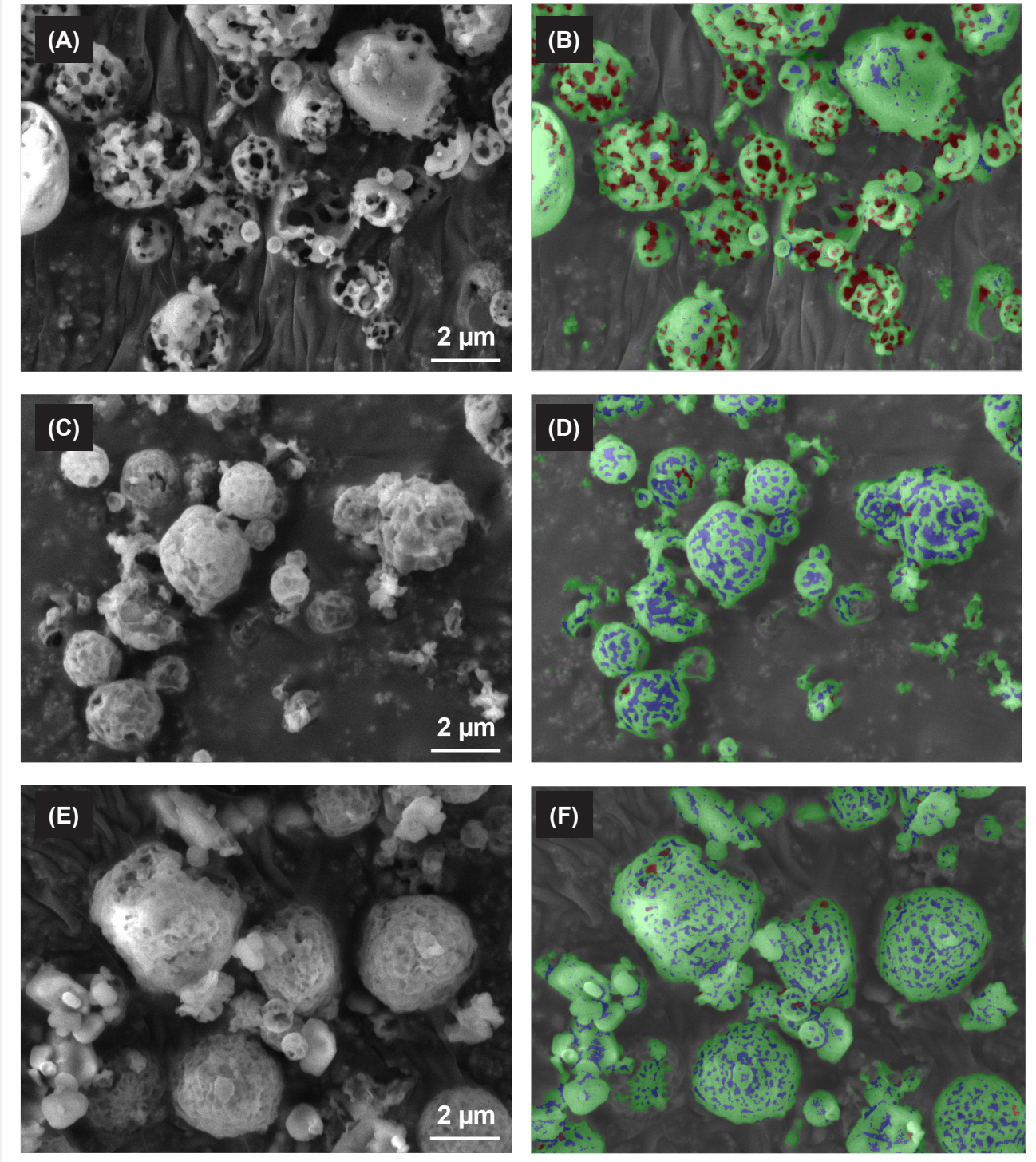


Figure 1. SEM images (20 kx magnification) before and after machine learning segmentation for background (grey), particle surface (green), pores (red) and indentation (blue). (**A**) and (**B**) Tobi Podhaler DPI; (**C**) and (**D**) Bevespi Aerosphere MDI; (**E**) and (**F**) Breztri Aerosphere MDI.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008379) *ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products* with Yu Feng at Oklahoma State University

Continuing Grants and Contracts

- Grant (U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina at Chapel Hill
- Grant (U01FD007987) *A Prospective Study to Support Validation of Lung Deposition Models* with Nuclear Medicine Imaging Methods with Benjamin Lavon at Fluidda, Inc.
- Grant (U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University
- Grant (ORS-INT-2022-02-A) *Developing a Regulatory Framework for Emerging Pulmonary Drug Delivery Technology through Morphological and Performance Evaluation of Spray-Dried Phospholipid Porous Particles* with the Office of Pharmaceutical Quality at FDA
- Grant (U01FD007936) *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
- Grant (U01FD007657) *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 (75F40123C00201) *Development of a Laser-Based Testing Platform for Dry Powder Inhaler (DPI) Evaluation and In-Silico Model Validation* with Agisilaos Kourmatzis at The University of Sydney
- 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 Malmlöf at Inhalation Sciences Sweden AB (ISAB)
- 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
- Contract (75F40123C00186) *Research Challenges Related to Environmentally Friendly Propellants In Metered Dose Inhalers* with Jag Shur at AptarGroup, Inc.

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Completed Grants and Contracts

- 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

Active FDA Research

- *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways*
- *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*
- *Dissolution for Inhalation Products*
- *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*
- *Nebulizer Formulations and Device Effects on BE of Complex Inhalation Suspensions*
- *Post-Market Evaluations of Generic OINDPs*
- *Predicting APSD Parameters of Orally Inhaled Drug Products Using Artificial Intelligence and Machine Learning Algorithms*

OUTCOMES

Product-Specific Guidances

There were seven new and four revised PSGs published in FY2024 related to *Inhalation* products that were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance for Albuterol Sulfate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Budesonide; Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate; Salmeterol Xinafoate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Levalbuterol Tartrate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Levodopa Powder.* (May 16, 2024) Link to Posting
- *New Draft Guidance for Mannitol Powder* (NDA 202049). (Feb. 15, 2024) Link to Posting

OUTCOMES *continued*

- *New Draft Guidance for Mannitol Powder* (NDA 022368). (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Tobramycin Powder.* (May 16, 2024) Link to Posting
- *New Draft Guidance for Zanamivir Powder.* (Feb. 15, 2024) Link to Posting

Articles

- Chopski S, Hu M, Walenga R, Boc S, Newman B, Kakhi M, Zhao L, and Guha S. *Novel Method for Aerodynamic Particle Size Distribution Measurements from Respimat® Inhalers.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 436-439.
- Clerman A, and Luke M. Comment to *Comparative Effectiveness and Safety of Generic Versus Brand-Name Fluticasone–Salmeterol to Treat Chronic Obstructive Pulmonary Disease.* Annals of Internal Medicine. (2024) 177: eL230428. https://doi.org/10.7326/L23-0428. PMID: 37549393.
- Dutta R, Kolanjiyil A, Walenga R, Chopski S, Kaviratna A, Mohan A, Newman B, Golshahi L, and Longest W. *CFD-PK Model for Nasal Suspension Sprays: Validation with Human Adult In Vivo Data for Triamcinolone Acetonide.* International Journal of Pharmaceutics. (2024) 665:124660. https://doi.org/10.1016/j.ijpharm.2024.124660. PMID: 39236773.
- Esmaeili A, Wilkins J, Hosseini S, Alfaifi A, Hejazi M, Hindle M, Longest W, Schuman T, Dhapare S, Kaviratna A, Walenga R, Newman B, and Golshahi L. *In Vitro Evaluation of Intersubject Variability in Pediatric Intranasal Drug Delivery Using Nasal Spray Suspension Products.* Journal of Aerosol Science. (2024) 179: 106387. https://doi.org/10.1016/j.jaerosci.2024.106387.
- Hastedt J, Backman P, Cabal A, Clark A, Ehrhardt C, Forbes B, Hickey A, Hochhaus G, Jiang W, Kassinos S, Kuehl P, Prime D, Son Y, Teague S, Tehler U, and Wylie J. *iBCS: 3. A Biopharmaceutics Classification System for Orally Inhaled Drug Products.* Molecular Pharmaceutics. (2024) 21: 164-172. https://doi.org/10.1021/acs.molpharmaceut.3c00685. PMID: 38059771.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 440-443.
- Joseph B, Khanal D, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, Chan H, and Banaszak Holl, M. *The Use of Atomic Force Microscope-Infrared Spectroscopy to Assess Co-Localization of Fluticasone/ Salmeterol/ Lactose in Advair Diskus® 100/50 Formulations.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 461-464.
- Khanal D, Haque S, Joseph B, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, Chan H, and Banaszak Holl M. *Optical Photothermal Infrared Spectroscopic Assessment of Fluticasone/ Salmeterol/ Lactose Co-Association in Advair Diskus® and Wixela Inhub®.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 499-503.
- Khadka P, Hejazi M, Hindle M, Schuman T, Longest W, Kaviratna A, Chopski S, Walenga R, Newman B, Golshahi L. *Anatomically-Detailed Segmented Representative Adult and Pediatric Nasal Models for Assessing Regional Drug Delivery and Bioequivalence with Suspension Nasal Sprays.* International Journal of Pharmaceutics. (2024) 666: 124743. https://doi.org/10.1016/j.ijpharm.2024.124743. PMID: 39343330.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Pharmacokinetic Models for Inhaled Fluticasone Propionate and Salmeterol Xinafoate to Quantify Batch-to-Batch Variability.* The AAPS Journal. (2024) 26: 56. https://doi.org/10.1208/s12248-024-00913-x. PMID: 38671158.

OUTCOMES *continued*

- Reed N, Lee Y, Ballard B, Feibus K, Luke M, and Changning G. *Characterizing Adasuve® (Loxapine, 10 mg) Inhalation Powder Particle Size Distribution Using Laser Diffraction.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 444-447.
- Walenga R, Tsakalozou E, Chopski S, Fang L, and Zhao L. *Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 448-451.
- Wanasathop A, Sonju J, Boc S, Mohan A, Dhapare S, Bielski E, Newman B, Ashraf M, Xu X, and Yang Y. *Characterization of Spray-dried Phospholipid Porous Particles for Inhalation Drug Delivery.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 432-435.
- Zhu Q, Kakhi M, Jayasundara C, Walenga R, Behara S, Chan H, and Yang R. *CFD-DEM Investigation of the Effects of Aperture Size for a Capsule-based Dry Powder Inhaler.* International Journal of Pharmaceutics. (2023) 647: 123556. https://doi.org/10.1016/j.ijpharm.2023.123556. PMID: 37890648.

Posters

- Chopski S, Hu M, Walenga R, Boc S, Newman B, Kakhi M, Zhao L, and Guha S. *Novel Method for Droplet Size Distribution Measurements from Respimat Inhalers.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Geiger R, Rahman S, Roni M, Tariq I, Ismaiel O, Shea K, Matta M, Ribeiro A, Jiang W, Walenga R, Newman B, and Ford K. *Assessment of Drug Permeability Using a Lung Microphysiological System.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.
- Yang Y, Wanasathop A, Zhang Y, Sonju J, Mohan A, Boc S, Dhapare S, Bielski E, Newman B, Ashraf M, and Xu X. *Understanding How the Manufacturing Process Affects the Quality of Spray-dried Phospholipid Porous Particles for Inhalation.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Joseph B, Khanal D, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, Chan H, and Holl M. *The Use of Atomic Force Microscope-Infrared Spectroscopy to Assess Co-localization of Fluticasone Propionate/Salmeterol Xinafoate/Lactose Monohydrate in Advair Diskus 100/50 and Wixela Inhub 100/50.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 04, 2024.
- Walenga R, Tsakalozou E, Chopski S, Fang L, and Zhao L. *Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Reed N, Lee Y, Ballard B, Feibus K, Luke M, and Guo C. *Characterizing Adasuve® (Loxapine, 10 mg) Inhalation Powder Particle Size Distribution Using Laser Diffraction.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 05, 2024.

OUTCOMES *continued*

- Boc S, Wanasathop A, Sonju J, Mohan A, Dhapare S, Bielski E, Newman B, Ashraf M, Xu X, and Wang Y. *Characterization of Spray-dried Phospholipid Porous Particles for Inhalation Drug Delivery.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 04, 2024.
- Khanal D, Haque S, Joseph B, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, Chan H, and Holl M. *Optical Photothermal Infrared Spectroscopic Assessment of Fluticasone/Salmeterol/Lactose Co-Association in Advair Diskus 100/50 and Wixela Inhub 100/50.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 04, 2024.
- Hejazi M, Khadka P, Esmaeili A, Schuman T, Kaviratna A, Newman B, Walenga R, Hindle M, Longest W, and Golshahi L. *Understanding the Relationship Between In Vitro Nasal Spray Characteristics and Intranasal Deposition in the Adult and Pediatric Populations.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Kaviratna A, Mohan A, Newman B, Walenga R, Dutta R, Kolanjiyil A, Longest P, and Golshahi L. *In Silico Predictive Modeling of the Pharmacokinetic (PK) Profiles of Nasal Sprays in Adults and Children.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Mohan A, Berger S, Dhapare S, Newman B, Svensson M, Elfman P, Winner L, Bulitta J, and Hochhaus G. *Evaluating the Dissolution of Commercially Available Metered Dose Inhaler (MDI) Drug Products from Realistic In Vitro Experiments.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Walenga R. *Orally Inhaled Drug Product PSGs: Considerations for Using Modeling and Simulation with Alternative BE Approaches.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Han L. *Orally Inhaled Drug Product PSGs: General Considerations Using the Alternative Bioequivalence (BE) Approach In Lieu of Comparative Clinical Endpoint (CCEP) BE Study for Suspension-Based Metered Dose Inhalers.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.
- Clerman A. *Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled Drug Products.* Presentation at the American Thoracic Society (ATS) 2024 International Conference. San Diego, CA, May 22, 2024.
- Newman B and Luke M. *FDA Perspective on Scientific and Regulatory Considerations for MDIs Transitioning to a Low Global Warming Potential Propellant.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 09, 2024.
- Walenga R. *FDA Recommendations for Alternative Bioequivalence Approaches: Design, Validation, and Use Case for In Silico Studies.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 07, 2024.

OUTCOMES *continued*

- Bielski E, and Boc S. *FDA Recommendations for Alternative Bioequivalence Approaches: Design and Rationale for In Vitro and In Vivo Studies.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 07, 2024.
- Chopski S, Hu M, Walenga R, Boc S, Newman B, Kakhi M, Zhao L, and Guha S. *Novel Method for Aerodynamic Particle Size Distribution Measurements from Respimat Inhalers.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Joseph B, Khanal D, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, and Chan H. *The Use of Atomic Force Microscope-Infrared Spectroscopy to Assess Co-localization of Fluticasone Propionate/ Salmeterol Xinafoate/Lactose Monohydrate in Advair Diskus 100/50 and Wixela Inhub 100/50.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Khanal D, Haque S, Joseph B, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc S, Chan H, and Holl M. *Optical Photothermal Infrared Spectroscopic Assessment of Fluticasone/Salmeterol/Lactose Co-association in Advair Diskus 100/50 and Wixela Inhub 100/50.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Yang Y, and Boc S. *Characterization of Spray-dried Phospholipid Porous Particles for Inhalation Drug Delivery.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tuscon, AZ, May 06, 2024.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Walenga R, Tsakalozou E, Chopski S, Fang L, and Zhao L. *Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Bielski E. *Recent Updates for the Use of Alternative Approaches for Demonstrating Bioequivalence with OIDPs.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 17, 2024.
- Han L, Bielski E, and Ma T. *Bioequivalence Approaches for Orally Inhaled Drug Products.* Presentation at the Meeting with Japan Pharmaceuticals and Medical Devices Agency (PMDA). Silver Spring, MD, Apr. 15, 2024.
- Yang Y. *Effect of the Manufacturing Process Parameters on Critical Quality Attributes of Emerging Spray-Dried Phospholipid Porous Particles for Inhalation Drug Delivery.* Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2024. Bethesda, MD, Mar. 04, 2024.
- Chopski S, Al Ghabeish M, Babiskin A, Zhao L, and Walenga R. *Physiologically Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.
- Kozak D. *Generic Drug User Fee Amendments (GDUFA) Research and the Product-Specific Guidance (PSG) Program for Complex Products: Challenges and Notable Advances.* Presentation at the 2023 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 03, 2023.

OPHTHALMIC & OTIC PRODUCTS

Summary of FY 2024 Activities

FDA's research efforts during FY 2024 focused on tackling challenges related to the development and evaluation of generic ophthalmic and otic products, with two major emphases: (1) identifying and characterizing critical physicochemical properties of complex products that influence in vitro, ex vivo, and in vivo performance, and (2) advancing and integrating in silico approaches to deepen the understanding of how drug product properties relate to ocular pharmacokinetics (PK) and pharmacodynamics (PD).

Internal research at FDA has laid a strong scientific foundation to support the revision of multiple guidance documents by streamlining bioequivalence (BE) recommendations. Specifically, FDA concluded that comparative in vitro microbial kill rate studies do not provide meaningful data for demonstrating ophthalmic antimicrobial drug product equivalence. Moreover, research at FDA continued to investigate novel implantable and insertable ophthalmic products, aiming to support future guidance with cutting-edge research.

Externally, in collaboration with Pharmaron (Contract 75F40119D10024-75F40120F19002), FDA completed a preclinical evaluation of ophthalmic suspension drug products aimed at reducing intraocular pressure. This evaluation provided critical insights into how variations in critical quality attributes (CQAs)—such as viscosity and particle size distribution—affect ocular PK/PD, ultimately influencing the in vivo performance of these products. Furthermore, through a partnership with Simulations Plus Inc. (Grant U01FD006927), FDA developed and validated physiologically based PK/PD modeling strategies, supporting the translation of rabbit ocular models to human applications. This significant advancement is part of FDA's broader in silico efforts to establish more clinically relevant BE criteria for complex ophthalmic products, which are further discussed in Section 7.1 (Chapter 7) of this report.

Additionally, the University of Connecticut (Contract HHSF223201810114C) conducted research on ophthalmic ointments, examining the CQAs of complex ointment dispersions with multiple active ingredients. The study established in vivo, ex vivo, and in vitro relationships to estimate product performance, focusing on particle size distribution, rheology, and release kinetics. These findings supported FDA's recommendation of an in vitro-only BE approach for these products as reflected in FDA's Revised Draft Guidance for Dexamethasone; Tobramycin Ointment. Further details on this work are included in the **Research Highlight** below.

Looking ahead, additional GDUFA research initiatives from FY 2024 will continue into FY 2025, including: (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) investigating the impact of preservatives on the ocular BE of topical ophthalmic products (Contract 75F40123C00205).

RESEARCH HIGHLIGHT

Evaluating drug product equivalence in vitro for ophthalmic ointments containing active pharmaceutical ingredients (APIs) in suspended solid state poses significant challenges, particularly in understanding how formulation variables influence drug release. Thus, in collaboration with the University of Connecticut (Contract HHSF223201810114C), a comprehensive study was conducted exploring a series of in vitro studies that guided the selection of formulations for ex vivo and in vivo testing, targeted at deepening the scientific understanding of the interplay between drug product CQAs and performance in terms of in vitro and in vivo drug release.

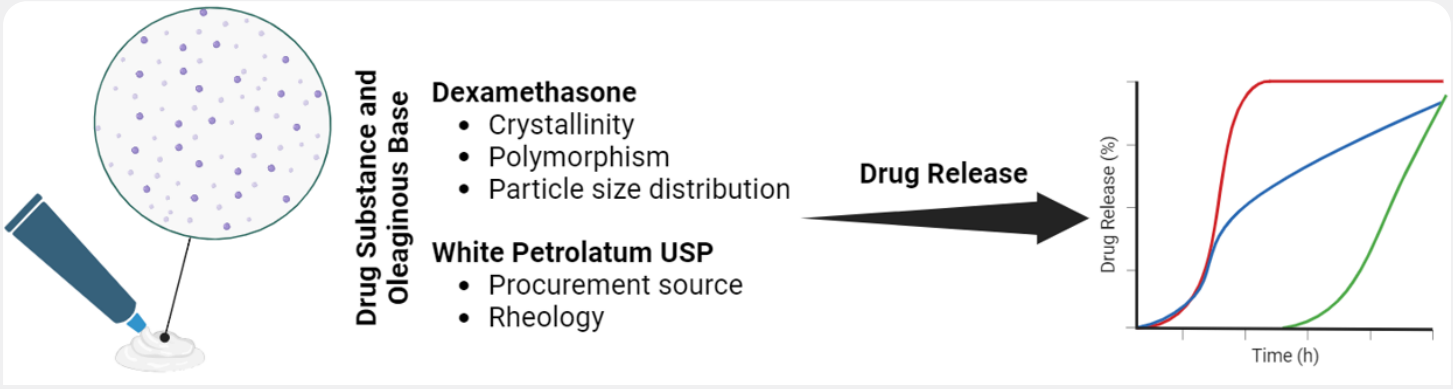


Figure 1. Graphical summary of the study.

A key aspect of the study focused on the impact of polymorphic forms, crystallinity, and particle size distribution of dexamethasone on the in vitro release performance of ophthalmic ointments (Figure 1). In vitro testing showed that ointments containing amorphous dexamethasone exhibited significantly higher release rates compared to crystalline forms. Additionally, dexamethasone form B was associated with slightly higher release rates than form A, although the difference was minor compared to formulations containing partially amorphous dexamethasone. In vitro release performance was mostly impacted by the choice of white petrolatum source (Figure 2A), which led to variations in the rheology of the finished product due to intrinsic variabilities of the oleaginous base. Conversely, variations in average particle diameter (ranging from 5.4 to 21.2 µm) did not significantly impact drug release, with similar release rates observed across different particle sizes (Figure 2B).

These findings from the in vitro release testing (IVRT) study informed the design of an ex vivo study using frozen-thawed rabbit eyeballs incubated with various formulations, including a commercial drug product and test formulations differing in viscosity (Figure 2C). The results indicated that viscosity was the most influential factor affecting the ex vivo release of this lipophilic API from the oleaginous base. The ex vivo release profiles were consistent with the IVRT data, following the same trend, although appearing less discriminating to formulation differences.

An in vivo ocular pharmacokinetic study in rabbits was also conducted to further evaluate the performance of the formulations, focusing on the concentration of dexamethasone in the aqueous humor. The in vivo results followed a similar trend to the IVRT and ex vivo studies but were even less sensitive to differences in the rheological properties of the formulations. Despite these differences, the consistency across in vitro, ex vivo, and in vivo data provides valuable insights into the formulation factors—particularly viscosity—that affect the release of lipophilic APIs from ophthalmic ointments.

In conclusion, the findings from this study emphasize the critical role of rheological properties in controlling drug release from ophthalmic ointments, overshadowing the potential influence of particle size distribution for

RESEARCH HIGHLIGHT *continued*

lipophilic drugs suspended in an oleaginous base, such as dexamethasone in white petrolatum. The results provide a robust framework for the design and evaluation of generic ophthalmic formulations.

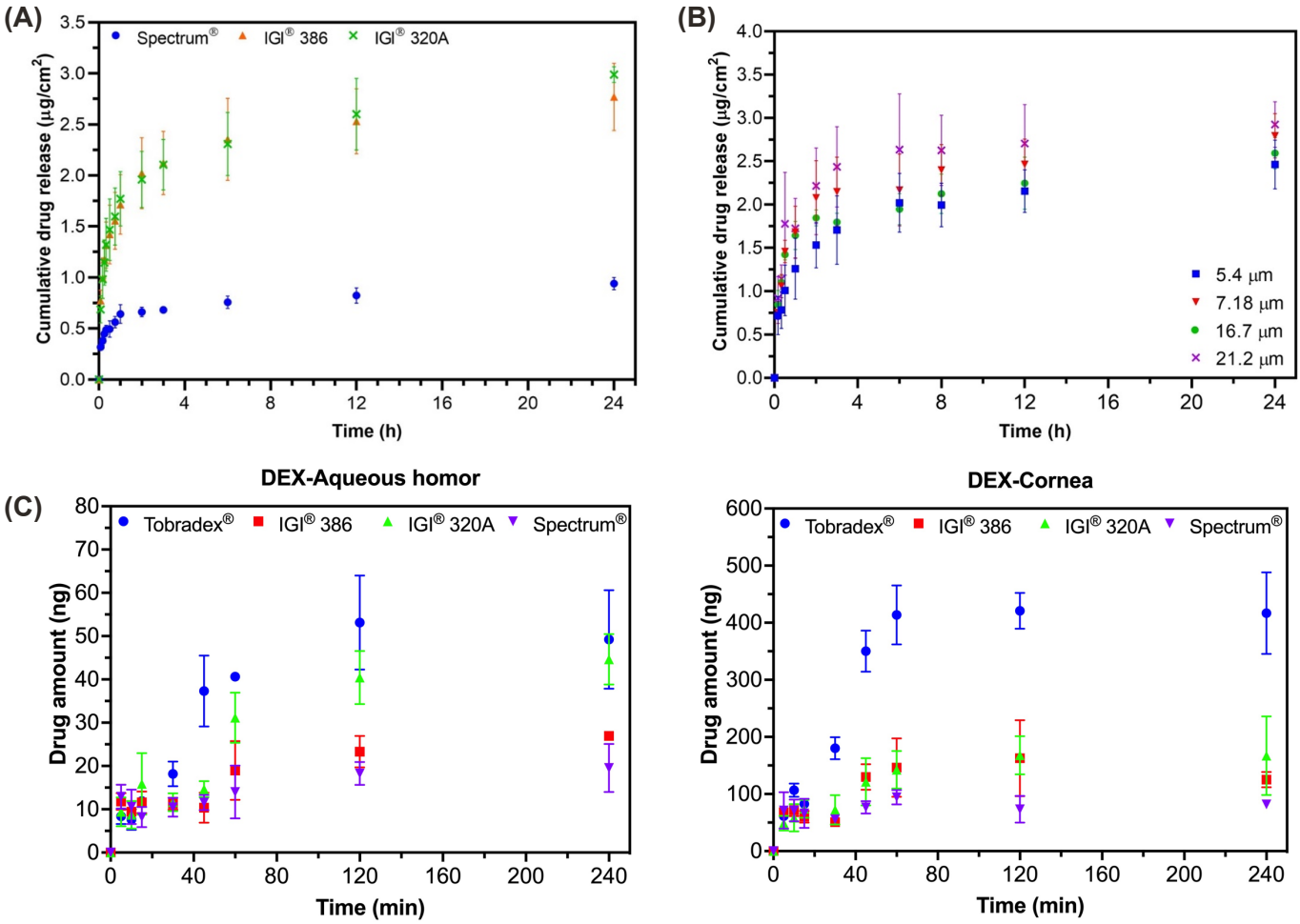


Figure 2. Drug product performance evaluation. (**A**) Impact of white petrolatum source, which varies in viscosity, on dexamethasone in vitro release. (**B**) Impact of dexamethasone particle size in ointment on in vitro release. (**C**) Ex vivo drug distribution content in aqueous humor and cornea as a function of petrolatum source. Data partially available at Mekjaruskul et al. 2023[5] and 2024.[6] Data-points presented as mean ± standard deviation (n=3).

[5] 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.

[6] Mekjaruskul C, Beringhs AO, Qin B, Wang Y, and Lu X. *Impact of Active Pharmaceutical Ingredient Variables and Oleaginous Base on the In Vitro Drug Release from Ophthalmic Ointments: an Investigation Using Dexamethasone as a Model Drug.* International Journal of Pharmaceutics. (2024) 658: 124184. https://doi.org/10.1016/j.ijpharm.2024.124184. PMID: 38692497.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40123C00205) *Understanding Non-Q1Q2 Preservative Effects on Bioequivalence of Topical Ocular Products* with Arto Urtti at University of Eastern Finland

Continuing Grants and Contracts

- 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

Completed Grants and Contracts

- Grant (U01FD006927) *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 Feng Zhang at University of Texas at Austin
- Contract (75F40119D10024-75F40120F19002) *PK/PD of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Pharmaron Laboratory Services Inc. (Former Absorption Systems)

Active FDA Research

- *Assessing New Analytical Methods for Characterization of Complex Excipients in Long Acting Drug Products*
- *Development of an Ophthalmic PBPK Modeling Platform*
- *Evaluation of Dexamethasone Intracanalicular Insert to Support Determination of Bioequivalence*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

OUTCOMES

General Guidance

There was one new general guidance published in FY 2024 related to *Ophthalmic* products.

- Guidance for Industry. *Quality Considerations for Topical Ophthalmic Drug Products.* (Dec., 2023) Link to Posting

Product-Specific Guidances

There were three new and eight revised PSGs published in FY2024 related to *Ophthalmic* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

OUTCOMES *continued*

PSG Research Outcomes

- *Revised Draft Guidance for Ciprofloxacin Hydrochloride; Hydrocortisone Suspension/Drops.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Ciprofloxacin; Dexamethasone Suspension/Drops.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Dexamethasone; Neomycin sulfate; Polymyxin B Sulfate Suspension/ Drops.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dexamethasone; Tobramycin Suspension/Drops* (NDA 050592). (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dexamethasone; Tobramycin Suspension/Drops* (NDA 050818). (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dexamethasone; Tobramycin Ointment.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate Suspension/ Drops.* (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Loteprednol Etabonate Ointment.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Loteprednol Etabonate; Tobramycin Suspension/Drops.* (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Risperidone for Suspension, Extended Release.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance on Tafluprost Solution/Drops.* (Aug. 22, 2024) Link to Posting

Articles

- Beringhs AO, Mekjaruskul C, Qin B, Wang Y, and Lu X. *Exploring the Influence of Drug Substance Solid-State Properties on the In Vitro Drug Release Performance of Dexamethasone Ophthalmic Ointments.* IOVS: Investigative Ophthalmology & Visual Science. (2024) 65: 3961.
- Costello M, Liu J, Kuehster L, Wang Y, Qin B, Xu X, Li Q, Smith W, Lynd N, and Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Molecular Pharmaceutics. (2023) 20(12): 6330-6344. https://doi.org/10.1021/acs.molpharmaceut.3c00742. PMID: 37955890.
- Kuehster L, Dai J, Thompson A, Jhon Y, Wang Y, Bin Q, Smith W, Xu X, Zhang F, and Lynd N. *Analysis of Copolymerization with Simultaneous Reversibility and Transesterification by Stochastic Model Regression.* Macromolecules. (2024) 57(9): 4034-4044. https://doi.org/10.1021/acs.macromol.4c00037.
- Le Merdy M, Spires J, Tan M-L, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for a Complex Ophthalmic Suspension Using Physiologically Based Pharmacokinetic Modeling and Simulation.* Pharmaceutics. (2024) 16(7): 914. https://doi.org/10.3390/pharmaceutics16070914. PMID: 39065612.
- Mekjaruskul C, Beringhs AO, Qin B, Wang Y, and Lu X. *Impact of Active Pharmaceutical Ingredient Variables and Oleaginous Base on the In Vitro Drug Release from Ophthalmic Ointments: an Investigation Using Dexamethasone as a Model Drug.* International Journal of Pharmaceutics. (2024) 658: 124184. https://doi.org/10.1016/j.ijpharm.2024.124184. PMID: 38692497.

OUTCOMES *continued*

Posters

- Beringhs AO, Naageshwaran V, Gum G, Malla S, Vo A, Smith W, Tan M, Babiskin A, Wang Y, Xu X, and Kozak D. *Preclinical Evaluation of Brinzolamide Ophthalmic Suspensions with Variations in Critical Quality Attributes and Considerations for Pharmacokinetic and Pharmacodynamic Study Designs.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Plavchak C, Smith W, Vandenberg M, Zaman R, Beringhs A, Wang Y, and Xu X. *Assessing Q1/Q2 Sameness of Polyethylene Glycol Star Polymers as Polymeric Excipients in Ophthalmic Implants Using Size Exclusion Chromatography and Thermal Field-Flow Fractionation.* Poster Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 18, 2024.
- Plavchak C, Smith W, Vandenberg M, Zaman R, O'Reilly Beringhs A, Wang Y, and Xu X. *Assessing Q1/Q2 Sameness of Polyethylene Glycol Star Polymers as Polymeric Excipients in Dexamethasone Ophthalmic Inserts.* Poster Presentation at the 23rd International Symposium on Field- and Flow-based Separations. Nantes, France, Jun. 03, 2024.
- Beringhs AO, Mekjarusku C, Qin B, Lu X, and Wang Y. *Exploring the Influence of Drug Substance Solid-State Properties on the In Vitro Drug Release Performance of Dexamethasone Ophthalmic Ointments.* Poster Presentation at the 2024 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Seattle, WA, May 05, 2024.
- Alqaraghuli F, Le Merdy M, Tan M-L, and Lukacova V. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Ofloxacin Ointment Case Study.* Poster Presentation at the 2024 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Salt Lake City, UT, May 04, 2024.
- Beringhs AO, Naageshwaran V, Gum G, Malla S, Vo A, Smith W, Tan M, Babiskin A, Xu X, and Kozak D. *Preclinical Evaluation of Brinzolamide Ophthalmic Suspensions with Variations in Critical Quality Attributes and Considerations for Pharmacokinetic/Pharmacodynamic Study Designs.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Costello M, Liu J, Kuehster L, Wang Y, Qin B, Lynd N, and Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Le Merdy M, Alqaraghuli F, Mullin J, and Lukacova V. *Development of an Ocular PBPK-PD Model to Predict Drug-Mediated Intraocular Pressure Reduction in Preclinical Species.* Poster Presentation at the American Conference on Pharmacometrics (ACoP) 2023. National Harbor, MD, Nov. 06, 2023.

Presentations

- Zhu D. *Application of Adaptive Perfusion as In Vitro Release Testing Method to Improve Understanding and Assessment of Complex Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.
- German C. *A Synergistic In Vitro-In Silico Framework Using MPS Combined with Computational Modeling as a Tool for Translational Research and Drug/Toxicity Screening.* Presentation at the Microphysiological Systems (MPS) World Summit 2024. Seattle, WA, Jun. 11, 2024.

OUTCOMES *continued*

- Xu X. *In Vitro Release Test for Complex Drug Products: Thinking Outside the Box.* Presentation at the Disso America 2024. Dissolution Science: Complex Drug Products Conference. Piscataway, NJ, Jun. 11, 2024.
- Xu X. *Perception and Perspective: Fundamentals to Advance Complex Drug Product Development.* Presentation at the AAPS Student Chapter at University of Texas. Austin, TX, Apr. 09, 2024.
- Le Merdy M. *PBPK Models of Complex Injectable and Ophthalmic Drug Products: Case Studies.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Zhang F. *Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.

TOPICAL PRODUCTS

Summary of FY 2024 Activities

During fiscal year (FY) 2024, 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. Since 2018, efficient bioequivalence (BE) approaches developed and implemented within the scope of the program have supported the approval of >75 abbreviated new drug applications (ANDAs).

The research program continued to focus on 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 2024, data from FDA-funded research studies supported the development of dermal physiologically based pharmacokinetic (PBPK) models by leveraging the physicochemical and structural (Q3) characterization data, in vivo pharmacokinetic (PK) data and in vitro permeation test (IVPT) data. The enhanced understanding of the relationship of the Q3 characteristics of single-phase gels to their in vivo performance provided by the PBPK modeling substantially minimizes the risk of potential differences in local or systemic bioavailability (BA) for test products that meet the criteria for no significant difference in components and composition relative to the reference

standard. The research supported revisions to product-specific guidances (PSGs).[7,8,9] A more detailed description of these research can be found in Chapter 7 "Quantitative Methods & Models", and specifically in Subsection 1 describing "Mechanistic Modeling for Non-Orally Administered Drug Products".

The GDUFA research program also supported the development and evaluation of in vitro release test (IVRT) and IVPT methods to support demonstrations of BE for generic topical drug products. During FY 2024, internal FDA research demonstrated the feasibility of developing IVPT methods to assess the rate and extent to which clascoterone and other molecules permeate across the skin from their respective topical products.[10,11] These IVPT studies supported the development and revisions of PSGs to include efficient characterization-based BE approaches. External GDUFA funded research at the University of Rhode Island (Grant U01FD007656) is ongoing to develop characterization-based BE approaches for complex vaginal and rectal products, such as suppositories and creams, including the evaluation of methodologies for assessing local bioavailability for such products.

FDA also prioritized research to understand mechanisms that allow 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/ex vivo experiments were performed through collaborations with the University of South Australia (Grant U01FD006496) and the Topical Product Testing LLC (Grant U01FD006507) (see **Research Highlight** below). In FY 2024, new collaborations were initiated with Mercer University (Contract 75F40123C00204) and Rutgers, the State University of New Jersey (Contract 75F40123C00213). 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 BA. Additionally, a research collaboration with the University of Queensland (Grant U01FD006700) studied how differences in specific Q3 attributes that can impact sensorial properties of topical products (e.g., spreadability, smoothness) may be perceived by human subjects. A distinct research initiative focused on developing efficient in vivo PK-based methods to directly monitor the drug's bioavailability at or near its site(s) of action in the skin. During FY 2024, studies were conducted to address the remaining challenges associated with the utilization of dermal open flow microperfusion (dOFM) and dermal microdialysis (dMD) as efficient cutaneous PK-based BE approaches at Joanneum Research (Grant U01FD007669). Independently, research at the University of Bath (Grant U01FD006533) and Massachusetts General Hospital/Harvard Medical School (Grant U01FD006698) developed sensitive and discriminating non-invasive cutaneous PK-based methods using advanced confocal Raman imaging techniques.

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[7] *Revised Draft Guidance for Dapsone Gel* (NDA 207154). (Feb. 15, 2024) Link to Posting

[8] *Revised Draft Guidance for Dapsone Gel* (NDA 021794). (Feb. 15, 2024) Link to Posting

[9] Tsakalozou E. *Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation – A Case Study with Dapsone Topical Gel.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024

[10] Yang Y, Wang J, Wanasathop A, Niu M, Ghosh P, Zidan A, Gu J, Hunt R, Faustino P, Ashraf M, and Xu X. *Evaluation of In Vitro Skin Permeation of Clascoterone from Clascoterone Topical Cream, 1% (w/w)*. AAPS PharmSciTech. (2024) 25(6): 186. https://doi.org/10.1208/s12249-024-02887-7. PMID: 39138712.

[11] *Revised Draft Guidance for Clascoterone Cream.* (Aug. 16, 2023) Link to Posting

RESEARCH HIGHLIGHT

Evaporative metamorphosis of topical products can lead to significant changes in the quantitative composition of the formulation (residue) on the skin over time. As the solvent(s) evaporate, the concentration of solubilized active pharmaceutical ingredient (API) increases in the diminishing amount of solvent(s), typically up to the saturation solubility of the API. This phenomenon can be characterized as a function of the fractional solubility (α) versus time, where the parameter α is defined as the ratio of the concentration of API in a formulation to the saturation solubility of the API in the same formulation at any given time. Topical products that have differences in their formulations may have differences in their fractional solubility-time profiles, which would correspond to differences in the thermodynamic activity of the API in the formulation over time, and to potential differences in the rate and extent of BA. Over the last few years, FDA has funded research to develop new tools that can be used to assess the impact of differences in formulation on BA. The data generated so far encompass metronidazole, lidocaine and diclofenac sodium, three APIs with distinct physicochemical properties. The goal of the research was to assess the feasibility of using fractional solubility-time profiles in conjunction with IVPT to evaluate the impact of quantitative differences in formulation on the performance of topical products. Topical gels comprised of polyethylene glycol (PEG-200), ethylenediaminetetraacetic acid (EDTA), sodium benzoate, hydroxyethylcellulose and water were manufactured. The concentration of PEG-200 was varied across the formulations from 1% to 20% w/w based on the assumption that changes in the amount of the solubilizing agent would lead to changes in the saturation solubility of the API in the formulations during metamorphosis. A drying study was performed on human cadaver skin in Franz diffusion cells where the donor compartment was sampled periodically for up to 6 h to assess the changing composition of the formulation during evaporative metamorphosis. The data (in conjunction with saturation solubility data of each of the APIs in PEG 400- water solutions) were used to calculate α. A semi-finite dose IVPT study was conducted using similar study conditions as the drying rate study described above. The current datasets suggest that when there are differences in fractional solubility-time profiles between formulations, such differences may result in differences in BA of the API from the topical formulations as evaluated using IVPT. Therefore, it may be feasible to utilize fractional solubility-time profiles in conjunction with IVPT to evaluate the impact of quantitative differences in inactive ingredients on the performance of topical products. Additional research is underway to develop and generalize such methodologies for multiple inactive ingredients.[12,13]

[12] Rangappa S, Ghosh P, Jiang Y, Raney SG, and Narasimha Murthy S. *Impact of Quantitative Differences in an Inactive Ingredient on the Performance of Topical Products Containing Lidocaine or Diclofenac Sodium.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

[13] Ramezanli T. *Approaches for Evaluation of Formulation Differences on Performance of Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid meeting, Bethesda, MD, Sep. 24, 2024.

RESEARCH HIGHLIGHT *continued*

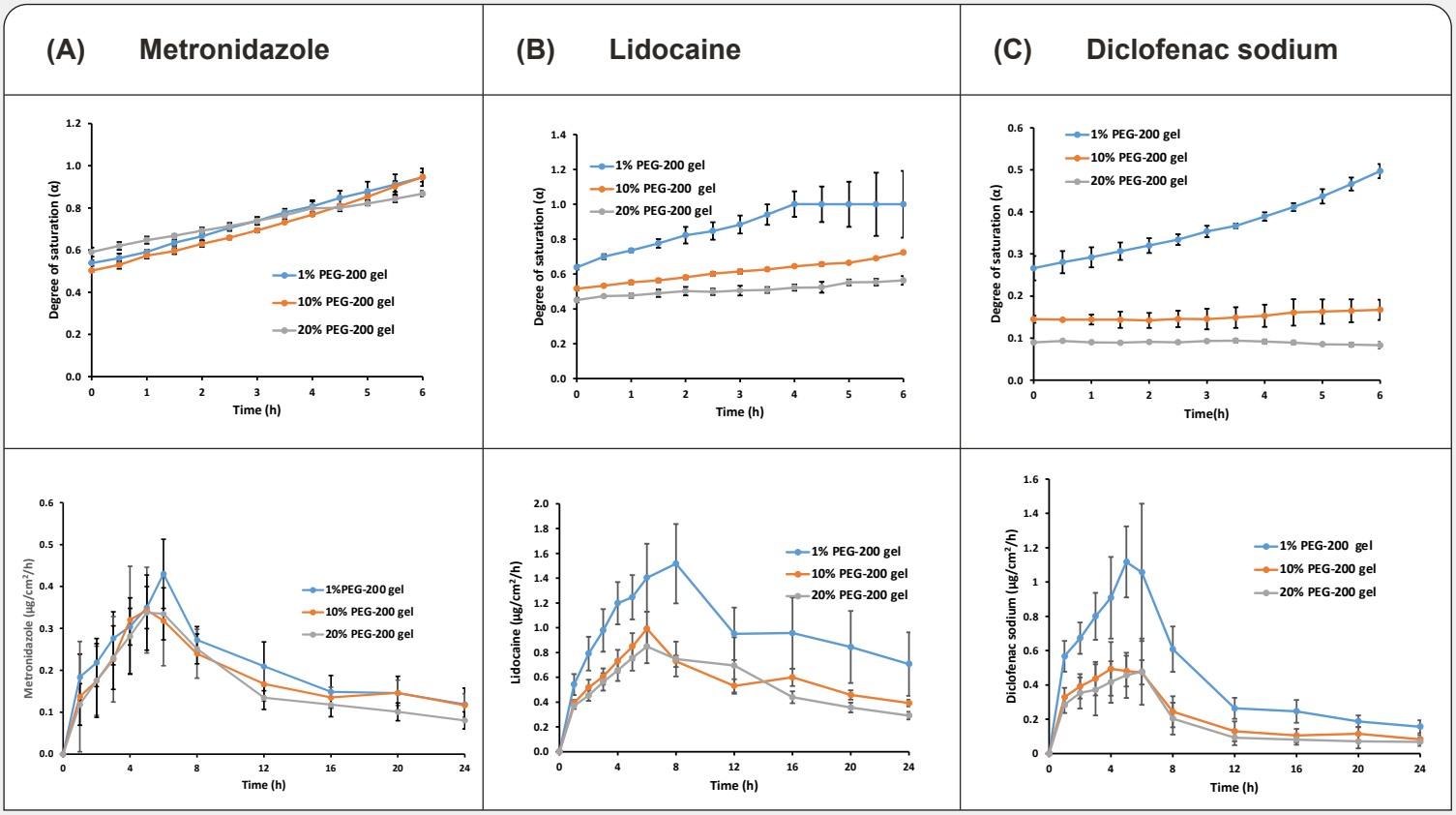

Figure 1. Drug product performance evaluation. Fractional solubility (n=3) and IVPT (n=3 donors, 6 replicates per donor) of (**A**) metronidazole from 0.75% metronidazole containing topical gels (**B**) 0.25% lidocaine containing topical gels, and (**C**) 0.5% diclofenac sodium containing topical gels. Data-points presented as mean ± standard deviation for fractional solubility data and mean ± standard error for IVPT data.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Grant (U01FD006700) *Bioequivalence of Topical Products: Elucidating the Sensorial and Functional Characteristics of Compositionally Different Topical Formulations* with Yousuf Hussain Mohammed at University of Queensland
- Grant (U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques (U01)* with Richard H. Guy at University of Bath
- Grant (U01FD007957) *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 (U01FD007954) *Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients* with James Clarke at Certara UK Limited

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- Grant (U01FD007656) *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 (U01FD007669) *Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics* with Frank Sinner at Johanneum Research
- Grant (U01FD007323) *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
- Grant (U01FD007348) *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
- Grant (U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Contract (75F40123C00204) *In Vitro Tests to Support Bioequivalence Determination When Generic Dermatological Formulation has Differences from the Brand Product Formulation* with Ajay K. 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 at Rutgers University

Completed Grants and Contracts

- Grant (U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at University of South Australia
- Grant (U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Sathyanarayana N Murthy at University of Mississippi
- Grant (U01FD006521) *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 (U01FD007320) *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 (U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with David Taft at Long Island University, Brooklyn Campus

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *Methodologies to Support in Vitro Based BE Approaches (Internal Research)*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-Based Approach*

OUTCOMES

Product-Specific Guidances

There were five new and ten revised PSGs published in FY2024 related to *Topical* products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *Revised Draft Guidance for Azelaic Acid Cream.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Benzoyl Peroxide; Erythromycin Gel* (NDA 050769). (May 16, 2024) Link to Posting
- *Revised Draft Guidance for Benzoyl Peroxide; Erythromycin Gel* (NDA 050557). (May 16, 2024) Link to Posting
- *Revised Draft Guidance for Betamethasone Dipropionate; Clotrimazole Lotion.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Betamethasone Dipropionate; Clotrimazole Cream.* (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Caffeine; Ergotamine Tartrate Suppository.* (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Chlorhexidine Gluconate Solution.* (Nov. 16, 2023) Link to Posting
- *Revised Draft Guidance for Dapsone Gel (NDA 207154).* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dapsone Gel (NDA 021794).* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dexamethasone; Tobramycin Ointment.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Halobetasol Propionate Ointment.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Halobetasol Propionate; Tazarotene Lotion.* (Nov. 16, 2023) Link to Posting
- *New Draft Guidance for Progesterone Insert.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Tapinarof Cream.* (Nov. 16, 2023) Link to Posting
- *Revised Draft Guidance for Tretinoin Gel.* (May 16, 2024) Link to Posting

Articles

- Elfakhri K, Niu M, Ghosh P, Ramezanli T, Raney S, Kamal N, Ashraf M, and Zidan A. *Understanding the Impact of Formulation Design on Microstructure and Drug Release from Porous Microparticle-Based Tretinoin Topical Gels.* International Journal of Pharmaceutics. (2024) 653: 123794. https://doi.org/10.1016/j.ijpharm.2024.123794. PMID: 38216074.
- Iliopoulos F, Tu D, Pence I, Li X, Ghosh P, Luke M, Raney S, Rantou E, and Evans C. *Determining Topical Product Bioequivalence with Stimulated Raman Scattering Microscopy.* Journal of Controlled Release. (2024) 367: 864-876. https://doi.org/10.1016/j.jconrel.2024.02.010. PMID: 38346503.
- Luke M. *Locally Acting Dermatology Drug Products: Pharmaco-analytic Considerations for Bioequivalence.* European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences. (2024) 199: 106815. https://doi.org/10.1016/j.ejps.2024.106815. PMID: 38797441.
- Mohammed Y, Namjoshi S, Jung N, Windbergs M, Benson E, Grice J, Raney S, and Roberts M. *Topical Semisolid Drug Product Critical Quality Attributes with Relevance to Cutaneous Bioavailability and Pharmacokinetics: Part I - Bioequivalence of Acyclovir Topical Creams.* Pharmaceutical Research. (2024) 41: 1507-1520. https://doi.org/10.1007/s11095-024-03736-9. PMID: 38955999.

OUTCOMES *continued*

- Mohammed Y, Namjoshi S, Telaprolu K, Jung N, Shewan H, Stokes J, Benson H, Grice J, Raney S, Rantou E, Windbergs M, and Roberts M. *Impact of Different Packaging Configurations on a Topical Cream Product.* Pharmaceutical Research. (2024) 41(10):2043-2056. https://doi.org/10.1007/s11095-024-03772-5. PMID: 39349693.

- Moore K, Grégorie S, Eilstein J, Begona Delgado-Charro M, and Guy R. *Reverse Iontophoresis: Noninvasive Assessment of Topical Drug Bioavailability.* Molecular Pharmaceutics. (2024) 21(1): 234- 244. https://doi.org/10.1021/acs.molpharmaceut.3c00791. PMID: 38060844.

- Pal A, Wu F, Walenga R, Tsakalozou E, Alam K, Gong Y, Zhao L, and Fang L. *Leveraging Modeling and Simulation to Enhance the Efficiency of Bioequivalence Approaches for Generic Drugs: Highlights from the 2023 Generic Drug Science and Research Initiatives Public Workshop.* The AAPS Journal. (2024) 26: 45. https://doi.org/10.1208/s12248-024-00916-8. PMID: 38589695.

- Raney S, Senemar S, Burke M, Lee C, Shah J, Li K, Anand O, and Warner K. *Advances in Product Quality and Performance Tests for Topical and Transdermal Products: View of the USP Expert Panel.* Dissolution Technologies. (2024) 31: 6-12. https://doi.org/10.31003/USPNF_S203204_10101_01.

- Tiffner K, Ramezanli T, Boulgaropoulos B, Birngruber T, Bodenlenz M, Lackner B, Raml R, Jiang Y, Raney S, and Sinner F. *Cutaneous Pharmacokinetics-based Bioequivalence: A Clinical Dermal Open Flow Microperfusion Verification Study Using Lidocaine and Prilocaine Combination Topical Products.* European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences. (2024) 200: 106827. https://doi.org/10.1016/j.ejps.2024.106827. PMID: 38857708.

- Tsakalozou E, Mohamed M, Polak S, and Heimbach T. *Applications of Modeling and Simulation Approaches in Support of Drug Product Development of Oral Dosage Forms and Locally Acting Drug Products: a Symposium Summary.* The AAPS Journal. (2024) 25(6): 96. https://doi.org/10.1208/s12248-023-00862-x. PMID: 37783902.

- Van Osdol W, Novakovic J, Le Merdy M, Tsakalozou E, Ghosh P, Spires J, and Lukacova V. *Predicting Human Dermal Drug Concentrations Using PBPK Modeling and Simulation: Clobetasol Propionate Case Study.* AAPS PharmSciTech. (2024) 25: 39. https://doi.org/10.1208/s12249-024-02740-x. PMID: 38366149.

- Yang Y, Wang J, Wanasathop A, Niu M, Ghosh P, Zidan A, Gu J, Hunt R, Faustino P, Ashraf M, and Xu X. *Evaluation of In Vitro Skin Permeation of Clascoterone from Clascoterone Topical Cream, 1% (w/w).* AAPS PharmSciTech. (2024) 25(6): 186. https://doi.org/10.1208/s12249-024-02887-7. PMID: 39138712.

- Zarmpi P, Tsikritis D, Vorng J, Belsey N, Bunge A, Woodman T, Begona Delgado-Charro M, and Guy RH. *Evaluation of Chemical Disposition in Skin by Stimulated Raman Scattering Microscopy.* Journal of Controlled Release. (2024) 368: 797-807. https://doi.org/10.1016/j.jconrel.2024.02.011. PMID: 38350493.

OUTCOMES *continued*

Posters

- Chauhan A, Xie L, Kelchen M, Ghosh P, Raney S, and Shen J. *Development of an In Vitro Release Test Method for Miconazole Nitrate (MN) Vaginal Suppositories.* Poster Presentation at the Controlled Release Society (CRS) 2024 Annual Meeting and Exposition. Bologna, Italy, Jul. 08, 2024.

- Phan K, Leite-Silva V, Prakash S, Liu D, Ramezanli T, Ghosh P, Natarajan K, Raney S, Luke M, Roberts M, and Mohammed Y. *Critical Quality Attributes Enhance Understanding of Skin Sensory Perceptions.* Poster Presentation at the Controlled Release Society (CRS) 2024 Annual Meeting and Exposition. Bologna, Italy, Jul. 08, 2024.

- Tabosa M, Zhang Y, Polak S, and Clarke J. *Analysis of Topical Formulations: Investigating Inactive Ingredients and their Volatility.* Poster Presentation at the 19th Skin Forum Annual. London, UK, Jun. 25, 2024.

- Kelchen M, Xie L, Ramezanli T, Jiang Y, Luke M, and Ghosh P. *Impact of Formulation and Manufacturing on Drug Delivery from Topical Drug Products Applied to the Skin.* Poster Presentation at the 2024 SID Annual Meeting - Society for Investigative Dermatology. Dallas, TX, May 15, 2024.

- Xie L, Kelchen M, Luke M, and Ghosh P. *Current Bioequivalence Approaches Utilized in Generic Drug Applications for Topical Drug Products Applied to the Skin.* Poster Presentation at the 2024 International Dermatology Outcome Measures (IDEOM) Annual Meeting. Washington, DC, Apr. 05, 2024.

- Tiffner K, Ramezanli T, Birngruber T, Bodenlenz M, Teles F, Schwagerle G, Raml R, Kainz S, Raney S, and Sinner F. *A Clinical Dermal Open Flow Microperfusion Study to Assess Bioequivalence of Topically Applied Diclofenac Products Using Cutaneous Pharmacokinetic Endpoints.* Poster Presentation at the PBP 2024: 14th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology. Vienna, Austria, Mar. 18, 2024.

- Mangion S, Dalton J, Mackenzie L, Tsakalozou E, Clarke J, Polak S, and Roberts M. *Mapping Skin Properties in Psoriasis for Improved Understanding of Topical Absorption.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

- Russo J, Jiang Y, and Ghosh P. *Correlation Between Generic Product Approvals and Price for Drug Products Applied to the Skin.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

- Russo J, Jiang Y, Ghosh P, and Luke M. *Irritation and Sensitization Potential of Approved Topical and Transdermal Delivery Systems – A Retrospective Study.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

- Phan K, Leite-Silva V, Prakash S, Liu D, Namjoshi S, Panchal B, Ramezanli T, Ghosh P, Natarajan K, Raney S, Luke M, Roberts M, and Mohammed Y. *Sensory Panel Tests for Topical Semi-Solid Gels: Role of Critical Quality Attributes in Predicting Sensorial Perceptions.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Rangappa S, Ghosh P, Jiang Y, Raney SG, and Narasimha Murthy S. *Impact of Quantitative Differences in an Inactive Ingredient on the Performance of Topical Products Containing Lidocaine or Diclofenac Sodium.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

- Tiffner K, Ramezanli T, Birngruber T, Bodenlenz M, Teles F, Raml R, Kainz S, Raney S, and Sinner F. *A Clinical Study to Assess the Bioequivalence of Topical Diclofenac Products Using Dermal Open Flow Microperfusion.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

OUTCOMES *continued*

- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Ghosh P, Belsey N, Woodman T, Jane White K, Bunge A, Delgado-Charro M, and Guy R. *Assessment of Bio(in)equivalence of Metronidazole Topical Formulation Using Stimulated Raman Scattering Microscopy.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Ghosh P. *Analysis of ANDA Approval and Major Deficiencies - A Case Study with Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Kelchen M. *Current Trends in Product-Specific Guidance Development & Revisions for Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Ramezanli T. *Approaches for Evaluation of Formulation Differences on Performance of Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid meeting, Bethesda, MD, Sep. 24, 2024.
- Tsakalozou E. *Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation – A Case Study with Dapsone Topical Gel.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Tsakalozou E. *Applications of Mechanistic Modeling and Simulation Tools on the Performance of Locally Acting Complex Drug Products.* Presentation at the MIDD + (Pharmacometry). São Paulo, Brazil, Aug. 15, 2024.
- Luke M. *An FDA Dermatologist's Perspective on Medical Product Regulation in the United States: Including a Focus on Generic Drugs.* Presentations at the Washington University. St. Louis, MO, Jun. 06, 2024.
- Raney S. *Influence of Physicochemical & Structural Formulation Attributes on Topical Bioavailability.* Presentation at the New York Chapter of the Society of Cosmetic Chemists - Sunscreen Formulations: Misconceptions and Future Direction for Innovation. Virtual Meeting, Jun. 03, 2024.
- Walenga R. *Regulatory Perspective on MMF Applications for OIDPs, Ophthalmic Drug Products, and Drug Products Applied on the Skin.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Hybrid Meeting. Rockville, MD, May 03, 2024.
- Luke M. *History of Dermatology and Dermatologists at the U.S. Food and Drug Administration.* Presentation at the Noah Worcester Dermatology Society Annual Meeting. Charleston, SC, Apr. 30, 2024.
- Luke M. *FDA's Regulation of Drug Products Used by Dermatologists and Dermatologic Surgeons.* Presentation at the 43rd ASLMS Annual Conference on Energy-Based Medicine & Science. Baltimore, MD, Apr. 11, 2024.
- Luke M. *FDA Science and Regulation for the Physician Scientist.* Presentation at the Johns Hopkins University School of Medicine. Baltimore, MD, Mar. 28, 2024.

OUTCOMES *continued*

- Luke M. *FDA Forum 2024: FDA for Dermatologists.* Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 10, 2024.
- Tu D, Lemberger N, Wallmeier K, Riseman J, Kuzma B, Wei Y, Khoo T, Fallnich C, and Evans C. *Dual Modality Monitoring of Topical Formulations within Human Skin Using Stimulated Raman Scattering (SRS) Microscope.* Presentation at the SPIE Photonics West. San Francisco, CA, Jan. 27, 2024.
- Luke M. *FDA Update: FDA and Dermatologic DEIA.* Presentation at the American Dermatological Association Annual Meeting. Washington, DC, Oct. 25, 2023.
- Yue W. *Impact of Material Differences on In Vitro Performance of Clindamycin Phosphate Vaginal Creams.* Presentation at the International Pharmaceutical Excipients Council (IPEC) Foundation 2023 Awards Ceremony. Virtual Meeting, Oct. 24, 2023.
- Guy RH. *Hot Topic: Drug Delivery Technology: Quo Vadis?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.

CHAPTER 5: DRUG–DEVICE COMBINATION PRODUCTS

A major GDUFA science and research priority area during GDUFA III[1] 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 (RLD) on the bioequivalence (BE), therapeutic equivalence, or post-marketing safety of generic drug-device combination products. Research during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

Summary of FY 2024 Activities

In FY 2024, GDUFA research on complex drug-device combination products (DDCPs) focused on evaluating the impact of differences between a generic DDCP and its RLD on substitutability, BE, therapeutic equivalence, and post-marketing safety.

One of the main goals of this research area is to improve comparative use human factors (CUHF) study design and analysis. For example, paucity of use error data for a proposed generic DDCP and its RLD limits the selection of an appropriate non-inferiority margin. This lack of use error data has delayed the development of generic DDCPs including generic pen injector DDCPs with "other" design differences relative to the RLD. In task order 1 (75F40123F19001) under the indefinite delivery indefinite quantity (IDIQ) Contract (75F40123D00028) awarded to Core Human Factors, Inc., a CUHF study protocol was developed with input from FDA experts to compare "other" design differences between a semi-automated and a manual pen injector platform, and the CUHF study is planned to be completed in FY 2025. The outcomes from this study will inform the selection of the non-inferiority margin, as well as informing elements of the study design and the analysis approach, for future CUHF studies comparing manual pen injector products with their respective RLDs.

FDA continued its internal research to better understand the utilization of, and the challenges faced by, various autoinjector and pen injector technologies currently available in the market. This project explored manufacturing issues that could hinder generic autoinjector and pen injector development and identified user interface differences across these device platforms. The findings from this ongoing research are expected to inform the development of device language in product-specific guidances (PSGs) for products that utilize these platforms.

During FY 2024, FDA and the Center for Research on Complex Generics (CRCG) also hosted a public workshop titled "Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability."[2] The sessions of this workshop were designed to systematically address the challenges currently impacting the development and review of generic DDCPs. Specifically, the workshop explored different types of data and/or information that may justify the acceptability of "other" design differences.

Another goal of complex DDCP research is to support a demonstration of BE using in vitro methods, including developing new BE criteria, or improving current BE criteria for device performance assessments. Two external research projects addressed this research goal in FY 2024, along with multiple internal research projects.

A questionnaire was developed as part of a Contract research project (HHSF223201710072C) investigating the perception of airflow resistance from a dry powder inhaler device. The reliability and validity of the questionnaire in asthma and chronic obstructive pulmonary disease (COPD) patients was evaluated in a pilot study that was completed in FY 2024. Factor analysis of the pilot study questionnaire data identified four factors (effort/difficulty, confidence, inhale-ability, and breathing/overall comfort) that influenced patients' perceptions of airflow resistance, and their clinical implications were probed. The final questionnaire will be used in an upcoming clinical study in which inspiratory flow profiles, in conjunction with a patient's perception of airflow resistances captured by the questionnaire, will be investigated in asthma and COPD patients.

As previously reported in FY 2023, a study was completed on the complexities and aerosolization process of a thermally assisted drug delivery platform for loxapine inhalation powder. These findings were disseminated in conference proceedings at Respiratory Drug Delivery 2024 and SBIA: Advancing Generic Drug Development: Translating Science to Approval 2023. This work supported PSG recommendations published in FY 2023 to facilitate generic development of this product. Another FDA-initiated project completed in FY 2024 aimed to understand the effect of aerosolization and deposition mechanisms on the in vitro performance attributes of the thermally assisted drug delivery platform. The knowledge gained through these projects informs FDA's in vitro characterization approach for demonstrating the BE of brand and generic thermally assisted drug delivery devices.

[2] FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability - The Center for Research on Complex Generics (CRCG).

In FY 2024, FDA also successfully completed a research project that explored the key challenges in characterizing the quality and performance of polymeric microneedles. This project specifically assessed the effect of the polymer-to-API ratio on the critical quality attributes (CQAs) that are crucial for the successful development and clinical application of microneedles. These CQAs include attributes such as microneedle formation, topographical characteristics, the spatial distribution of the active pharmaceutical ingredient (API), mechanical properties: fracture force and skin insertion ability, and needle disintegration as well as drug release.

The use of artificial intelligence (AI)-assisted characterization techniques and the introduction of a novel drug release testing method further advanced the understanding of microneedle performance. By addressing key challenges in characterizing these innovative drug delivery systems, this work helps prepare the FDA to support more efficient product development and review of microneedle drug product applications.

In addition, a new subaward (Grant U18FD007054-04S1) under the existing Grant for the CRCG (Grant U18FD007054 awarded to University of Maryland and University of Michigan) was awarded to the University of Queensland to develop in vitro test methods for evaluating and comparing the adhesive qualities and adhesion performance of transdermal and topical delivery systems (collectively, TDS). The in vitro test methods developed during this subaward are expected to provide meaningful insights that can assist in the development or reformulation of generic TDS, as well as support the comparative assessment of a test and reference TDS to determine whether any differences have the potential to alter their in vivo adhesion performance.

The research in the complex DDCP space also aims to assist generic firms, helping them navigate their transition to utilizing more environmentally friendly propellants in metered dose inhalers (MDIs) by identifying appropriate equivalence approaches. A Contract awarded to Aptar Pharma Rx (75F40123C00186) addresses this research goal for complex DDCPs and aims to help define the potential target product profile of low global warming potential (LGWP) propellant MDIs to achieve comparability in CQAs to existing MDIs. This study will incorporate conventional and advanced in vitro BE methods to determine if current FDA guidance on the use of in vitro BE and alternative BE methods is viable for assessing the performance of LGWP propellants. In FY 2024, the awardee completed a review of formulation specifications for Proventil and Qvar from a previous FDA study (U01FD004943) and investigated in vitro delivered dose and aerodynamic particle size distribution (APSD) data for these branded MDIs. Ongoing research under this award is focused on the manufacture of model formulations of albuterol suspension and beclomethasone solution MDI formulations with LGWP propellants, including an optimized container closure system and device constituent parts to match emitted aerosol mass from Proventil and Qvar. The data from this study will form part of a wider study, which will seek to systematically demonstrate in vitro product performance and systemic absorption of drug substance in a pharmacokinetic study using LGWP propellant MDIs.

RESEARCH HIGHLIGHT

Recognizing a knowledge gap in comparative human factors methodology, Grant U91FD007360 was awarded to the University of Detroit in FY 2021 to develop methods for evaluating the impact of differences in user interface (UI) designs between generic DDCPs and their RLDs. The Grant had three objectives, 1) to develop a body of knowledge of key stakeholder perspectives on existing strategies for assessing user interface designs, 2) to develop a visual taxonomy to systematically analyze combination product UI design attributes and to facilitate the identification of minor and other design differences as they relate to potential use errors that could cause harm or compromise medical treatment, and 3) to develop a method for the comparative analyses of a proposed generic DDCP and its RLD that is based on evaluating UI design differences related to the potential for introducing use errors on critical tasks that could result in harm or compromised medical care when the user interacts with the UI.

In the first year of the Grant, an extensive literature search was undertaken to establish the existing landscape around comparative use studies. This served

RESEARCH HIGHLIGHT *continued*

as the basis for interviews conducted with human factors experts in industry to gain a greater understanding of their scope of knowledge, identify areas of need, and gain industry perspective. In addition, work began on classifying combination products by category (e.g., inhaler, autoinjector) and identifying their UI design features. A task analysis was developed and to identify known or potential use errors associated with each task, a risk assessment was also completed. The UI design features identified were then linked to the use-related risks identified from the risk assessment.

Development of a hierarchical classification system in the second year resulted in linking UI design features to risk and creation of a library of design features (e.g., shape, size) for use in developing a UI device taxonomy. The UI device taxonomy allows users to classify DDCP design features into categories and subcategories to ultimately relate design features to use-related risk, as well as to define what qualifies as "minor" versus "other" design differences. The process for linking UI design features to risk is shown in Figure 1 below. Once the UI device taxonomy was developed, it was tested in an interrater reliability study which allowed for refinements to the UI device taxonomy.

To achieve the final objective, a case report was prepared comparing a generic DDCP to its RLD product using the refined UI device taxonomy, and to generate a CUHF study determination report. This report utilized a comparative task analysis, a comparative use error and use-related risk analysis, and identification of critical design differences to determine the need for additional data, such as a CUHF study.

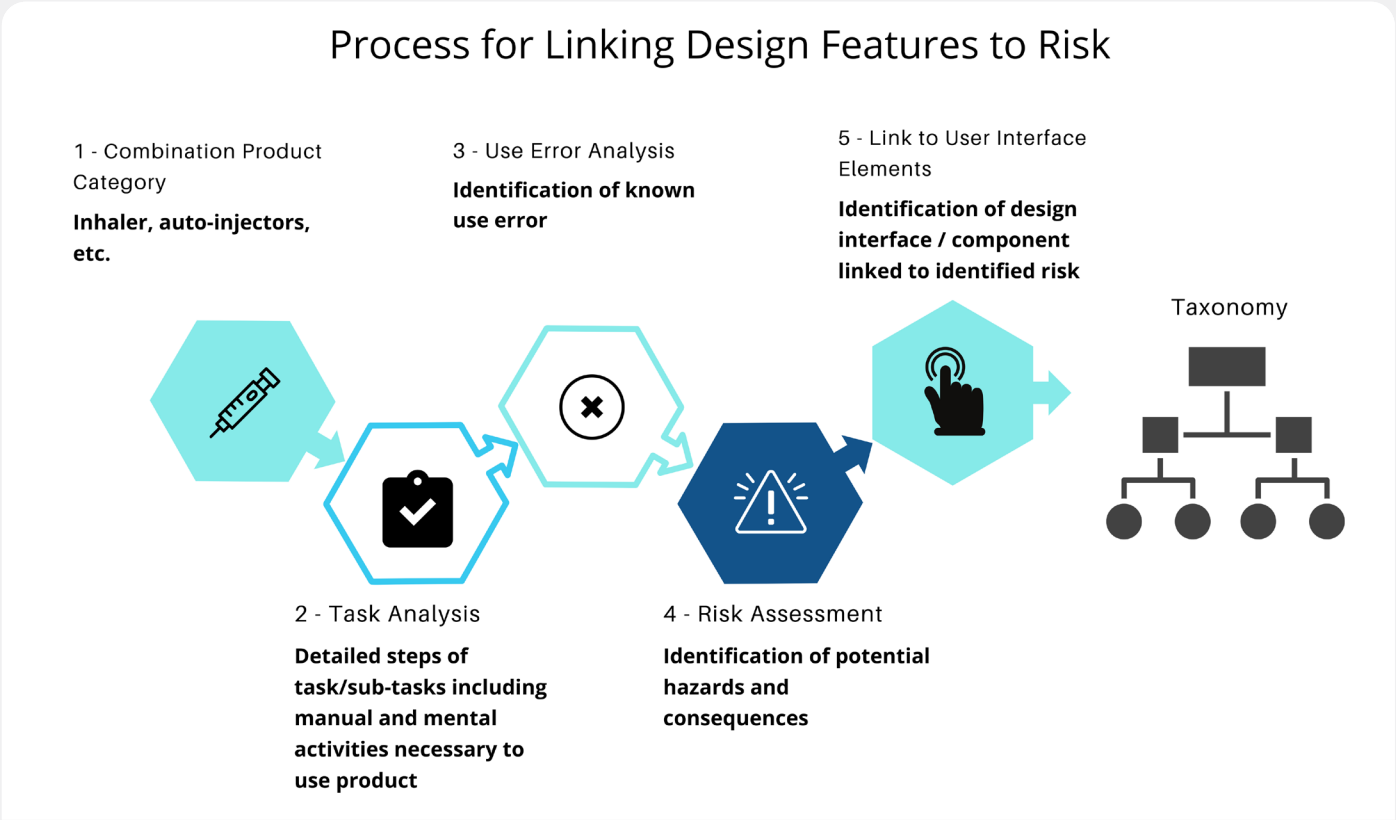

Figure 1. Process for Linking Design Features to Risk

This research provides a framework for organizing design features of different DDCPs by creating a common vocabulary for those features and linking the design feature to task(s) and risk. The framework provides evaluators with a tool to assess the impact of a design difference on substitutability of a generic for its RLD.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008316) T*he Safety of Switching Between Complex Branded and Generic Drugs: Developing a Semi-Automated Sequential Surveillance System Using Tree-Based Scan Statistics* with William Brand Feldman at the Brigham and Women's Hospital
- Contract (75F40123D00028-75F40123F19002) *Comparative Use Human Factors Study to Assess Whether Certain User Interface Differences Between Combination Products* with Different Syringe Designs Affect User Error Rates with Jennifer Soosaar at Core Human Factors, Inc.
- Contract (75F40124D00022-75F40124F19001) *3D Microscopy, Artificial Intelligence-Based Quantification and Modeling for Non-Clinical Evaluation and Regulatory Support of Complex Injectable and Insertable Drug Products* with Shawn Zhang at DigiM Solution LLC

Continuing Grants and Contracts

- Grant (U01FD007360) *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 (75F40123D00028-75F40123F19001) *Comparative Use Human Factors Studies to Assess the Impact of Differences in the User Interface of Generic Drug-Device Combination Products as Compared to the Reference Listed Drug* with Jennifer Soosaar at Core Human Factors, Inc.
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Active FDA Research

- *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*
- *Developing Clinically Meaningful Disintegration and Dissolution Methods for Teriparatide Loaded Microneedles*
- *Pen Injectors and Auto-Injectors Used in the Drug Marketplace: Landscape Assessment and Supply Chain*
- *Investigate the Impact of Sources and Grades of Collagen Matrix and their Manufacturing Process on the In Vitro Performance of Collagen-Matrix Implants*

OUTCOMES

Product-Specific Guidances

There were six new PSGs and three revised PSGs published in FY 2024 related to *Complex Combination Products*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance for Albuterol Sulfate; Ipratropium Bromide Spray, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Dextroamphetamine System.* (Nov. 16, 2023) Link to Posting
- *New Draft Guidance for Liraglutide Solution.* (May 16, 2024) Link to Posting
- *New Draft Guidance for Olodaterol Hydrochloride Spray, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Olodaterol Hydrochloride; Tiotropium Bromide Spray, Metered.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Semaglutide Solution.* (Nov. 16, 2023) Link to Posting
- *New Draft Guidance for Teriparatide Solution.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Tiotropium Bromide Powder.* (Nov. 16, 2023) Link to Posting
- *New Draft Guidance for Tiotropium Bromide Spray, Metered.* (Aug. 22, 2024) Link to Posting

Articles

Raney S, Senemar S, Burke M, Lee C, Shah J, Li K, Anand O, and Warner K. *Advances in Product Quality and Performance Tests for Topical and Transdermal Products: View of the USP Expert Panel.* Dissolution Technologies. (2024) 31: 6 - 12. https://doi.org/10.31003/USPNF_S203204_10101_01.

Posters

- Srinivasan P, Y S, Korang Yeboah M, Xu X, Ashraf M, Y W, Qin B, and Kamal N. *Effect of Collagen Sources on the In-Vitro Performance of Bupivacaine Collagen Implants.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Bethesda, MD, Sep. 24, 2024.
- Reed N, Lee Y, Ballard B, Feibus K, Luke M, and Guo C. *Characterizing Adasuve® (Loxapine, 10 mg) Inhalation Powder Particle Size Distribution Using Laser Diffraction.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 05, 2024.
- Laird ME, Conrad MO, Privitera MB, Lemke ME, and Story MF. *Validation of a User Interface Design Taxonomy for Categorizing "Minor" vs "Other" Design Differences in Combination Products.* Poster Presentation at the International Symposium on Human Factors and Ergonomics in Healthcare. Chicago, IL, Mar. 24, 2024.
- Russo J, Jiang Y, and Ghosh P. *Correlation Between Generic Product Approvals and Price for Drug Products Applied to the Skin.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

OUTCOMES *continued*

- Russo J, Jiang Y, Ghosh P, and Luke M. *Irritation and Sensitization Potential of Approved Topical and Transdermal Delivery Systems – A Retrospective Study.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.
- Srinivasan P, Korang-Yeboah M, Xu X, Ashraf M, Wang Y, Qin B, and Kamal N. *Effect of Collagen Source on the In-vitro Performance of Collagen Implant.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.

Presentations

- Ballard B. *Drug-Device Combination Products: A New Methodology for Evaluation - Part 2.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Wang J. *Approaches to Analyzing Comparative Use Human Factors Studies.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.
- Kamal N. *Impact of Polymer to API Ratio on the Critical Quality Attributes of Polymeric Microneedles.* Presentation at the American Chemical Society (ACS) Fall 2024. Denver, CO, Aug. 19, 2024.
- Mohammed Y. *Toolkit to Assess Adhesion Performance of Topical and Transdermal Delivery Systems (TDS) In Vitro.* Presentation at the American Association Pharmaceutical Sciences (AAPS)/USP Joint Webinar on USP Panel Findings on Development of a Novel In Vitro TDS Adhesion Test. Virtual Meeting, Aug. 13, 2024.
- Raney S. *Overview of the Topical and Transdermal Stimuli Article "Advances in Product Quality and Performance Tests for Topical and Transdermal Products - View of the USP Expert Panel" - Feedback to USP and Next Steps.* Presentation at the American Association Pharmaceutical Sciences (AAPS)/USP Joint Webinar on USP Panel Findings on Development of a Novel In Vitro TDS Adhesion Test. Virtual Meeting, Aug. 13, 2024.
- Lemke M. *We Muddled Our Way Through the CUHF Process, Now What Does It Mean?* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 21, 2024.
- Natarajan K. *Device and User Interface Assessment Recommendations in Drug-Device Combination Product PSGs.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Facilitating Generic Drug Product Development through Product-Specific Guidances (PSGs). Virtual Meeting, Apr. 25, 2024.
- Conrad M, Privetera M, Laird ME, Lemke ME, Story MF, and Feibus K. *User Interface Design Taxonomy: A Systemic and Repeatable Method for Identifying and Categorizing Design Differences in Combination Products.* Presentation at the International Symposium on Human Factors and Ergonomics in Healthcare. Chicago, IL, Mar. 24, 2024.
- Feibus K. *User Interface Design Taxonomy: A Systematic and Repeatable Method for Identifying and Classifying Design Differences in Combination Products.* Presentation at the 13th International Symposium on Human Factors and Ergonomics in Health Care. Chicago, IL, Mar. 26, 2024.
- Hoffmann M. *FDA Perspective on Device Shortages and Supply Chain Issues.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Rockville, MD, Mar. 15, 2024.

OUTCOMES *continued*

- Gibson K. *ISO 11608-1 Development & Overview.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Rockville, MD, Mar. 15, 2024.
- Kwok K. *Navigating Quality Challenges and Considerations in Drug-Device Combination Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Rockville, MD, Mar. 15, 2024.
- Bercu L. *Current Regulation, Policy, Guidance on Generic DDCPs.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Rockville, MD, Mar. 14, 2024.
- Ibrahim S. *Patient Perspectives on Generic Substitution of Complex Drug-Device Combination Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Hybrid Meeting. Rockville, MD, Mar. 14, 2024.
- Feibus K, Fine A, and Flint J. *An FDA Perspective on Best Practices for Comparative Analyses: Challenges & Opportunities.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Hybrid Meeting. Rockville, MD, Mar. 14, 2024.
- Conrad M, and Privitera M. *Determining "Other Design Differences" and Ways to Support Generic Substitutability.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability. Hybrid Meeting. Rockville, MD, Mar. 14, 2024.
- Hartka K. *Understand Best Practices of User Interface Assessment for Generic Drug-Device Combination Products.* Presentation at the 4th Human Factors Engineering & Usability Studies Congress. Philadelphia, Pennsylvania. Oct. 04, 2023.
- Luke M, Berry K, and Ren K. *Generic Drug-Device Combination Product Assessment.* Presentation at the 2023 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 02, 2023.

CHAPTER 6: ORAL PRODUCTS

A major GDUFA science and research priority area during GDUFA III[1] is to enhance the efficiency of bioequivalence (BE) approaches for generic oral products. The advancement of research in this area focuses on understanding how ingredients in oral drug products may modulate bioavailability; improving biorelevant dissolution methods as well as in silico models to support the expansion of biowaivers and global harmonization under ICH M13A[2] and ICH M13B; conducting internal research to seek data-driven harmonization of BE criteria for Narrow Therapeutic Index (NTI) drugs to support future harmonization under ICH M13C; and acquiring data needed to support future harmonization for the modified release (MR) oral products.

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[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

[2] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms. https://www.ema.europa.eu/en/ich-guideline-m13a-bioequivalence-immediate-release-solid-oral-dosage-forms-scientific-guideline.

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 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. Additional research priorities include the development of in vivo BE study designs that maintain subject safety and ensure 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 to assess the equivalence of therapeutic outcomes in diverse populations more efficiently. Research during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

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

Summary of FY 2024 Activities

In FY 2024, FDA continued research to modernize BE approaches for oral drug products by developing biopredictive in vitro methods to evaluate the impact of different product designs and food- and drug-drug interactions on BE assessments, and by evaluating the substitutability of generic drug products. These research efforts were supported by numerous internal FDA research projects (listed below) as well as by external research collaborations through four Contracts (75F40121C00132, 75F40121C00020, 75F40120C00200, and 75F40121P00621) and four Grants (U01FD005978, U01FD007959-01, U01FD008388, and U01FD008305). The intended outcomes of these research awards included mitigating failure modes for therapeutic equivalence for high-risk IR drug products, establishing patient centric quality standards, supporting the approval of additional strengths of MR drug products, and evaluating in

vitro testing methods to predict BE outcomes. In addition, physiologically based biopharmaceutics/pharmacokinetics (PBBM/PBPK) modeling was utilized to elucidate the impact of intrinsic and extrinsic variables (e.g., the formulation design or the presence of food) on BE assessments under Contracts 75F40121C00020 and 75F40120C00200 and Grant U01FD007959-01 (research involving PBBM/PBPK modeling is discussed further in Chapter 7).

The research under Grant U01FD007959 sought to identify critical quality attributes (CQAs) and design features of MR products, and to determine the appropriate factors to develop additional strengths (scaling factors) for MR tablet formulations. In FY 2024, this research developed comparative characterization and dissolution methodologies using quetiapine fumarate extended-release tablets as a model drug. A surface dissolution imaging system was utilized to determine the drug release mechanism and in vitro dissolution. Formulations are being developed using a quality-by-design (QBD) approach, i.e., achieving desirable quality product profile by identifying and controlling the CQAs.

To study the impact of excipients on the oral absorption of IR fexofenadine (Grant U01FD005978), sodium laurel sulfate (SLS) at two levels (3 and 30 mg) was selected. SLS is an inhibitor of organic anion transporter protein 2B1 (OATP2B1) and commonly co-formulated with fexofenadine, a substrate of OATP2B1. The clinical study started in FY 2024, and 5 of 12 subjects completed the study.

The development of biopredictive methods for setting patient-centric quality standards was investigated under Contract 75F40120C00200. This project measures in vivo drug release rate of glipizide ER tablet in different gastrointestinal tract regions using an incubation tube, records GI physiological conditions (e.g., pH and pressure) with a smart pill, and analyzes the drug plasma concentrations. The outcomes of this research are expected to elucidate how in vitro differences may be associated with variable absorption in vivo.

Formulation variables can potentially influence in vivo performance of oral products under fed conditions (Contract 75F40121C00020). Biorelevant disintegration and dissolution methods that can simulate mechanical pressure, hydrodynamic stress, and food induced viscosity were used to identify the impact of excipients on disintegration and dissolution under simulated fed conditions. The research team incorporated in vitro results and PK data to establish a PBPK model to predict food effect.

Contract 75F40121C00132 was completed in FY 2024 and identified Robotic Soft Esophagus (RoSE) and esophageal transit time (ETT) as a promising tool and metric, respectively, to assess the swallowability of solid oral drug products (SODFs). An experimental protocol suitable for biomimetic swallowing of SODFs in RoSE was first established. The ETT of SODFs varying in size, shape and weight was then tested under pre-defined wavelength and velocity settings in RoSE. RoSE ETT for SODFs was sensitive to velocity but not wavelength variations. Testing under different velocity settings may be needed to discern the differences in ETT of SODFs differing in size, shape and weight. A machine learning model was used to explore the relationship of observed ETT to product physical attributes but additional data with varying physical attributes that can inform a robust model is warranted.

Two new Grants were awarded in FY 2024. Grant U01FD008388 awarded to Simulations Plus, Inc. plans to use biopredictive in vitro method (i.e., TinyTIM) to predict the impact of food and acid reducing agents on the absorption of amorphous solid dispersion drug products. In Grant U01FD008305, Texas AM University Health System Science Center aims to determine the drug- and formulation-related factors of alcohol dose dumping (ADD) for specific MR products as part of an effort to improve and support the PSG development for MR drug products with regard to ADD evaluation.

To support the development of ICH M13A, FDA conducted internal research to survey the U.S. FDA-approved oral IR product landscape, and evaluate and compare the current BE recommendations by reviewing PSGs from both the U.S. FDA and European Medicines Agency (EMA).[3] The most significant difference among regulatory authorities lied in whether BE studies need to be conducted under both fasting and fed conditions

[3] Kotsybar J, Hakeem S, Zhang L, and Jiang W. *Global Harmonization of Immediate-Release Solid Oral Drug Product Bioequivalence Recommendations and the Impact on Generic Drug Development.* Clinical and Translational Science (2023) 16 (12): 2756-2764. https://doi.org/10.1111/cts.13670. PMID: 37904315

or one condition only (fasting or fed). ICH M13A, which was adopted by ICH in July 2024, recommends a risk-based determination on the need to conduct BE studies under both fasting and fed conditions or one condition only (fasting or fed). FDA's research work helped to understand the scope of U.S. IR solid oral drug products impacted by ICH M13A. Furthermore, it helped FDA to prepare for the implementation of ICH M13A by revising more than 800 PSGs to remove recommendation on BE study under either fasting or fed conditions to align with M13A. The harmonized BE recommendations streamline generic drug development and improve patient access to generic medications globally.

RESEARCH HIGHLIGHT

During FY 2024, FDA internal research evaluating the current study design utilized for clinical swallowability assessment (CSA) was published in the scientific literature, in an article titled "Designs of clinical swallowability assessments of solid oral dosage forms in regulatory submissions."[4]

Solid oral dosage forms (SODFs) are the most common dosage forms on the market due to various advantages including ease of use, pharmaceutical stability, dosing accuracy, and cost of manufacturing. Therefore, swallowability of SODFs is a critical property for medication safety and patient adherence to prevent inappropriate end-user manipulation of SODFs. However, there are no best practices or definitive guidelines for assessing swallowability. Such resources are important for regulatory agencies and sponsors to ensure that swallowable SODFs are available to patients.

The research identified notable CSA study design trends that were coupled with substantial variations in methodology. Assessing swallowability as a non-primary endpoint in 76% of CSAs was associated with insufficient power to robustly measure swallowability. In addition, 76% of the subjects enrolled in CSAs were pediatric patients, likely due to the need for applicants to comply with the Pediatric Research Equity Act in identifying a suitable formulation for this population. Despite the various methods to assess swallowability, questionnaires were the only assessment tool utilized across all the CSAs evaluated. Questionnaire designs used in CSAs differed by the respondent, type of questions, and response scoring systems (Figure 1). Data analysis approaches for CSAs were straightforward, mostly using a dichotomizing scoring system and descriptive statistics without a pre-established percent swallowability threshold (Figure 2). Given the variation in CSA methodologies, cross-comparing swallowability results is not possible without extensive normalization.

The variation in CSA methodologies can affect swallowability measurement and subsequently the interpretation and reliability of data to support regulatory decision-making. Therefore, it is imperative to develop standardized designs and validated assessment tools to produce high-quality, clinically relevant swallowability data. These resources will benefit not only new drug applicants, but also generic drug applicants when the physical attributes of their proposed generic SODFs deviate from the recommendations[5], especially for products intended for pediatric use.

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[4] McGuire MR, Mostofa A, Shon J, Frost M, Kim MJ, Li K. *Designs of Clinical Swallowability Assessments of Solid Oral Dosage Forms in Regulatory Submissions.* International Journal of Pharmaceutics. (2024) 659:124229. https://doi.org/10.1016/j.ijpharm.2024.124229. PMID: 38762166.

[5] FDA Guidance for Industry. *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (October 2022). Link to Posting.

RESEARCH HIGHLIGHT *continued*

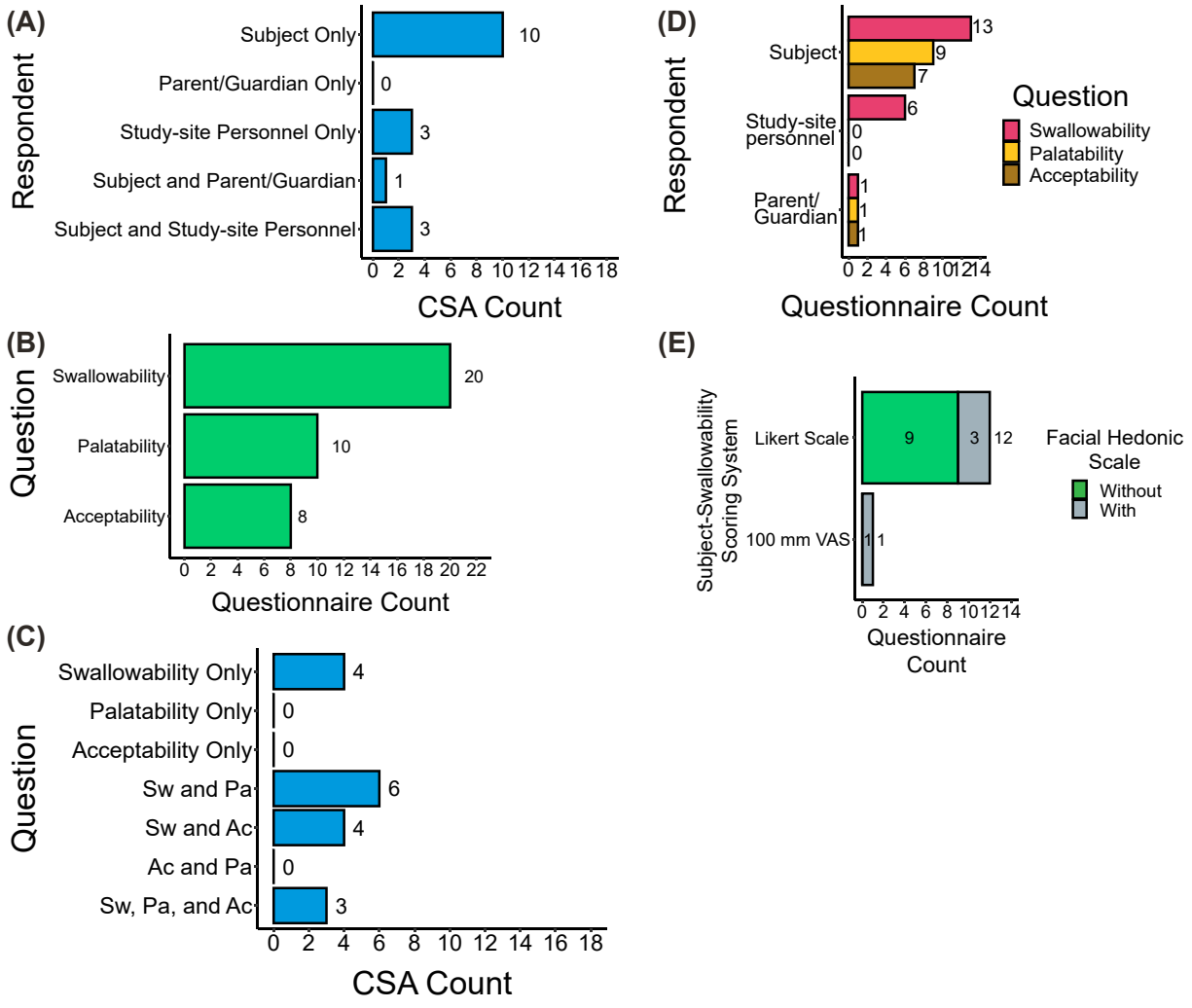

Figure 1. Questionnaire assessment tool used in CSAs
A) Questionnaire respondents for CSAs (n = 17). **B**) Most common questions on questionnaires (n = 21). **C**) Most common questions for CSAs (n = 17). A question was counted for a CSA if at least one questionnaire respondent in a CSA was asked the question. **D**) Most common questions by respondent. **E**) The scoring system that subjects used to respond to the swallowability question (n = 13). Scoring systems were sometimes accompanied by a facial hedonic scale. Sw-swallowability, Pa-palatability, Ac-acceptability, VAS-Visual Analog Scale.[6]

[6] See footnote 4.

RESEARCH HIGHLIGHT *continued*

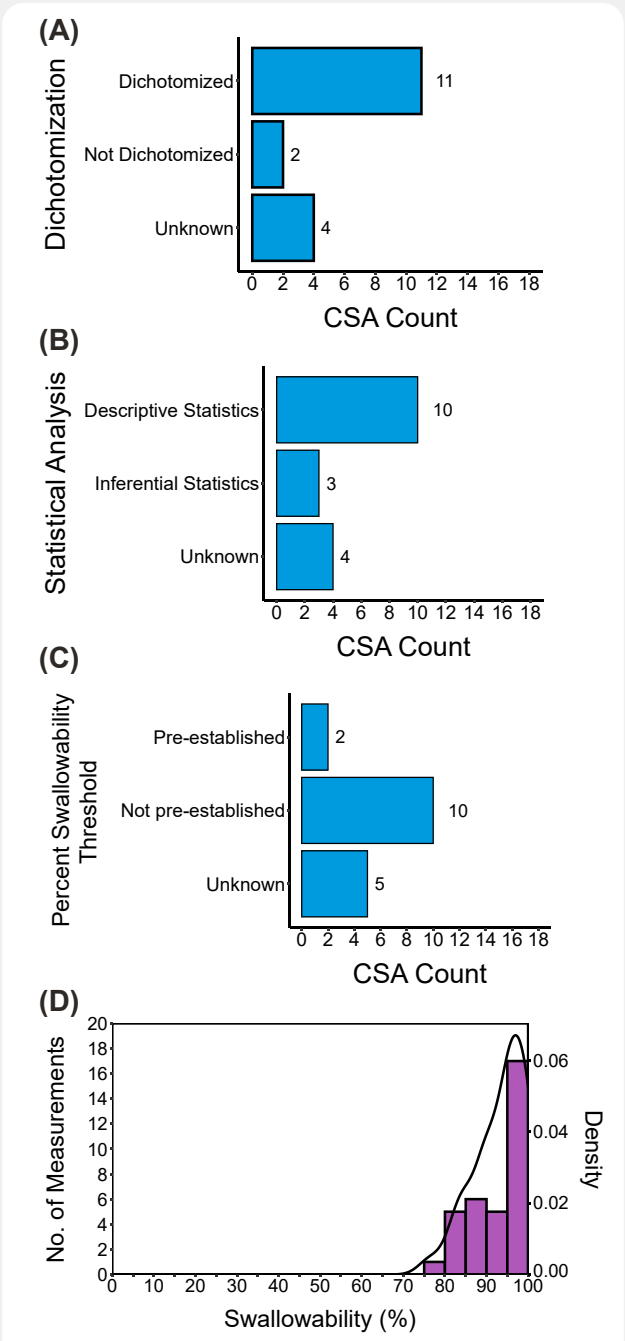

Figure 2. Analyzing CSA questionnaire results
A) Use of dichotomization as an approach to analyzing raw responses on questionnaires by dividing them into positive and negative categories (n = 17). **B**) Statistical analysis approach for questionnaire results (n = 17). **C**) A priori establishment of a percent swallowability threshold whereby an SODF would be determined to be swallowable (n = 17). **D**) Frequency of all reported experimental percent swallowability values (i.e., percent of positive responses to the ease of swallowability question) measured for CSAs where results were available, irrespective of study design (n = 34). Line is probability density function. [If data was not available for a CSA, it was categorized as "Unknown"].[7]

[7] See footnote 4.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008305) *Factors Related to Drug and Formulation Affecting Alcohol Dose Dumping in Modified Release Oral Drug Products* with Mansoor A Khan at Texas AM University Health System Science Center
- Grant (U01FD008388) *From Bench to Bioequivalence: In Vitro Mechanistic Understanding of ASD Drug Products in Simulated Gastrointestinal Conditions* with Yung-Yi Mosley at Simulations Plus, Inc.

Continuing Grants and Contracts

- Grant (U01FD007959) *Evaluation of Oral Modified-Release Tablets to Support the Approval of Additional Strengths* with Jie Shen at Northeastern University
- 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
- Grant (U01FD005978-04S3) *The Effect of Sodium Lauryl Sulfate on the Oral Absorption of Fexofenadine in Humans* with Katherine Yang at University of California, San Francisco

Completed Grants and Contracts

- Contract (75F40121C00132) *Applying a Robotic Soft Esophagus (Rose) to Assess the Swallowability of Opioid Drugs* with Peter Xu at The University of Auckland

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 a Decision Making Procedure in Relation to Male Reproductive Toxicity for the Selection of Bioequivalence Study Population*
- *Data Mining Hypoglycemic Safety Events in Clinical Trials Involving Combination and Single Products for Treatment of Type 2 Diabetes*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Establish the Framework for Partial AUC Recommendations*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *Evaluation of the Need for Sprinkle BE Studies*
- *Exploration of Food Conditions in Bioequivalence Studies with Pharmacokinetic Endpoints Enrolling Patients in Generic Drug Development*
- *GDUFA III Product Specific Guidance Improvement for Oral Product*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - M13A*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *Qualitative Sameness and Quantitative Sameness/ Similarity (Q1Q2) for Oral Drug Products*
- *Reassessment of REMS Recommendations in PSGs for Generic Drug Development*
- *Safety Considerations for the Selection of Patients as the Subject Population in Bioequivalence Studies with Pharmacokinetic Endpoints for Generic Drug Development*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approved Standards*
- *Utilization of Pharmacogenomic Information for Subject Recruitment in Bioequivalence Studies*

OUTCOMES

Product-Specific Guidances

There was 1 new and 26 revised PSGs published in FY2024 related to *Bioequivalence Methods and Analysis, IR and MR Oral Products, and Human Subject Safety* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Futibatinib Tablet.* (Nov. 16, 2023) Link to Posting
- *Revised Draft Guidance for Betamethasone Acetate; Betamethasone Sodium Phosphate Injectable.* (Nov. 16, 2023) Link to Posting
- *Revised Draft Guidance on Bupropion Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Carvedilol Phosphate Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Cladribine Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Dalfampridine Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Dapagliflozin; Metformin Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Donepezil Hydrochloride; Memantine Hydrochloride Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Hydrochlorothiazide; Metoprolol Succinate Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Hydromorphone Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Levomilnacipran Hydrochloride Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Memantine Hydrochloride Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Metformin Hydrochloride; Saxagliptin Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting

OUTCOMES *continued*

- *Revised Draft Guidance on Metformin Hydrochloride; Sitagliptin Phosphate Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Morphine Sulfate Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Morphine Sulfate Capsule* (NDA 020616). (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Morphine Sulfate Capsule* (NDA 021260). (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Oxcarbazepine Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Oxymorphone Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Phentermine Hydrochloride; Topiramate Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Posaconazole Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Pramipexole Dihydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Quetiapine Fumarate Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Tacrolimus Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Tapentadol Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Tramadol Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Trospium Chloride Capsule.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance on Venlafaxine Hydrochloride Tablet.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Verteporfin Injectable.* (Aug. 22, 2024) Link to Posting

Articles

- Coutinho A, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, and Polli J. *Relative Performance of Volume of Distribution Prediction Methods for Lipophilic Drugs with Uncertainty in LogP Value.* Pharmaceutical Research. (2024) 41(6): 1121 - 1138. https://doi.org/10.1007/s11095-024-03703-4. PMID: 38720034.
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- Kulkarni CP, Yang J, Koleske ML, Lara G, Alam K, Raw A, Rege B, Zhao L, Lu D, Zhang L, Yu LX, Lionberger R, Giacomini KM, Kroetz DL, and Yee SW. *Effect of Antioxidants in Medicinal Products on Intestinal Drug Transporters.* Pharmaceutics. (2024) 10(16): 647. https://doi.org/10.3390/pharmaceutics16050647. PMID: 38794309.
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- Patel R, Cristofoletti R, Wu F, and Al Shoyaib A. *In Vitro Lipolysis Model to Predict Food Effect of Poorly Water-Soluble Drugs Itraconazole, Rivaroxaban, and Ritonavir.* Journal of Pharmaceutical Sciences. (2024) 113(8): 2361 - 2373. https://doi.org/10.1016/j.xphs.2024.04.007. PMID: 38614321.

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- Bae J, Tran T, Nguyen D, Borges S, Kim M, Shon J, and Li K. *FDA and EMA Regulatory Recommendations on Fed Bioequivalence Study in Healthy Subjects vs. Patients for Generic Drug Development.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 08, 2024.

- Tran T, Bae J, Nguyen D, Borges S, Kim M, Li K, and Shon J. *A Comparative Review of Study Population and Dose Recommendations for In Vivo Bioequivalence Studies with Pharmacokinetic Endpoints between FDA and EMA Guidances.* Poster Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 08, 2024.

- Abdelnabi M, Watts L, Singh P, Li R, Lkhagva A, Duan S, Liu S, Wen B, Baker J, Matvekas A, Chey W, Hasler W, Raofi S, Sun W, Boyce H, Kinjo M, Pai M, Sun D, and Nojkov B. *Gastrointestinal Intubation Using a Multi-Port Aspiration Catheter to Study Drug Release of Extended-Release Glipizide Drug Products in The Gastrointestinal Tract of Healthy Humans.* Poster Presentation at the Digestive Disease Week 2024. Washington, DC, May 18, 2024.

- Bae J, Tran T, Shon J, Kim M, Borges S, and Li K. *A Survey on Recommendation of Food Conditions in Bioequivalence Studies with Pharmacokinetic Endpoints for Generic Oral Antineoplastic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

OUTCOMES *continued*

- Du P, Fang L, Zhao L, and Wu F. *Identify Biopredictive Dissolution for Predicting In Vivo Performance of a BCS II Drug Product Under Fed Conditions.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

- Kotsybar J, Hakeem S, Zhang L, and Jiang W. *Global Harmonization of Immediate-Release Solid Oral Drug Product Bioequivalence Recommendations and the Impact on Generic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

- Mina M, Anno KA, Zhang Z, Sun W, Zhang L, and Jiang W. *Deep Dive into Generic Drug Applications to Seek Data-driven Harmonization of Bioequivalence Criteria for Narrow Therapeutic Index Drugs.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

- Park SJ, Nguyen D, Tran T, Li K, Kim M, Borges S, and Shon J. *Assessment of Male Infertility Risks to Support Product-Specific Guidance Development for Generic Oral Products.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

- Tran T, Bae J, Nguyen D, Shon J, Kim M, Borges S, and Li K. *Safety Considerations of Subject Population Selection in Bioequivalence Studies for Generic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.

- Sun W, Mahjabeen S, Kinjo M, Thomas S, Wu F, Ni Z, Frost M, Markollari A, Best R, Le S, Kim M, and Zhao L. *A Generic Tacrolimus Capsule Shown Not to Be Bioequivalent to the Brand Tacrolimus Capsule in a Post-approval Pharmacokinetic Bioequivalence Study in Healthy Subjects.* Poster presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 27, 2024.

- 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 for Promoting Affordable Generic Drugs Available to American Public.* Poster Presentation at the Society of Federal Health Professionals (AMSUS) 2024 Annual Meeting. National Harbor, MD, Feb. 13, 2024.

- Ren P, Yang W, Choi S, and Zhang Y. *Instrumental Findings for Optimal BE Recommendations for IR LAGI Products.* Poster Presentation at the Society of Federal Health Professionals (AMSUS) 2024 Annual Meeting. National Harbor, MD, Feb. 13, 2024.

- Cheng Y, Wu F, Zhao L, and Fang L. *Utilizing PBPK Absorption Modeling to Evaluate Impact of Single-Sex on Bioequivalence Evaluation of Atorvastatin Immediate Release Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 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 Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

OUTCOMES *continued*

- Rana M, Feng X, Sun W, Xia L, Nwakama P, Kim M, Tampal N, Boyce H, and Tian L. *In Vitro Evaluation of Two Morphine Sulfate Extended-Release Products Sprinkled on Soft Foods.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Siddique A, Shaklah M, Anand O, Li M, Wu F, Raines K, O'connor T, Ashraf M, and Zidan A. *Development of In Vitro In Vivo Correlation for Establishing Clinically Relevant Dissolution Specifications of Lamotrigine ER Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Wang J, Campbell G, Hu M, Feng K, Chattopadhyay S, Zhao L, and Peck C. *Comparing a t-Distribution-Based Bayesian Approach with the Two One-Sided t-Test (TOST) for Bioequivalence Studies in Real-World Datasets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Willett D, Xi W, Yilmaz H, Gao Z, and Rodriguez J. *A Top-Down Spectroscopic Approach to Correlating Coating Thickness Distributions with the Dissolution Profile of Enterically Coated Drug Pellets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Zaker Y, Yilmaz H, Lex T, and Willett D. *Assessment of Laser Directed Infrared Imaging for In Vitro Characterization of Pharmaceutical Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Tan M, Gao Z, Babiskin A, Kim M, Fang L, Zhang L, and Zhao L. *Effect of Omeprazole Administration on the Pharmacokinetics of Oral Extended-Release Nifedepine: Physiologically based Pharmacokinetic Modeling.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Wu F. *Totality of Evidence Including PBPK Modeling to Support BE Assessment and Approval of Mesalamine Delayed Release Tablets (Part II).* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 25, 2024.
- Zhang, L. *Introduction & Overview: Current Regulatory Horizon of Narrow Therapeutic Index Drugs & ICH Guideline Development for Bioequivalence Assessment.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Fang, L. *Narrow Therapeutic Index Drug Classification: US FDA Current Process.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Jiang W. *Data-driven & Science-based Recommendation on Harmonization of Bioequivalence Standards for Narrow Therapeutic Index Drugs.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Wu F. *Physiologically Based Pharmacokinetic Absorption Modeling to Support BCS-Based Waiver of In Vivo Bioequivalence Studies.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 20, 2024.
- Wu F. *Regulatory Perspective of Model Master Files Utilities for Oral Drug Products.* Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.

OUTCOMES *continued*

- Boyce H. *Development of Generic Drug products under Suitability Petition.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Facilitating Generic Drug Product Development through Product-Specific Guidances (PSGs). Virtual Meeting, Apr. 25, 2024.
- Shon J. *Consideration Factors for Study Population Selection in Bioequivalence Studies with Pharmacokinetic Endpoints.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Facilitating Generic Drug Product Development Through Product-Specific Guidances (PSGs). Virtual Meeting, Apr. 25, 2024.
- Zhang Q. *Beyond General Guidance: Tailored PSG Recommendations for Immediate Release Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Facilitating Generic Drug Product Development through Product-Specific Guidances (PSGs). Virtual Meeting, Apr. 25, 2024.
- Boyce H. *A Review of Internal Data on Bioequivalence Studies Conducted with Soft Food Administration.* Presentation at the FDA and Product Quality Research Institute (PQRI) Workshop: Challenges and Opportunities for Modified Release Oral Drug Product Development – A Forum for Stakeholder Engagement. Rockville, MD, Apr. 18, 2024.
- Lionberger R. *Scientific Foundations for Development of Generic MR Oral Products.* Presentation at the FDA and Product Quality Research Institute (PQRI) Workshop: Challenges and Opportunities for Modified Release Oral Drug Product Development – A Forum for Stakeholder Engagement. Rockville, MD, Apr. 18, 2024.
- Sun D. *Measuring Glipizide Release from Two Different ER Formulations vs. Oral Solution Using In Situ GI Intubation in Humans.* Presentation at the FDA and Product Quality Research Institute (PQRI) Workshop: Challenges and Opportunities for Modified Release Oral Drug Product Development– A Forum for Stakeholder Engagement. Rockville, MD, Apr. 18, 2024.
- Wu F. *Regulatory Perspective: PBPK Absorption Modeling to Support Bioequivalence Assessment for Modified Release Products.* Presentation at the FDA and Product Quality Research Institute (PQRI) Workshop: Challenges and Opportunities for Modified Release Oral Drug Product Development– A Forum for Stakeholder Engagement. Rockville, MD, Apr. 18, 2024.
- Jiang W. *Deep Dive into Generic Drug Applications to Seek Data-Driven Harmonization of Bioequivalence Criteria for Narrow Therapeutic Index Drugs.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 16, 2024.
- Zhang L. *Opening Remarks - Global Bioequivalence Harmonization: Enhancing Access to Affordable Medicines.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 16, 2024.
- Zidan A. *A Systematic Approach to Define Design Space of CM Granulation for ER tablets: Opportunities and Challenges.* Presentation at 2024 BioPharma Webinar. Virtual Meeting, Feb. 29, 2024.
- Wu F. *Using Physiologically Based Pharmacokinetic Absorption Modeling for Bioequivalence Evaluation in Adult and Pediatric Populations.* Presentation at the Product Quality Research Institute (PQRI) Workshop: MIDD Approaches in Pediatric Formulation Development. Virtual Meeting, Feb. 29, 2024.
- Zidan A, Sierra-Vega N, Eisa F, Ashraf M, O'Connor T. *Optimization of Design Space for Continuous Manufacturing of Extended-release Tablets.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.

OUTCOMES *continued*

- Al-Gousous J, Langguth P. *Role of Biopredictive Dissolution and Oral PBPK to Evaluate the Impact of Food on Drug Absorption.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Hybrid Meeting, Rockville, MD, Oct. 12, 2023.
- Wu F. *Advances on Using PBPK Modeling to Support BE Assessment for Oral Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Virtual Meeting, Oct. 12, 2023.
- Zhang L. *ICH M13 Guideline Series.* Presentation at the Medicines for Europe - 2nd Workshop on Bioequivalence. Brussels, Belgium, Apr. 26, 2023.

CHAPTER 7: QUANTITATIVE METHODS & MODELS

A major GDUFA science and research priority area during GDUFA III[1] is to facilitate the utility of model-integrated evidence (MIE) to support demonstrations of bioequivalence (BE). 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 – subsection on "Long-Acting Injectable,

[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendments of 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

Insertable, or Implantable 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 during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below, highlighting mechanistic modeling for non-orally administered drug products, oral absorption models and BE, and quantitative clinical pharmacology, independently in three separate subsections.

MECHANISTIC MODELING FOR NON-ORALLY ADMINISTERED DRUG PRODUCTS

Summary of FY 2024 Activities

In FY 2024, extramural research related to mechanistic modeling for non-orally administered drug products involved several contracts and grants. Alongside extramural research, internal FDA research advanced the development of modeling and simulation tools that integrate drug product specific knowledge obtained with in vitro characterization testing and in vivo clinical studies. These in silico tools are being utilized by the generic drug industry to support decision making during drug development and by the FDA to support regulatory recommendations and decisions.

Research related to orally inhaled drug products (OIDPs) focused on refining computational fluid dynamics (CFD) regional deposition and PBPK modeling approaches as well as the development of a new in vivo nuclear imaging method to support regional deposition model validation. Work continued on a new CFD regional deposition model for a solution-based metered dose inhaler (MDI) that was developed in support of Grant U01FD007353 as well as internal CFD regional deposition models for suspension-based MDIs, dry powder inhalers, and OIDPs that use capillary forces to generate an aqueous spray. Concurrently, work continued on the development of a protocol for Grant U01FD007987 for an in vivo nuclear imaging study that is intended to collect data relevant for regional deposition model validation. Enhancements

were added to a previously existing PBPK model in support of Contract 75F40122C00182, which were supported by in vitro permeability measurements. In addition, internal PBPK modeling efforts at FDA were conducted to answer questions pertaining to in vivo charcoal block PK BE studies.[2,3]

Ongoing work for nasal drug products addressed nose-to-brain drug delivery, regional drug delivery, and opioid overdose reversal. Development of a PBPK model for nose-to-brain drug delivery continued for Grant U01FD007657, supported by in vivo PK study data. FDA internal research continued with in vitro studies quantifying regional drug delivery for sumatriptan succinate nasal powder and being validated with in vivo data.[4,5] A combined CFD-PK modeling approach was used to predict systemic PK following administration of a nasally inhaled corticosteroid in three adult nasal anatomical models, which was validated with in vivo PK data.[6] PBPK models for naloxone hydrochloride in nasal spray formulations were developed, providing insight on factors governing naloxone permeability.[7]

The research related to ophthalmic drug products resulted in successful case studies of interspecies extrapolation for ophthalmic suspensions and ointments (Grant U01FD006927).[8,9,10] In vitro characterization data with ex vivo measured cornea/conjunctiva permeabilities were integrated into a CFD-PBPK modeling framework for ophthalmic suspensions (Contract 75F40123C00072). This framework is currently being evaluated for virtual BE assessments with these products.

For products intended to be applied on the skin, research (ongoing Grants U01FD007323, U01FD007954, and U01FD007957 and completed Grant U01FD007320) focused on assessing the capability of mechanistic skin absorption models to account for metamorphosis phenomena post application. Additional model verification/validation enhancements related to predicting skin permeation in the presence of certain inactive ingredients. Modeling efforts contributed to the development of an in silico psoriasis model leveraging structural and functional skin parameters collected in psoriasis patients and healthy subjects (Grant U01FD006521).[11] Under Grant U01FD007320, a model validated against dermal Open Flow Microperfusion data was developed to describe the impact of formulation characteristics of a clobetasol

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[2] Walenga R, Tsakalozou E, Chopski SG, Fang L, and Zhao L. *Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 448-451.

[3] Walenga R, Tsakalozou E, Chopski SG, Fang L, and Zhao L. *Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate.* Poster Presentation at Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, USA. May 6, 2024.

[4] Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 440-443.

[5] Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Poster Presentation at Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, USA. May 6, 2024.

[6] Dutta R, Kolanjiyi AV, Walenga RL, Chopski SG, Kaviratna A, Mohan AR, Newman B, Golshahi L, *Longest W. CFD-PK Model for Nasal Suspension Sprays: Validation with Human Adult In Vivo Data for Triamcinolone Acetonide.* International Journal of Pharmaceutics. (2024) 665: 124660. https://doi.org/10.1016/j.ijpharm.2024.124660. PMID: 39236773.

[7] Chopski S, Al Ghabeish M, Babiskin A, Zhao L, and Walenga R. *Physiologically Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.

[8] Le Merdy M, AlQaraghuli F, Tan M-L, and Lukacova V. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Ofloxacin Ointment Case Study.* Poster Presentation at the 2024 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Seattle, WA. May 4-8, 2024.

[9] Le Merdy M, AlQaraghuli F, Mullin J, and Lukacova V. *Development of an Ocular PBPK-PD Model to Predict Drug-Mediated Intraocular Pressure Reduction in Preclinical Species.* Poster Presentation at the American Conference on Pharmacometrics (ACoP) 2023. National Harbor, MD. November 5-8, 2023.

[10] Le Merdy M, Spires J, Tan M-L, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for a Complex Ophthalmic Suspension Using Physiologically Based Pharmacokinetic Modeling and Simulation.* Pharmaceutics. (2024) 16(7): 914. https://doi.org/10.3390/pharmaceutics16070914. PMID: 39065612.

[11] Mangion S, Dalton J, Mackenzie L, Tsakalozou E, Clarke J, Polak S, and Roberts M. *Mapping Skin Properties in Psoriasis for Improved Understanding of Topical Absorption.* Poster Presentation at the American Academy of Dermatology (AAD) 2024 Annual Meeting. San Diego, CA, Mar. 08, 2024.

RESEARCH HIGHLIGHT *continued*

propionate (CP) cream on CP skin absorption.[12] Internally, the FDA utilized dermal PBPK modeling approaches to understand the product microstructure-performance relationship of dapsone topical gels by evaluating the impact of physicochemical and structural (Q3) attributes of these products (e.g., the particle size distribution and rheology) on local and systemic bioavailability following their topical application in virtual subjects. The developed models were validated (internal and external validation) using in vivo PK data from the in vivo BE studies with PK endpoints and in vitro permeation testing (IVPT) data. The evidence from this PBPK modeling work aligns with BE recommendations in the revised product specific guidances (PSGs) for dapsone topical gels that do not involve direct assessments of local and systemic bioavailability from IVPT and in vivo PK BE studies for these gels. The PSGs for these products were revised in February 2024 to reflect the Agency's current thinking.[13]

Contract 75F40119C10139 with the Institute of Quantitative Systems Pharmacology focused on evaluating target site BE of liposomal doxorubicin through in silico system-based multi-scale modeling and establishing a link between certain nanoparticle attributes and target site bioavailability. Research led by the University of Connecticut (75F40121C00133) on long acting injectable (LAI) suspensions focused on the development of a mechanistic PBPK model of Depo-subQ Provera® 104, a medroxyprogesterone acetate subcutaneous injectable suspension, to identify physiological events and product attributes critical for the in vivo performance of the tested LAIs.[14]

Under Contract HHSF223201810188C awarded to State University of New York at Buffalo, a PBPK modeling platform of drug delivery to the female reproductive tract was developed using an R-Shiny application. Levonorgestrel (LNG) was used as a model compound. In building the model, physiological information was obtained from literature, tissue-specific permeability rates were measured from freshly excised human cervicovaginal and uterine tissue samples, and in vitro release was measured from three commercially available intrauterine systems (IUSs) releasing LNG. Relevant model parameters were informed by measurements of uterine arterial blood flow, pelvic organ volumes (ultrasound), protein binding, and pH (vaginal fluid collection) in 12 healthy subjects. The model predicted reasonably well plasma, uterine endometrium, and uterine myometrium LNG concentrations after intrauterine administration. The validated model can be leveraged to assess drug product performance, support alternative BE approaches and, ultimately, remove critical barriers to generic drug development for complex drug products affecting women's health.[15]

In FY 2024, two new Grants were awarded with the aim to develop PBPK model-based mechanistic in vitro-in vivo correlations (IVIVCs) for LAI suspensions and implants. Grant U01FD008304 with the University of Connecticut aims to comprehensively investigate the interplay between formulation attributes of LAI suspensions and physiological factors at the local site to accurately predict in vivo drug release using PBPK models. Grant U01FD008303, awarded to the University of Texas at Austin, aims to develop IVIVCs for long-acting poly(lactic-co-glycolic) acid

[12] Van Osdol W, Novakovic J, Le Merdy M, Tsakalozou E, Ghosh P, Spires J, and Lukacova V. *Predicting Human Dermal Drug Concentrations Using PBPK Modeling and Simulation: Clobetasol Propionate Case Study.* AAPS PharmSciTech. (2024) 25: 39. https://doi.org/10.1208/s12249-024-02740-x. PMID: 38366149.

[13] Tsakalozou E. *Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation- A Case Study with Dapsone Topical Gel.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Bethesda, MD, USA. September 24, 2024.

[14] Amaral Silva D, Le Merdy M, Alam KD, Wang Y, Bao Q, Malavia N, Burgess D, and Lukacova V. *Development of Mechanistic In Vitro-In Vivo Extrapolation to Support Bioequivalence Assessment of Long-Acting Injectables.* Pharmaceutics. (2024) 16(4):552. https://doi.org/10.3390/pharmaceutics16040552. PMID: 38675213.

[15] Donnelly M, Tsakalozou E, Sharan S, Straubinger T, Bies R, and Zhao L. *Review of Complex Generic Drugs Delivered Through the Female Reproductive Tract: The Current Competitive Landscape and Emerging Role of Physiologically Based Pharmacokinetic Modeling to Support Development and Regulatory Decisions.* Journal of Clinical Pharmacology. (2020) 60 Suppl 2:S26-S33. https://doi.org/10.1002/jcph.1760. PMID: 33274513.

(PLGA)-based solid implant using a PBPK modeling approach. This research will focus on understanding how the physicochemical properties of drug molecules/polymer, implant specific properties, critical formulation attributes, and physiology, among other things, influence the in vivo release mechanisms of PLGA implant drug products and their disposition characteristics. To support the development of OIDPs, Grant U01FD008379 was awarded to Oklahoma State University Stillwater. This research aims to improve CFD utilization through machine learning methods. A more detailed description on the Grant aims is available in Chapter 8 -"Data Analytics and Artificial Intelligence".

RESEARCH HIGHLIGHT

Five new PSG documents were posted in February 2024, as well as four revised PSG documents in August 2024, that included recommendations for the use of mechanistic modeling to support BE determination for OIDPs, where the PSG document for formoterol fumarate; glycopyrrolate inhalation metered aerosol includes detailed language that the other PSG documents refer to.[16,17,18,19,20] The recommendations in these new PSG documents were based on outcomes from external and internal GDUFA-funded research as well as experience from assessments of modeling approaches included in Pre-ANDA communications and ANDAs, as shown in Figure 1. The expected applications for mechanistic modeling for OIDPs were provided in the PSG document for formoterol fumarate; glycopyrrolate inhalation metered aerosol. They include establishing biorelevant BE limits for recommended in vitro BE studies and conducting virtual BE assessments that may support regulatory decision making. The utility of various types of mechanistic modeling, the use of in vivo regional deposition data for model validation, model credibility establishment, and acceptance criteria for model validation and statistical analysis of virtual BE simulation results were described in detail. Altogether, these recommendations are expected to facilitate development of effective and efficient mechanistic modeling approaches that may be used to support BE approaches for OIDPs that do not include comparative clinical endpoint or pharmacodynamic BE studies.

[16] *Draft Guidance on Formoterol Fumarate; Glycopyrrolate* (Feb. 15, 2024) Link to Posting
[17] *Draft Guidance on Budesonide; Formoterol Fumarate; Glycopyrrolate* (Feb. 15, 2024) Link to Posting
[18] *Draft Guidance on Mannitol* (Feb. 15, 2024) Link to Posting
[19] *Draft Guidance on Mannitol* (Feb. 15, 2024) Link to Posting
[20] *Draft Guidance on Zanamivir* (Feb. 15, 2024) Link to Posting

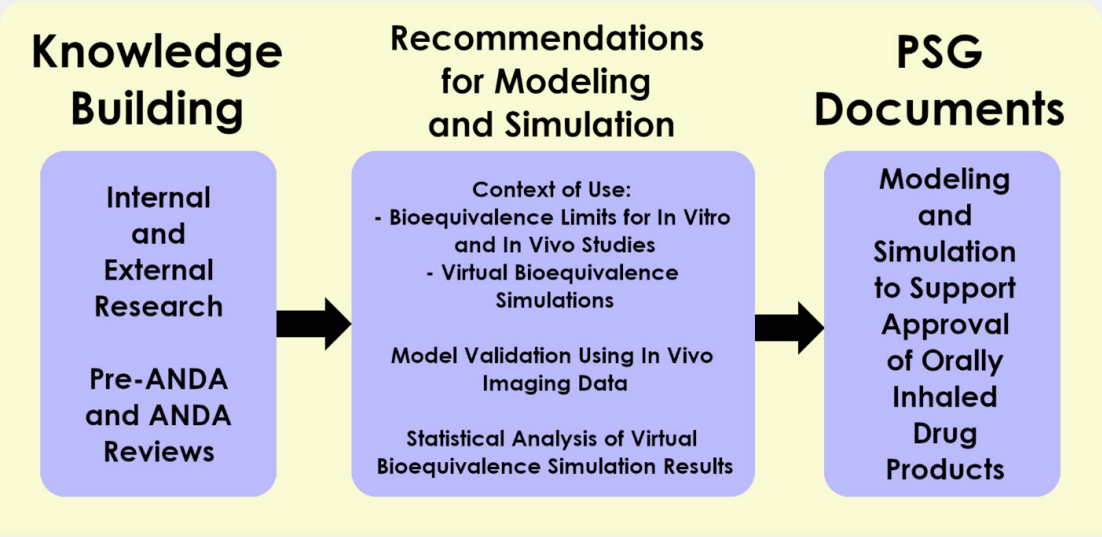

Figure 1. Flowchart that illustrates how internal research, external research, and reviews for Pre-ANDA communications and ANDAs were used to create PSG documents (new and revised) for OIDPs that include recommendations on modeling and simulation.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008304) *Development of PBPK Model-Based Mechanistic IVIVCs for Long-Acting Injectable Suspensions* with Diane Burgess at University of Connecticut
- Grant (U01FD008303) *Developing PBPK-Model Based Mechanistic IVIVC for PLGA Implants* with Feng Zhang at University of Texas at Austin
- Grant (U01FD008379) *ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products* with Yu Feng at Oklahoma State University

Continuing Grants and Contracts

- Grant (U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina at Chapel Hill
- Grant (U01FD007987) *A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods* with Benjamin Lavon at Fluidda, Inc.
- Grant (U01FD007904) *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 Limited
- Grant (U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University
- Grant (U01FD007957) *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 (U01FD007906) *Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies Using PBBM-PBPK Models* with Frederico Martins at Simulations Plus, Inc.
- Grant (U01FD007954) *Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients* with James Clarke at Certara UK Limited
- Grant (U01FD007657) *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 (U01FD007323) *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
- Grant (U01FD007348) *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

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- Contract (75F40123C00072) *A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs* with Carrie German at CFD Research Corporation
- 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 Burgess at University of Connecticut
- 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 (U01FD006521) *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 (U01FD007320) *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 (U01FD006927) *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 (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 (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

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*

OUTCOMES

Product-Specific Guidances

- There were five new and six revised PSGs published in FY2024 related to *Mechanistic Modeling for Non-Orally Administered Drug Products*. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

OUTCOMES *continued*

- *Revised Draft Guidance for Albuterol Sulfate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Budesonide; Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dapsone Gel* (NDA 021794). (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Dapsone Gel* (NDA 207154). (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate; Salmeterol Xinafoate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Formoterol Fumarate; Glycopyrrolate Aerosol, Metered.* (Feb. 15, 2024) Link to Posting
- *Revised Draft Guidance for Levalbuterol Tartrate Aerosol, Metered.* (Aug. 22, 2024) Link to Posting
- *New Draft Guidance for Mannitol Powder* (NDA 022368). (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Mannitol Powder* (NDA 202049). (Feb. 15, 2024) Link to Posting
- *New Draft Guidance for Zanamivir Powder.* (Feb. 15, 2024) Link to Posting

Articles

- Chen R, Schumitzky A, Kryshchenko A, Nieforth K, Tomashevskiy M, Hu S, Garreau R, Otalvaro J, Yamada W, and Neely M. *RPEM: Randomized Monte Carlo Parametric Expectation Maximization Algorithm.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 13: 759-780. https://doi.org/10.1002/psp4.13113. PMID: 38622792.
- Dutta R, Kolanjiyil A, Walenga R, Chopski S, Kaviratna A, Mohan A, Newman B, Golshahi L, and Longest W. *CFD-PK Model for Nasal Suspension Sprays: Validation with Human Adult In Vivo Data for Triamcinolone Acetonide.* International Journal of Pharmaceutics. (2024) 665: 124660. https://doi.org/10.1016/j.ijpharm.2024.124660. PMID: 39236773.
- Esmaeili A, Wilkins J, Hosseini S, Alfaifi A, Hejazi M, Hindle M, Longest W, Schuman T, Dhapare S, Kaviratna A, Walenga R, Newman B, and Golshahi L. *In Vitro Evaluation of Intersubject Variability in Pediatric Intranasal Drug Delivery Using Nasal Spray Suspension Products.* Journal of Aerosol Science. (2024) 179: 106387. https://doi.org/10.1016/j.jaerosci.2024.106387.
- Fang L, Gong Y, Hooker A, Lukacova V, Rostami-Hodjegan A, Sale M, Grosser S, Jereb R, Savic R, Peck C, and Zhao L. *The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA.* The AAPS Journal. (2024) 26: 28. https://doi.org/10.1208/s12248-024-00897-8. PMID: 38413548.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 440-443.
- Khadka P, Hejazi M, Hindle M, Schuman T, Longest W, Kaviratna A, Chopski S, Walenga R, Newman B, Golshahi L. *Anatomically-Detailed Segmented Representative Adult and Pediatric Nasal Models for Assessing Regional Drug Delivery and Bioequivalence with Suspension Nasal Sprays.* International Journal of Pharmaceutics. (2024) 666: 124743. https://doi.org/10.1016/j.ijpharm.2024.124743. PMID: 39343330.

OUTCOME *continued*

- Le Merdy M, Spires J, Tan M-L, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for a Complex Ophthalmic Suspension Using Physiologically Based Pharmacokinetic Modeling and Simulation.* Pharmaceutics. (2024) 16(7): 914. https://doi.org/10.3390/pharmaceutics16070914. PMID: 39065612.

- Pal A, Wu F, Walenga R, Tsakalozou E, Alam K, Gong Y, Zhao L, and Fang L. *Leveraging Modeling and Simulation to Enhance the Efficiency of Bioequivalence Approaches for Generic Drugs: Highlights from the 2023 Generic Drug Science and Research Initiatives Public Workshop.* The AAPS Journal. (2024) 26: 45. https://doi.org/10.1208/s12248-024-00916-8. PMID: 38589695.

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Posters

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- Tsakalozou E. *Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation – A Case Study with Dapsone Topical Gel.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Walenga R. *Orally Inhaled Drug Product PSGs: Considerations for Using Modeling and Simulation with Alternative BE Approaches.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Tsakalozou E. *Applications of Mechanistic Modeling and Simulation Tools on the Performance of Locally Acting Complex Drug Products.* Presentation at the MIDD + (Pharmacometry). São Paulo, Brazil, Aug. 15, 2024.
- Zhao L. *Advancing the Use of Model-Integrated Evidence in Generic Drug Development and Assessment.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 20, 2024.
- Walenga R. *Leveraging Modeling Approaches to Support Bioequivalence Determination for Generic Orally Inhaled Drug Products in the United States.* Presentation at the Drug Information Association (DIA) China 2024 Annual Meeting. Suzhou, China, May 17, 2024.
- Wang Y, and Tsakalozou E. *Maximize the Impact of the Redesigned PSUB Meetings on Generics Approvals.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Redesigned Pre-Submission Meetings in GDUFA III: Benefits for ANDA Submission and Approval. Virtual Meeting, May 09, 2024.

OUTCOME *continued*

- Walenga R. *FDA Recommendations for Alternative Bioequivalence Approaches: Design, Validation, and Use Case for In Silico Studies.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 07, 2024.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Presentation at Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, USA. May 06, 2024.
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- Walenga R. *Regulatory Perspective on MMF Applications for OIDPs, Ophthalmic Drug Products, and Drug Products Applied on the Skin.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, USA. May 03, 2024.
- Lionberger R. *Clearing the Path for Modeling and Simulation in Drug Applications.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Zhao L. *The Development and Framework of MMF as a Regulatory Initiative.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Tsakalozou E. *Considerations and Potential Regulatory Applications for a Model Master File.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, USA. May 02, 2024.
- Silva D. *Model Master File in the Context of Long Acting Injectables.* Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Lionberger R. *Quantitative Medicine Innovations in the Generic Drug Program.* Presentation at the FDA Virtual Workshop on Streamlining Drug Development and Improving Public Health through Quantitative Medicine: An Introduction to the CDER Quantitative Medicine Center of Excellence. Virtual Meeting, Apr. 25, 2024.
- Babiskin A. *Potential Topics for Discussion Through the MIE Industry Meeting Pilot Program.* Presentation at the Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs. Virtual Meeting, Jan. 18, 2024.
- Le Merdy M. *PBPK Models of Complex Injectable and Ophthalmic Drug Products: Case Studies.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Characterization of Complex Excipients and Formulations. Shady Grove, MD, Dec. 08, 2023.
- Chopski S, Al Ghabeish M, Babiskin A, Zhao L, and Walenga R. *Physiologically Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.

ORAL ABSORPTION MODELS AND BIOEQUIVALENCE

Summary of FY 2024 Activities

In FY 2024, external contracts and grants as well as multiple internal research projects continuously focused on the development of biorelevant/biopredictive in vitro testing and physiologically based pharmacokinetics (PBPK) modeling to predict the impact of product design (formulations and manufacturing techniques), food and gastric pH on bioequivalence (BE) assessment for immediate release (IR) oral products. In addition, there was one Grant focusing on the development of biorelevant/biopredictive in vitro testing and PBPK modeling for the BE assessment for modified release (MR) products and two Grants investigating the best practices of conducting virtual BE simulations using PBPK modeling. The internal (FDA) and external (Grant and Contract) research projects related to oral absorption models for BE assessment encompassed four scientific areas including the utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions for IR products, potential expansion of biowaivers for Biopharmaceutics Classification System (BCS) Class III Drugs, exploration of in vitro biopredictive testing and PBPK modeling for MR products, and enhancement of PBPK absorption modeling capabilities (e.g., best practices for virtual BE study design).

One research initiative in this area related to studying how PBPK models could help assess the impact of food on BE evaluations for high-risk IR oral products. This research continued to focus on exploring the utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions. A goal of this work was to support recommendations in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M13A, Bioequivalence for Immediate-Release Solid Oral Dosage Forms guideline that was adopted by ICH in July 2024. Grant U01FD007352 focused on the development and validation of a best practice framework for PBPK analysis in support of model-informed biowaivers of fed state BE studies for BCS Class II drugs. In FY 2024, this research generated in vitro biopharmaceutics data as well as developed and validated in vitro in vivo extrapolation (IVIVE)-PBPK models for rivaroxaban and ritonavir and established a flowchart to recapitulate product-specific and dose-specific food effect (refer to the **Research Highlight** below for more details). Another, 75F40121C00020, explored formulation factors that could potentially impact BE under fed conditions by using in vitro disintegration and dissolution tests that can simulate the food induced viscosity, mechanical pressure, and hydrodynamic stress. The research demonstrated that some excipients such as microcrystalline cellulose, an insoluble excipient, can slow down disintegration and dissolution in viscous media but not in media of normal viscosity. This Contract involved construction of a semi-physiologic PBPK modelling approach that was used to back calculate in vivo dissolution profiles for IR tablet formulations. It helped to guide the development of a new flow-through-based in vitro method that provided the correct rank order for the absorption kinetics between two generic midodrine tablet products. This work helped establish in vitro dissolution conditions which are more biopredictive.

A second research initiative in this area related to studying how PBPK models could help support the expansion of biowaivers for BCS Class III drugs. As part of internal FDA research projects, dissolution data with degradation for cladribine (considered a BCS III drug product), were incorporated in PBPK modeling to predict the impact of the cladribine degradation at acidic conditions on BE. This project demonstrated that cladribine's degradation in acidic conditions does not impact the BE of a generic cladribine tablet to the

RLD, supporting the addition of a BCS III biowaiver option in the revised product-specific guidance (PSG) for cladribine tablets (published in August 2024). This option provides an alternative BE approach to alleviate the challenge of conducting in vivo BE studies in patients with relapsing forms of multiple sclerosis due to the patient recruitment difficulties.

A third research initiative in this area related to studying how PBPK models could help support the evaluation of additional strengths for oral MR tablets. Grant U01FD007959 sought to determine the appropriate factors to scale the MR tablet formulation for additional strengths, and to identify the critical quality attributes (CQAs) and formulation design spaces for oral MR tablets with different formulation design strategies. This research is intended to develop mechanistic models with various dissolution testing technologies to establish dissolution safe spaces and identify CQAs across strengths. The established model is expected to predict clinical exposure of extended-release tablet formulation variants. In FY 2024, the project mainly focused on measuring the in vivo drug release and pharmacokinetics of two orally administered extended-release formulations of glipizide with the same therapeutic equivalence rating in healthy subjects. The study demonstrated that glipizide concentrations and pH were measurable in different regions of the gastrointestinal (GI) tract. This confirmed that serial fluid sampling from the GI tract using intubation is feasible and may help inform in vivo drug release performance.

A fourth research initiative in this area related to studying how PBPK models could enhance oral absorption modeling. During FY 2024, two grant projects, Grants U01FD007904 (Certara UK Limited) and U01FD007906 (Simulations Plus), involved the development of mechanistic in silico tools, methodologies, and informative workflows to support virtual bioequivalence (VBE) assessments for oral dosage forms and long acting injectable (LAI) products. The objective of these two Grants was to develop workflows that can guide the conduct of VBE assessments with PBPK models considering several sources of population variability, the mechanistic nature of these PBPK models, the routes of delivery and their complexities, and characteristics of virtual trials such as the study design, size, and population. The research efforts during FY 2024 focused on the selected drug products and subsequent development and validation of PBPK models for these products.

In addition, to enhance research collaborations with the generic industry, and maximize the predictive capabilities of these VBE models, the Center for Research on Complex Generics (CRCG) announced open invitations for generic industry stakeholders (non-federal entities) to provide in vitro and/or in vivo preclinical and/or clinical study data for specific drug products within the scope of these Grants (refer to CRCG Announcement for Data Contribution to Grant U01FD007904 awarded to Certara UK, Ltd[21] and CRCG Announcement for Data Contribution to Grant U01FD007906 awarded to Simulations Plus.[22] The goal was to afford the Grant awardees access to relevant experimental data that could be leveraged when developing and validating their models. Multiple generic industry stakeholders responded to the announcements and were willing to contribute experimental data to the awardees of these research Grants. Specifically, Capstone Development Services and the University of Maryland agreed to contribute to the research under Grant U01FD007904. Adium, Galenicum Health S.L.U, Libbs Farmacêutica, and Sandoz agreed to contribute to the research under Grant U01FD007906.[23]

Another Contract (75F40120C00150) developed a mechanistic in silico model, describing the in vitro EpiOral model, in MembranePlus™ to determine active pharmaceutical ingredient (API) properties (drug diffusivity (Dm) and unbound fraction in epithelium tissue (fut)) within the oral mucosal barrier in vitro. In

[21] Center for Research on Complex Generics (CRCG). Call for Data Contribution. Available at https://complexgenerics.org/research-capabilities/funding-opportunities/call-for-data-contribution/.

[22] Center for Research on Complex Generics (CRCG). Call for Data Contribution #2. Available at https://complexgenerics.org/research-capabilities/funding-opportunities/call-for-data-contribution-2/.

[23] Note that the terms of the contribution were negotiated directly between each Grant awardee and each external contributor. Each awardee and contributor understood that the contributions would not result in undue influence on FDA regulatory decisions, not result in an endorsement of the identified contributors or any of their products or activities by FDA, and not provide access to non-public product specific information from FDA. It was also agreed that the contributions may be publicly acknowledged by the identified contributors, but the contributors may not promote themselves as having a relationship with FDA.

parallel, baseline PBPK models were developed using GastroPlus® to describe the absorption, distribution, metabolism, and excretion (ADME) of sufentanil, fentanyl, buprenorphine, zolpidem, and rizatriptan. For these five compounds, a consistent scaling factor was used to enhance clinical PK predictions, validating the IVIVE method. The next step will include measurements of in vitro dissolution profiles for the drug products (DPs) and development of IVIVEs for each DP. The novel PBPK-based IVIVE method with a consistent scale factor can predict multiple APIs' and DPs' clinical PK following oral cavity administration and may support the development of new and generic oral cavity drug products.

In addition, FDA and the CRCG co-organized a workshop titled "Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development" that was held on October 12, 2023. This workshop discussed the challenges, experiences, and advances related to the development of oral PBPK absorption modeling. The workshop also reported research project results, including the establishment of biopredictive in vitro testing (e.g., dissolution) to address risks associated with the extrapolation of BE from a fasting to a fed state, from subjects with normal to elevated gastric pH, for assessing BE from adults to pediatrics, and for other risk-based BE assessments for oral drug products.

RESEARCH HIGHLIGHT

The research project supported by Grant U01FD007352 generated *in vitro* biopharmaceutics data and developed and validated IVIVE-PBPK models for rivaroxaban and ritonavir. The rivaroxaban PBPK model predicted the rivaroxaban systemic exposure within the therapeutic dose range, including the non-dose proportional PK due to a solubility limitation. The research found that using particle size distribution measured in the drug product provided a good prediction of in vitro dissolution results as well as the rivaroxaban oral PK. This PBPK model also enabled us to predict the dose-dependent food effect observed for rivaroxaban. In turn, the ritonavir PBPK model recovered the systemic exposure of ritonavir amorphous solid dispersion under fasted and fed conditions. The IVIVE-PBPK model-based analysis revealed that despite the micelle-mediated solubilization enhancement of ritonavir under the fed condition, the high viscosity of intraluminal fluids under the fed condition seems to significantly delay drug diffusion and thus dissolution, leading to a slightly negative food effect. Finally, the ritonavir PBPK model enabled us to predict the impact of proton-pump inhibitors on ritonavir absorption. In summary, the workflow developed during this research (Figure 1) appears to be useful to predict the formulation-specific and dose-specific food effect, which will pave the way to inform virtual bioequivalence trials under the fed condition.

RESEARCH HIGHLIGHT *continued*

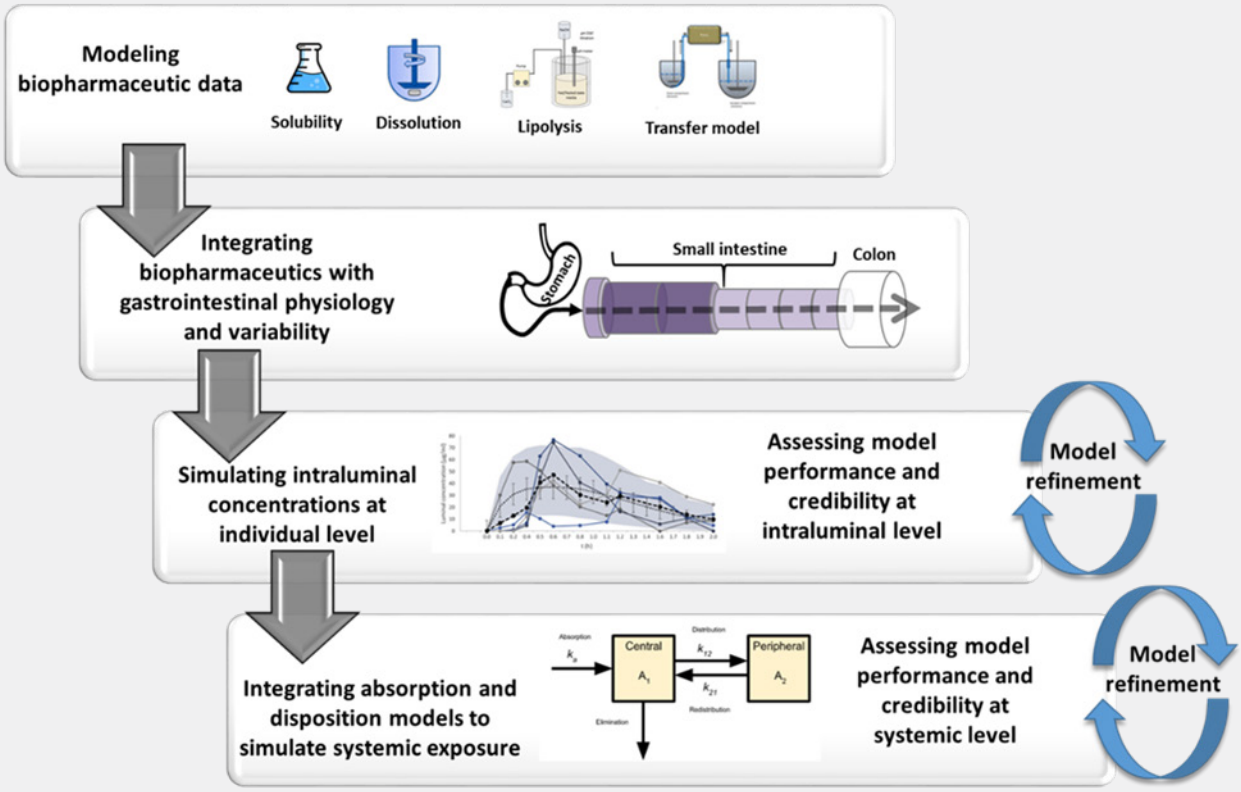

Figure 1. IVIVE-PBPK workflow related to the in vivo learning phase guided by intraluminal and/or PK data under the fasted condition.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Grant (U01FD007904) *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 Limited
- Grant (U01FD007906) *Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies Using PBBM-PBPK Models* with Frederico Martins at Simulations Plus, Inc.
- Grant (U01FD007959) *Evaluation of Oral Modified-Release Tablets to Support the Approval of Additional Strengths* with Jie Shen at Northeastern University
- 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

RESEARCH PROJECTS AND COLLABORATIONS *continued*

Completed Grants and Contracts

- Grant (U01FD007352) *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

Active FDA Research

- *Best practice for Using PBPK Modeling for Orally Absorbed Generic Drug Products*
- *Best Practice for Using Physiologically Based Pharmacokinetic (PBPK) Modeling for Orally Absorbed Generic Drug Products*
- *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - M13A*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

OUTCOMES

Product-Specific Guidances

There was one revised PSG published in FY 2024 related to *Oral Absorption Models and Bioequivalence*. The PSG listed below was directly impacted by GDUFA - funded research in this area.

- *Revised Draft Guidance on Cladribine Tablet.* (Aug. 22, 2024) Link to Posting

Articles

- Coutinho A, Cristofoletti R, Wu F, Al Shoyaib A, Dressman J, and Polli J. *Relative Performance of Volume of Distribution Prediction Methods for Lipophilic Drugs with Uncertainty in LogP Value.* Pharmaceutical Research. (2024) 41(6): 1121-1138. https://doi.org/10.1007/s11095-024-03703-4. PMID: 38720034.
- Gong Y, Barretto F, Tsong Y, Mousa Y, Ren K, Kozak D, Shen M, Hu M, and Zhao L. *Development of Quantitative Comparative Approaches to Support Complex Generic Drug Development.* The AAPS Journal. (2024) 26: 15. https://doi.org/10.1208/s12248-024-00885-y. PMID: 38267593.
- Lu D, Rege B, Rawlings K, Yang J, Alam K, Bode C, Zhao L, Faustino P, Wu F, Shakleya D, Nickum E, Li B, Wang R, Stier E, Miezeiewski B, Patel R, Boam A, Lionberger R, Keire D, and Yu L. *Antioxidants had No Effects on the In-Vitro Permeability of BCS III Model Drug Substances.* Journal of Pharmaceutical Sciences. (2024) 113(9): 2708-2714. https://doi.org/10.1016/j.xphs.2024.05.033v. PMID: 38862090.
- Pal A, Wu F, Walenga R, Tsakalozou E, Alam K, Gong Y, Zhao L, and Fang L. *Leveraging Modeling and Simulation to Enhance the Efficiency of Bioequivalence Approaches for Generic Drugs: Highlights from the 2023 Generic Drug Science and Research Initiatives Public Workshop.* The AAPS Journal. (2024) 26: 45. https://doi.org/10.1208/s12248-024-00916-8. PMID: 38589695.

OUTCOME *continued*

- Patel R, Cristofoletti R, Wu F, and Al Shoyaib A. *In Vitro Lipolysis Model to Predict Food Effect of Poorly Water-Soluble Drugs Itraconazole, Rivaroxaban, and Ritonavir.* Journal of Pharmaceutical Sciences. (2024) 113(8): 2361-2373. https://doi.org/0.1016/j.xphs.2024.04.007. PMID: 38614321.

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Posters

- Pal A, Mousa Y, Fang L, Zhao L, and Wu F. *PBPK Modeling to Predict the Effect of Gastric pH on Bioequivalence of Dabigatran Etexilate Capsules.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Du P, Fang L, Zhao L, and Wu F. *Identify Biopredictive Dissolution for Predicting In Vivo Performance of a BCS II Drug Product Under Fed Conditions.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Thomas S, Wu F, Zhao L, and Fang L. *Application of Physiologically Based Pharmacokinetic Modeling to Support Bioequivalence Evaluation of Mesalamine Delayed Release Tablets.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Kalra P, Le Merdy M, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Pauletti G, and Zhou H. *Physiologically Based Pharmacokinetic (PBPK) Oral Absorption Model to Predict Mucosal Permeability of Oral Cavity Drug Products.* Poster presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.
- Dwivedi P, Alam K, Tsakalozou E, and Pauletti G. *Oral Cavity Permeability Assessment Using Sublingual and Buccal In Vitro Tissue Models.* Poster presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.
- Cheng Y, Wu F, Zhao L, and Fang L. *Utilizing PBPK Absorption Modeling to Evaluate Impact of Single-Sex on Bioequivalence Evaluation of Atorvastatin Immediate Release Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Cui D, Li K, Al Ghabeish M, Mcguire M, Sun W, Hu M, Zhao L, and Kim M. *Application of Quantitative Models to Systematically Evaluate Factors Impacting Swallowability of Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Wu F. *Totality of Evidence Including PBPK Modeling to Support BE Assessment and Approval of Mesalamine Delayed Release Tablets (Part II).* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 25, 2024.
- Fang L. *Physiologically Based Pharmacokinetic Absorption Modeling to Support Bioequivalence Assessment for BCS Class III Drug Products.* Presentation at the 2024 Simulations Plus Webinar. Virtual Meeting, Sep. 24, 2024.

OUTCOME *continued*

- Wu F. *Physiologically Based Pharmacokinetic Absorption Modeling to Support BCS-Based Waiver of In Vivo Bioequivalence Studies.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 20, 2024.
- Wu F. *Regulatory Perspective of Model Master Files Utilities for Oral Drug Products.* Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Wu F. *Regulatory Perspective: PBPK Absorption Modeling to Support Bioequivalence Assessment for Modified Release Products.* Presentation at the FDA and Product Quality Research Institute (PQRI) Workshop: Challenges and Opportunities for Modified Release Oral Drug Product Development – A Forum for Stakeholder Engagement. Rockville, MD, Apr. 18, 2024.
- Wu F. *Using Physiologically Based Pharmacokinetic Absorption Modeling for Bioequivalence Evaluation in Adult and Pediatric Populations.* Presentation at the Product Quality Research Institute (PQRI) Workshop: MIDD Approaches in Pediatric Formulation Development. Virtual Meeting, Feb. 29, 2024.
- Al-Gousous J, and Langguth P. *Role of Biopredictive Dissolution and Oral PBPK to Evaluate the Impact of Food on Drug Absorption.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Rockville, MD, Oct. 12, 2023.
- Thomas S. *Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products: PART I.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Rockville, MD, Oct. 12, 2023.
- Fotaki N. *Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products: PART II.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Rockville, MD, Oct. 12, 2023.
- Wu F. *Advances on Using PBPK Modeling to Support BE Assessment for Oral Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Virtual Meeting, Oct. 12, 2023.
- Fang L. *Regulatory Applications and Research of Absorption Modeling for Pediatric Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Virtual Meeting, Oct. 12, 2023.
- Zhao L. *Overview of Workshop.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development. Virtual Meeting, Oct. 12, 2023.

QUANTITATIVE CLINICAL PHARMACOLOGY

Summary of FY 2024 Activities

FDA continues leveraging innovative quantitative clinical pharmacology (QCP), along with model-integrated evidence (MIE) approaches, to develop more effective in vivo study designs and methods for evaluating bioequivalence (BE). The goal is to help overcome challenges in the development and assessment of generics with complicated in vivo study considerations, such as long-acting injectable, insertable, or implantable (collectively, LAI), inhalation, and oncology drug products.

External research collaborations continued to advance population pharmacokinetics (PK) modeling techniques and methods to develop alternative BE study designs and approaches. FDA continued to collaborate with Uppsala University (Contract 75F40122C00139) to develop more feasible BE study designs for highly variable drugs (HVDs) with long half-lives. Preliminary results showed that MIE together with reference-scaled average BE (RSABE) analysis may be flexible enough for analyzing data from both conventional BE designs with a complete washout and novel BE designs with an incomplete washout (see **Research Highlight** for details).

Grant U01FD007936 with the University of Florida sought to predict regional lung exposure from systemic PK data of generic orally inhaled drug products using population PK modeling approaches. The preliminary results showed that empirical models have the potential to identify regional deposition across various scenarios created from mechanistic inhalation models. The goal is to provide a valuable means to inform BE in regional lung exposure, offering a practical alternative approach to comparative clinical endpoint or pharmacodynamic BE studies.

FDA continues to utilize internal QCP expertise to address complex or emerging regulatory issues, including partial AUC recommendations, narrow therapeutic index drug classifications, and harmonization with other regulatory agencies. FDA is also working on developing innovative study designs for PK BE studies conducted in patients. For instance, internal research is ongoing to evaluate reduced or sparse sampling scheme for studies with oncology products, alternative study designs for LAI products with shorter study durations or reduced sample size, and adaptive designs.

FDA discussed regulatory applications of Model Master Files (MMF) at a workshop CRCG co-hosted by FDA and the Center for Research on Complex Generics (CRCG)[24]. A population PK-based MIE framework developed through a collaboration between FDA and Uppsala University (Contract# HHSF223201710015C) was presented as a potential MMF type. This MIE framework, along with the associated user-friendly R packages, was published in FY 2024[25,26].

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[24] FDA and Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File (https://www.complexgenerics.org/education-training/considerations-and-potential-regulatory-applications-for-a-model-master-file/).

[25] Chen X, Nyberg HB, Donnelly M, Zhao L, Fang L, Karlsson MO, and Hooker AC. *Development and Comparison of Model-Integrated Evidence Approaches for Bioequivalence Studies with Pharmacokinetic End Points.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 13: 1734-1747. https://doi.org/10.1002/psp4.13216. PMID: 39177211.

[26] Bjugård Nyberg H, Chen X, Donnelly M, Fang L, Zhao L, Karlsson MO, and Hooker AC. *Evaluation of Model-Integrated Evidence Approaches for Pharmacokinetic Bioequivalence Studies Using Model Averaging Methods.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 00: 1-14. https://doi.org/10.1002/psp4.13217. PMID: 39205490.

RESEARCH HIGHLIGHT

The BE of highly variable drugs (HVDs) may be evaluated using the RSABE approach[27], which recommends a replicate crossover design (partial- or fully-replicate) for comparison in absorption rate and extent by measuring C_{max} and AUC, respectively, with non-compartmental analysis (NCA). However, BE studies using replicate crossover designs can be challenging for HVDs with a long half-life because a sufficient washout period between treatment periods is recommended for NCA analysis. Research conducted under Contract #75F40122C00139 used a previously developed MIE method[28,29] to analyze BE data for HVDs with a long half-life using complete and incomplete washout designs (Figure 1).

Datasets with rich sampling (18 samples per individual) were simulated 500 times using a one-compartmental PK model with first order absorption and elimination with a typical half-life of 55.5 hours. Two levels of within-subject standard deviation (S_{WR}) were evaluated: 30% (CV30) and 48% (CV50). Fully replicate crossover studies with complete washout (≥5 half-lives) and incomplete washout (a dosing interval of 72hr) were tested. Formulation differences were simulated by adding a treatment effect (test/reference ratio) on relative bioavailability (FTRT). Power and type I error were evaluated at FTRT=0.9 and at the expanded BE limits (FTRT=1.3 for CV30 and FTRT=1.53 for CV50), respectively. The MIE method was used to evaluate complete and incomplete washout designs. Also, standard NCA-based RSABE analysis methods were used to evaluate complete washout designs.

Both methods control type I error with complete washout designs, but MIE approaches trend towards higher power at higher variability (Figure 2). Also, the MIE method controls type I error and shows sufficient power with the incomplete washout design. Moreover, the incomplete washout design reduces the overall study duration from 37.5 days to 12 days (Figure 3). Thus, the MIE method with incomplete washout design serves as a promising strategy for the BE evaluation of HVDs with a long half-life by reducing the overall study duration.

[27] FDA Guidance for Industry. *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.* (August 2021). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug.

[28] See footnote 25.

[29] See footnote 26.

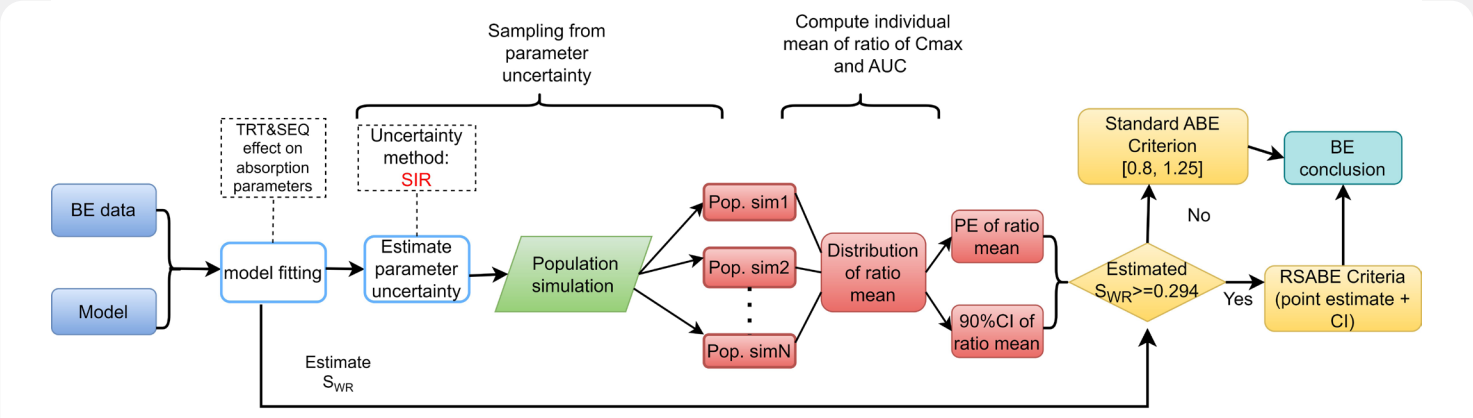

Figure 1. Overview of the developed MIE approach. The method consists of four steps: (1) model fitting using a pre-defined model (other approaches available including pre-defined model building and pre-defined model averaging) for the reference product with additional treatment effect (TRT) and sequence effect (SEQ) on absorption parameters including relative bioavailability (F, assumed to be 1 for the reference product); (2) model parameter uncertainty assessment using sampling importance resampling (SIR); (3) simulation to derive the point estimate (PE) and uncertainty distribution of the geometric mean ratios of summary PK parameter metrics (AUC, C_{max}) using simulations of populations of individuals from parameter values sampled via (2); and (4) conclusion based on nonparametric confidence intervals of the geometric mean ratios obtained from (3), utilizing the RSABE criteria if the within subject standard deviation of reference arm PK metrics (S_{wr}) is above 0.294, calculated from the simulation step.

RESEARCH HIGHLIGHT *continued*

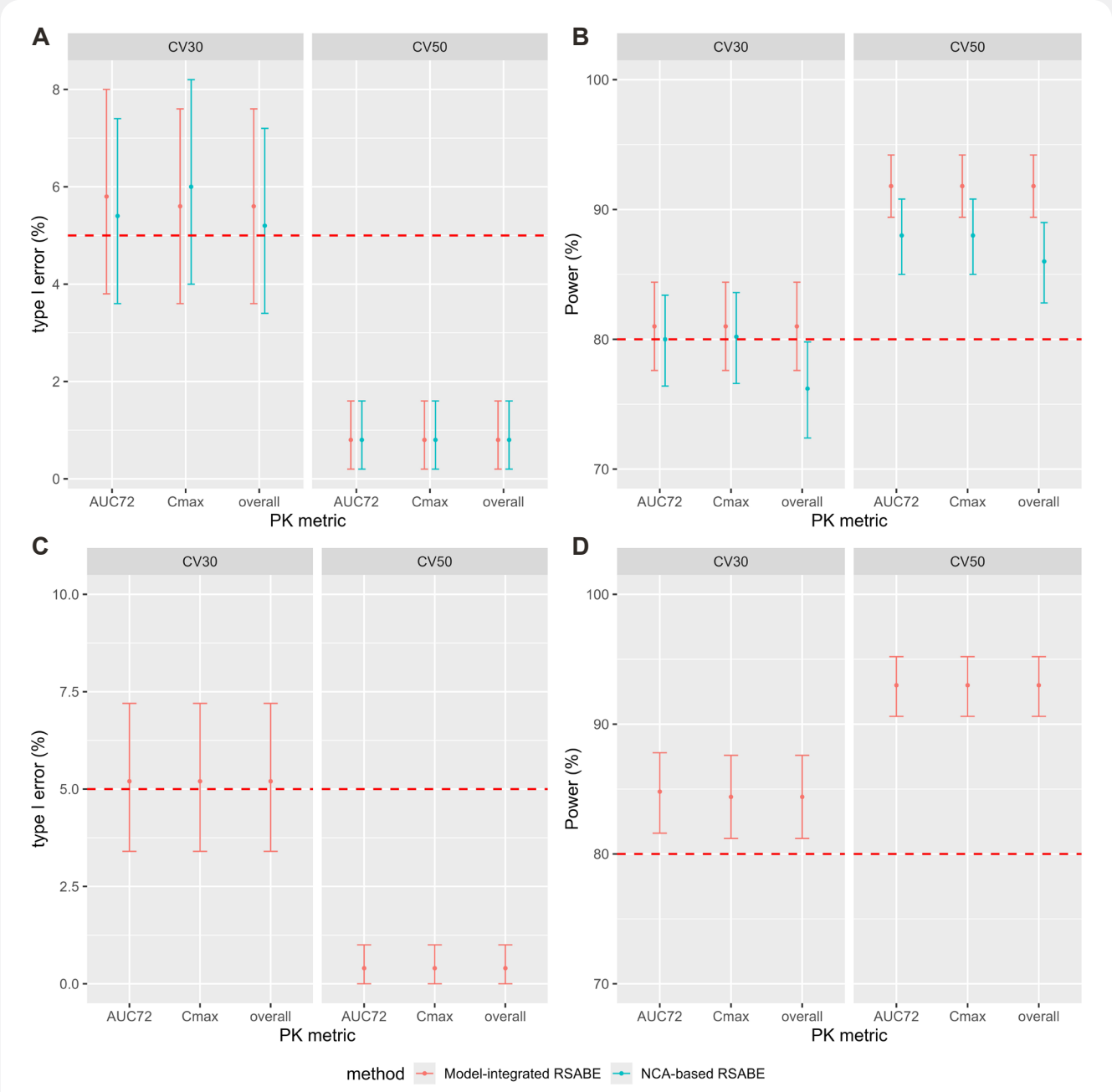

Figure 2. Type I error and power results with 95% confidence intervals (CIs) for BE analysis of a HVD with a long half-life (55.5 hours) using a fully-replicate crossover design, with complete washout period (**top, panels A and B**) or incomplete washout period (**bottom, panels C and D**; total period length, including washout, of 72 hours), and RSABE analysis involving model-integrated methods or the conventional NCA approach (only possible with complete washout).

RESEARCH HIGHLIGHT *continued*

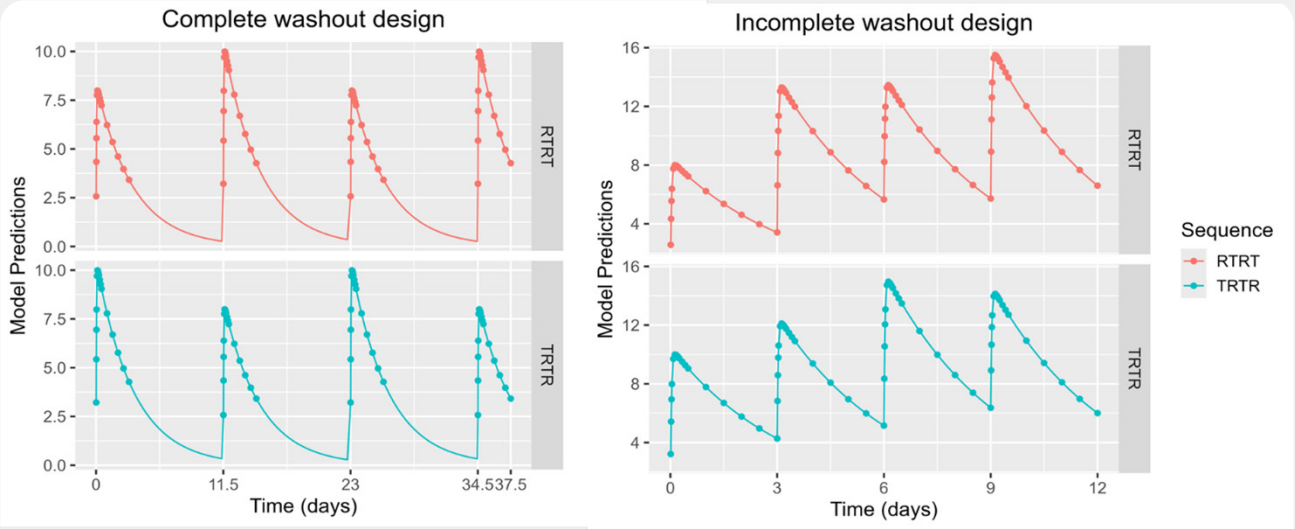

Figure 3. Study durations for complete and incomplete washout designs with the 4-way, fully replicate crossover study. The X-axis shows the different study durations: 37.5 days for the complete washout design and 12 days for the incomplete washout design.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Grant (U01FD007936) *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
- 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

Active FDA Research

- *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*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *Model-Based Assessment on Bioequivalence Limits for Anticoagulants*
- *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists*

RESEARCH PROJECTS AND COLLABORATIONS *continued*

- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Pharmacokinetic Data Analysis to Identify Chewing Methods for Opioid Drug*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-Based Approach*

OUTCOMES

Product-Specific Guidances

There were five new PSGs published in FY2024 related to *Quantitative Clinical Pharmacology*. Each of these PSGs, listed below, were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Dextroamphetamine Transdermal System* (Nov. 16, 2023) Link to the Posting
- *New Draft Guidance for Naloxone Hydrochloride Spray, Metered* (NDA 217722). (Aug. 22, 2024) Link to the Posting
- *New Draft Guidance for Naloxone Hydrochloride Spray, Metered* (NDA 208969). (Feb. 15, 2024) Link to the Posting
- *New Draft Guidance for Nalmefene Hydrochloride Spray, Metered* (May 16, 2024) Link to the Posting
- *New Draft Guidance for Risperidone for Suspension, Extended Release* (Aug. 22, 2024) Link to the Posting

Articles

- Chen X, Nyberg H, Donnelly M, Zhao L, Fang L, Karlsson M, and Hooker A. *Development and Comparison of Model-Integrated Evidence Approaches for Bioequivalence Studies with Pharmacokinetic End Points.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 00: 1-14. https://doi.org/10.1002/psp4.13216. PMID: 39177211.
- Chen R, Schumitzky A, Kryshchenko A, Nieforth K, Tomashevskiy M, Hu S, Garreau R, Otalvaro J, Yamada W, and Neely M. *RPEM: Randomized Monte Carlo Parametric Expectation Maximization Algorithm.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 13: 759-780. https://doi.org/10.1002/psp4.13113v. PMID: 38622792.
- Fang L, Gong Y, Hooker A, Lukacova V, Rostami-Hodjegan A, Sale M, Grosser S, Jereb R, Savic R, Peck C, and Zhao L. *The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA.* The AAPS Journal. (2024) 26: 28. https://doi.org/10.1208/s12248-024-00897-8. PMID: 38413548.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Pharmacokinetic Models for Inhaled Fluticasone Propionate and Salmeterol Xinafoate to Quantify Batch-to-Batch Variability.* The AAPS Journal. (2024) 26: 56. https://doi.org/10.1208/s12248-024-00913-x. PMID: 38671158.
- Li X, Sale M, Nieforth K, Craig J, Wang F, Solit D, Feng K, Hu M, Bies R, and Zhao L. *pyDarwin Machine Learning Algorithms Application and Comparison in Nonlinear Mixed-effect Model Selection and Optimization.* Journal of Pharmacokinetics and Pharmacodynamics. (2024) 51(6), 785–796. https://doi.org/10.1007/s10928-024-09932-9. PMID: 38941056.
- Li X, Sale M, Nieforth K, Bigos K, Craig J, Wang F, Feng K, Hu M, Bies R, and Zhao L. *pyDarwin: A Machine Learning Enhanced Automated Nonlinear Mixed-Effect Model Selection Toolbox.* Clinical Pharmacology and Therapeutics. (2024) 115: 758-773. https://doi.org/10.1002/cpt.3114. PMID: 38037471.

OUTCOME *continued*

- Nyberg H, Chen X, Donnelly M, Fang L, Zhao L, Karlsson M, and Hooker A. *Evaluation of Model-Integrated Evidence Approaches for Pharmacokinetic Bioequivalence Studies Using Model Averaging Methods.* CPT: Pharmacometrics & Systems Pharmacology. (2024) 13(10), 1748–1761. https://doi.org/10.1002/psp4.13217. PMID: 39205490.

- Pal A, Wu F, Walenga R, Tsakalozou E, Alam K, Gong Y, Zhao L, and Fang L. *Leveraging Modeling and Simulation to Enhance the Efficiency of Bioequivalence Approaches for Generic Drugs: Highlights from the 2023 Generic Drug Science and Research Initiatives Public Workshop.* The AAPS Journal. (2024) 26: 45. https://doi.org/10.1208/s12248-024-00916-8. PMID: 38589695.

- Philipp M, Tessier A, Donnelly M, Fang L, Feng K, Zhao L, Grosser S, Sun G, Sun W, Mentre' F, and Bertrand J. *Model-Based Bioequivalence Approach for Sparse Pharmacokinetic Bioequivalence Studies: Model Selection or Model Averaging?* Statistics in Medicine. 43(18): 3403-3416. https://doi.org/10.1002/sim.10088. PMID: 38847215.

- Tsakalozou E, Fang L, Bi Y, Van Den Heuvel M, Ahmed T, Tsang Y, Lionberger R, Rostami-Hodjegan A, and Zhao L. *Experience Learned and Perspectives on Using Model Integrated Evidence in the Regulatory Context for Generic Drug Products.* The AAPS Journal. (2024) 26: 14. https://doi.org/10.1208/s12248-023-00884-5. PMID: 38200397.

- Tsakalozou E, Gong Y, Babiskin A, Hu M, Mousa Y, Walenga R, Wu F, Yoon M, Raney S, Polli J, Schwendeman A, Krishnan V, Fang L, and Zhao L. *Application of Advanced Modeling Approaches Supporting Generic Product Development Under GDUFA for Fiscal Year 2023.* The AAPS Journal. (2024) 26: 55. https://doi.org/10.1208/s12248-024-00924-8. PMID: 38658449.

- Walenga R, Babiskin A, Bhoopathy S, Clark J, De Backer J, Ducharme M, Kelly M, Le Merdy M, Yoon M, and Roy P. *Use of the Same Model or Modeling Strategy Across Multiple Submissions: Focus on Complex Drug Products.* The AAPS Journal. (2024) 26: 12. https://doi.org/10.1208/s12248-023-00879-2. PMID: 38177638.

- Zhang P, Lee J, Feng K, Babiskin A, Yoon M, Fang L, and Zhao L. *Commentary on 'Exploration of Suitable Pharmacodynamic Parameters for Acarbose Bioequivalence Evaluation: a Series of Clinical Trials with Branded Acarbose' by Jie Huang et al.* British Journal of Clinical Pharmacology. 90(9): 2320-2322. https://doi.org/10.1111/bcp.16148. PMID: 38922996.

Posters

- Zhang P, Donnelly M, Feng K, Gong Y, Liu X, and Babiskin A. *Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions.* Poster Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.

- Li X, Sale M, Nieforth K, Craig J, Wang F, Solit D, Feng K, Hu M, Bies R, and Zhao L. *Performance of Machine Learning Algorithms for Model Selection.* Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 27, 2024.

OUTCOME *continued*

- Huang Z, Chen X, Donnelly M, Fang L, Zhao L, Karlsson M, and Hooker A. *Model-Integrated Bioequivalence Method for Highly Variable Drugs with Long Half-Life: a Simulation Study Comparing Complete Washout and Incomplete Washout Designs.* Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 26, 2024.
- Zhang P, Donnelly M, Feng K, Gong Y, Liu X, Babiskin A, Yoon M, Zhao L, and Fang L. *Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions.* Poster Presentation at the American Conference on Pharmacometrics (ACoP) 2023. National Harbor, MD, Nov. 06, 2023.

Presentations

- Gong Y. *Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs: First-Year Review.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Bethesda, MD, Sep. 25, 2024.
- Fang L. *Narrow Therapeutic Index Drug Classification: US FDA Current Process.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Jiang W. *Data-driven & Science-based Recommendation on Harmonization of Bioequivalence Standards for Narrow Therapeutic Index Drugs.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Babiskin A. *Regulatory Utility of MMF for Development of Long-Acting Injectable Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Hooker A. *Model-Based Bioequivalence Methods Serving as MMF for LAI Drug Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Considerations and Potential Regulatory Applications for a Model Master File. Rockville, MD, May 02, 2024.
- Fang L. *Partial Area Under Curve (pAUC): Product-Specific Guidance Development and Practice for Product Evaluation.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 17, 2024.
- Gong Y. *Considerations and Challenges of Pharmacokinetics Bioequivalence Studies for LAIs and the Application of Model-Integrated Evidence (MIE) Approaches.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 16, 2024.
- Gong Y. *Strategic Development of Generic Long-Acting Injectables: Model-Integrated Evidence Approaches.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Spring, CO, Mar. 29, 2024.
- Sale M. *Performance of Machine Learning Algorithms for Model Selection.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 29, 2024.

CHAPTER 8: DATA ANALYTICS & ARTIFICIAL INTELLIGENCE

A major GDUFA science and research priority area during GDUFA III[1] 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 during fiscal year (FY) 2024 that was aligned with this GDUFA science and research priority area is described below.

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[1] On July 9, 2012, the Food and Drug Administration Safety and Innovation Act was signed into law, which included the authorization of the Generic Drug User Fee Amendments of 2012 (GDUFA I). On August 18, 2017, the FDA Reauthorization Act of 2017 was signed into law, which included the Generic Drug User Fee Amendmentsof 2017 (GDUFA II). The FDA User Fee Reauthorization Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to reauthorize the GDUFA program for an additional 5 years from FY 2023 through FY 2027 (GDUFA III).

Summary of FY 2024 Activities

In FY 2024, the FDA continued the development of the BEAM (BioEquivalence Assessment Mate) tool, an enterprise-level automation platform designed to streamline labor-intensive tasks in the bioequivalence (BE) assessment process. Currently, BE assessors can use BEAM to facilitate assessments for ANDAs involving 2x2 crossover, fully and partially replicated designs (e.g., for highly variable drugs and narrow therapeutic index drugs), and parallel studies. Development is ongoing to expand BEAM's functionality to include more study types (e.g., multiple strengths) and dosage forms. Given the remarkable advancements in the performance and capabilities of large language models (LLMs), there is an increasing interest in how to effectively leverage them to enhance the FDA's daily operations. One prominent effort has been using ChatGPT to support the development of PSGs. In a proof-of-concept study, ChatGPT was employed to generate a summary of food effect information by analyzing publicly available new drug application (NDA) review documents available at Drugs@FDA. The results were validated by comparing the generated information with the food effect information found in drug labeling. This study serves as an important milestone in exploring the feasibility of using LLMs to aid regulatory assessments (additional details can be found in the **Research Highlight** section of this chapter). Furthermore, a Grant (U01FD005978-08: Large Language Models to Support BE Evaluation) was awarded to develop a suite of innovative tools leveraging LLMs to assist FDA reviewers in their critical work. The project aims to create an interactive expert system trained on publicly available FDA data and relevant publications to quickly respond to queries and summarize complex study information. Additionally, a Contract (75F40124P00142: Construction of a Biopharmaceutics Classification System (BCS) Database based on Large Language Models) was awarded to develop a BCS database. The BCS classification provides important information for regulatory assessments (e.g., recommended study designs in PSGs). However, identifying the BCS classification usually requires checking and confirming with numerous internal and external documents, which is often time-consuming. This project will utilize LLMs to extract BCS classification information from various public data sources to construct a comprehensive database containing the BCS classification of drug substances.

Another notable ongoing work is to develop an ML-assisted tool to improve the quality and assessment of PLGA (poly(lactic-co-glycolic acid)) formulations. Traditional approach of formulation development relies on iterative improvement such as design of experiment or even trial-and-error. This often necessitates extensive resources and time for conducting in vitro and in vivo experiments. In particular, significant challenges remain for the formulation and process design of PLGA-based long-acting injectable (LAI) products, where both material attributes and processing conditions are known to play a pivotal role in the quality and performance of the final products. The current study aims to tackle such challenges through automation of some important but repetitive data processing steps using ML methodologies. The study has developed a ML-assisted method to aid the analysis of PLGA-based LAI 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.

A Grant (U01FD008379: ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products) was awarded to develop a reproducible strategy that leverages ML to overcome certain limitations associated with computational fluid dynamics. This advancement aims to enhance regulatory approaches, ultimately facilitating the development and approval of generic dry powder inhalers.

During FY 2024, data analytics tools continued to play a key role in supporting regulatory assessments, particularly in areas such as in vitro release testing, active pharmaceutical ingredient (API) sameness, particle size distribution, and so on.

RESEARCH HIGHLIGHT

FDA publishes PSGs to outline the agency's current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to specific reference listed drugs. Extracting relevant information, such as absorption, distribution, metabolism, and excretion (ADME), from internal and external documents (e.g., drug labeling) is a critical step in PSG development. Automating this process could significantly streamline PSG development. LLMs, such as ChatGPT, have demonstrated exceptional performance in natural language processing tasks, including automatic information extraction and text summarization. However, their application in regulatory assessments was unclear. In this study, we assessed the potential of ChatGPT to provide a summary of food effect information from publicly available NDA review documents. We also validated its performance by comparing the generated results to the food effect information in the corresponding drug labeling. An intuitive strategy, known as iterative prompting, was developed to carry out this task through an interactive conversation with the chatbot. Specifically, we propose a three-turn iterative prompting approach[2] for food effect summarization, in which keyword-focused and length-controlled prompts are provided in consecutive turns to refine the quality of the generated summary (Figure 1). A series of extensive evaluations, ranging from automated metrics to assessments by FDA professionals—and even GPT-4 (the newest version of ChatPGT when this work was done)—were conducted on 100 publicly available NDA review documents selected over the past five years. We observed that the quality of the summaries progressively improved throughout the iterative prompting process. Moreover, GPT-4 outperformed ChatGPT, as evaluated by FDA professionals (43% vs. 12%, i.e., GPT-4 was considered to perform better for 43% of all the test cases, whereas ChatGPT was considered better for 12% of all the test cases) and GPT-4 itself (64% vs. 35%) (Figure 2). Importantly, all FDA professionals unanimously rated 85% of the summaries generated by GPT-4 as factually consistent with the golden reference summary (i.e., drug labeling). This finding was further supported by GPT-4, which rated the consistency at 72%. These results strongly suggest that GPT-4 has a great potential to provide food effect summaries that could be reviewed by FDA professionals, thereby improving the efficiency of the PSG development and promoting generic drug product development.

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[2] Shi Y, Ren P, Wang J, Han B, ValizadehAslani T, Agbavor F, Zhang Y, Hu M, Zhao L and Liang H. *Leveraging GPT-4 for Food Effect Summarization to Enhance Product-Specific Guidance Development via Iterative Prompting.* Journal of Biomedical Informatics. (2023) 148: 104533. https://doi.org/10.1016/j.jbi.2023.104533. PMID:37918623.

RESEARCH HIGHLIGHT *continued*

Summarize the following text related to food effect studies.

EMR200095-002: crossover study to investigate the food effect and relative BA of tepotinib in 2 groups of healthy subjects.

MS200095-0044: study with crossover design in each part to investigate the BE of the tablet formulation of tepotinib TF3 compared to TF2, and to investigate the influence of food on the PK of each tablet formulation TF2 and TF3 of tepotinib in healthy subjects.

The recommendation that tepotinib is administered with food is supported by the food effect study showing the mean AUC0-INF of tepotinib increased by 1.6-fold and Cmax increased by 2-fold (Table 18), following administration of a high-fat, high-calorie meal (approximately 800 to 1,000 calories, 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat). The median Tmax shifted from 12 hours to 8 hours. In addition, taking tepotinib with food is expected to mitigate the gastrointestinal toxicities including diarrhea, which were among the most common adverse reactions. The food effect is considered clinically meaningful, as a reduction in exposure following administration of tepotinib without food may potentially reduce anti-tumor activity and tepotinib was administered with food in VISION. ……

The food effect study shows that administering tepotinib with food increases its exposure and mitigates adverse reactions like diarrhea. The study also indicates that taking tepotinib without food may reduce its anti-tumor activity. The recommended mode of administration *for* tepotinib is with food. The crossover studies investigate the food effect and relative bioavailability of tepotinib in healthy subjects and compare the BE of the different formulations of tepotinib. FDA recommends administering tepotinib with food.

Add facts of AUC, Cmax, and Tmax in summary.

In the food effect study, it was found that taking tepotinib with a high-fat, high-calorie meal increased the mean AUC0-INF by 1.6-fold and Cmax by 2-fold. The median Tmax also shifted from 12 hours to 8 hours. Similarly, the crossover studies showed an increase in AUC and Cmax when tepotinib was administered with food. Thus, taking tepotinib with food is recommended to enhance its exposure and clinical outcomes.

Summarize it in 2-3 sentences and keep the detail of AUC, Cmax, and Tmax.

The food effect study found that taking tepotinib with a high-fat, high-calorie meal increased the mean AUC0-INF by 1.6-fold and Cmax by 2-fold, with a shift in median Tmax from 12 hours to 8 hours. The recommended mode of administration for tepotinib is with food to enhance its exposure and clinical outcomes.

Figure 1. An example to illustrate the iterative conversation with the ChatGPT for text summarization of food effect study (NDA214096) used in our approach.

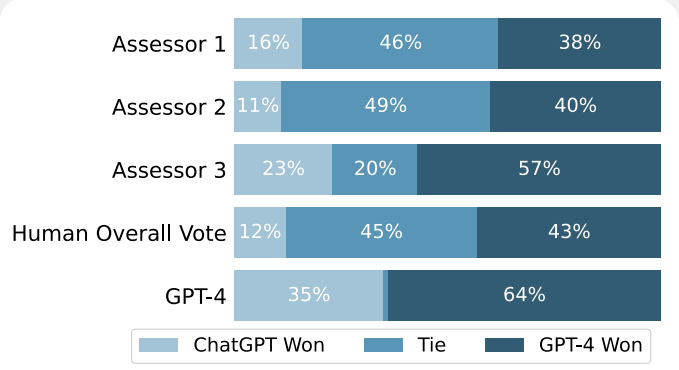


Figure 2. Human and GPT-4 evaluation results for comparing summaries generated by ChatGPT and GPT-4. Both human assessors and GPT-4 show a strong preference for the summary generated by GPT-4 over ChatGPT. However, GPT-4 has difficulty identifying the scenario where the summaries are equally good.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Grant (U01FD008379) *ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products* with Yu Feng at Oklahoma State University
- Grant FDA/CDER RSR 2023-2024 - *Accelerating Long-acting Injectable Formulation Development: A Deep Dive into Machine Learning Applications* with Kinam Park at Purdue University.
- Contract (75F40124P00142) *Construction of a Database Containing Drug Biopharmaceutics Classification System (BCS) Class Information* with Hualou Liang at Drexel University

Continuing Grants and Contracts

- Grant (U01FD005978) *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
- Grant (U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/ Harvard Medical School
- Contract (75F40122C00121) *Machine-Learning based Heterogeneous Treatment Effect Models for Informing Product-Specific Guidance Development* at Drexel University

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 f or 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

Articles

- Gong Y, Barretto F, Tsong Y, Mousa Y, Ren K, Kozak D, Shen M, Hu M, and Zhao L. *Development of Quantitative Comparative Approaches to Support Complex Generic Drug Development.* The AAPS Journal. (2024) 26: 15. https://doi.org/10.1208/s12248-024-00885-y. PMID: 38267593.
- Iliopoulos F, Tu D, Pence I, Li X, Ghosh P, Luke M, Raney S, Rantou E, and Evans C. *Determining Topical Product Bioequivalence with Stimulated Raman Scattering Microscopy.* Journal of Controlled Release. (2024) 367: 864-876. https://doi.org/10.1016/j.jconrel.2024.02.010. PMID: 38346503.
- Li X, Sale M, Nieforth K, Bigos K, Craig J, Wang F, Feng K, Hu M, Bies R, and Zhao L. *pyDarwin: A Machine Learning Enhanced Automated Nonlinear Mixed-Effect Model Selection Toolbox.* Clinical Pharmacology and Therapeutics. (2024) 115: 758-773. https://doi.org/10.1002/cpt.3114. PMID: 38037471.
- Li X, Sale M, Nieforth K, Craig J, Wang F, Solit D, Feng K, Hu M, Bies R, and Zhao L. *pyDarwin Machine Learning Algorithms Application and Comparison in Nonlinear Mixed-effect Model Selection and Optimization.* Journal of Pharmacokinetics and Pharmacodynamics. (2024). 51(6): 785–796 https://doi.org/10.1007/s10928-024-09932-9. PMID: 38941056.

Posters

- Li X, Sale M, Nieforth K, Craig J, Wang F, Solit D, Feng K, Hu M, Bies R, and Zhao L. *Performance of Machine Learning Algorithms for Model Selection.* Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 27, 2024.
- Wang J, Tong A, Sun W, Hu M, Fang L, Kim M, and Zhao L. *A Quantitative Modeling Approach to Predict Availability of Generic Orphan Drug Products.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Cui D, Li K, Al Ghabeish M, Mcguire M, Sun W, Hu M, Zhao L, and Kim M. *Application of Quantitative Models to Systematically Evaluate Factors Impacting Swallowability of Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Ghosh P, Belsey N, Woodman T, Jane White K, Bunge A, Delgado-Charro M, and Guy R. *Assessment of Bio(in)equivalence of Metronidazole Topical Formulation Using Stimulated Raman Scattering Microscopy.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Hu M. *Leveraging Artificial Intelligence (AI) and Machine Learning (ML) to Support Generic Drug Development and Regulatory Assessment.* Presentation at the ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop. Rockville, MD, Sep. 26, 2024.
- Wang J. *Approaches to Analyzing Comparative Use Human Factors Studies.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting, Bethesda, MD, Sep. 24, 2024.

OUTCOME *continued*

- Hu M. *Challenges in Processing PK Data from ANDA Submissions for BE Assessment and Current Perspectives on Updating the PK Data Standard.* Presentation at the 2024 Generic Drug Cluster. Virtual Meeting, Sep. 20, 2024.
- Zhao L. *Quick Points on AI FAIRification.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 29, 2024.
- Sale M. *Performance of Machine Learning Algorithms for Model Selection.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 29, 2024.
- Zhao L. *When Modeling & Simulation Meets AI.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 29, 2024.
- Das, J. *Applications of AI in Manufacturing of Pharmaceutical Products: Challenges and Opportunities.* Presentation at the International Forum for Process Analysis & Control. Bethesda, MD, Mar. 03, 2024.
- Tu D, Lemberger N, Wallmeier K, Riseman J, Kuzma B, Wei Y, Khoo T, Fallnich C, and Evans C. *Dual Modality Monitoring of Topical Formulations within Human Skin Using Stimulated Raman Scattering (SRS) Microscope.* Presentation at the SPIE Photonics West. San Francisco, CA, Jan. 27, 2024.
- Das J. *Applications of AI in Manufacturing of Pharmaceutical Products: Challenges and Opportunities.* Presentation at the Small Business and Industry Assistance (SBIA) Pharmaceutical Quality Symposium: Quality, Supply Chain & Advanced Manufacturing. Virtual Meeting, Nov. 01, 2023.
- Zhao L. *When Modeling & Simulation Meets AI.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.
- Zhao L. *The Behavioral and Clinical Pharmacology Seminar Series.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.
- Zhao L. *When Modeling & Simulation Meets AI.* Presentation at the International Symposium of Quantitative Pharmacology. Virtual Meeting, Oct. 15, 2023.

CHAPTER 9: OTHER GENERIC DRUG RESEARCH

The Generic Drug User Fee Amendments (GDUFA) science and research program advances research in a variety of areas informed by public input that help enhance patient access to safe, effective, and high-quality generic products. For example, research to ensure the availability of generic products that address the Secretary of the Department of Health and Human Service's Public Health Emergency for the treatment of opioid addiction and for rescue from overdose can help ensure the availability of medicines that address major public health needs. Research in this area is described below.

OPIOID DRUG PRODUCTS

Summary of FY 2024 Activities

In FY 2024, FDA investigated products designed to prevent relapse to opioid dependence or reverse an overdose and continued to execute on Contract research related to opioid products with abuse-deterrent formulations (ADFs). The four areas of focus were:

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

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

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

4. Conducting high-throughput surveillance of opioid products

Contract 75F40121C00178 supported research and development to validate in vitro chewing study methods. The results determine critical in vitro study design parameters when comparing abuse deterrence of an opioid product via the oral route between a generic product and its reference listed drug (RLD) when chewed.

Another Contract, HHSF223201610004I-HHSF22301002T, was designed to investigate the impact of particle size of manipulated oxycodone hydrochloride (HCl) and naloxone HCl extended-release (ER) tablets through a PK/pharmacodynamic (PD) intranasal (IN) study (see **Research Highlight**).

Two internal FDA research projects focused on quantifying drug delivery from nasally insufflated abuse of opioid drug products. The first project developed a combined computational fluid dynamic (CFD) and physiologically based pharmacokinetic (PBPK) model that can predict PK following nasal insufflation of manipulated oxycodone HCl and naloxone HCl ER tablets, which may be used to understand the observed PK data. The project quantifies regional deposition using a 3-D nasal model. Results from a study using a marketed nasal powder device as a test article showed that regional deposition estimates agreed reasonably well with available in vivo imaging data.[1]

Other internal research projects examined overdose reversal by naloxone and prevention of relapse because of opioid dependence. A biopredictive in vitro permeation test (IVPT) and an in vitro in vivo extrapolation (IVIVE) model was investigated for IN naloxone spray. The IVPT and IVIVE explain the relationship between the in vitro permeation data for a variety of naloxone IN solutions and the corresponding clinical data obtained from the literature. Another internal FDA naloxone study assessed the spray-dried naloxone nasal powder for opioid overdose reversal. The goal was to identify critical quality attributes for spray-dried naloxone nasal powder and develop in vitro dissolution and nasal permeation methods to support bio-predictive modeling. Nasal powder formulations continued to be developed and recognized as advantageous over liquid dosage forms due to increased stability and residence time on nasal mucosa, with improved bioavailability. These studies will provide data to support BE recommendations for IN naloxone drug products, which may encourage the development

[1] Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 440-443.

and marketing of generic IN naloxone drug products, a critical countermeasure to the opioid epidemic.

High-throughput surveillance of opioid product testing ensures patients have access to high quality medications. Quality and performance of opioid drug products are measured through laboratory testing to assess their integrity and the critical quality attributes. Implementation of high throughput automated instrumentation can streamline testing of opioid drug products, evaluate critical quality attributes including potency, uniformity, and drug release testing, which can then ensure that safe and effective opioid drug products remain available.

RESEARCH HIGHLIGHT

Oxycodone HCl and naloxone HCl ER tablets contain an opioid agonist, oxycodone, and an opioid antagonist, naloxone and are designed with abuse deterrent (AD) properties against IN abuse. When administered orally, naloxone has low bioavailability (< 3%); however, IN administration of the milled or manipulated products leads to an increase in the naloxone bioavailability (about 30%) and thus a reduction in the agonist effect of oxycodone. A study conducted by Biopharma Services USA Inc. under Contract HHSF223201610004I-HHSF22301002T aimed to: (1) evaluate the impact of particle size of manipulated products on the nasal PK parameters of oxycodone, naloxone, and oxycodone active metabolite, oxymorphone, (2) understand the effect of particle size on naloxone's ability to mitigate the drug liking and other PD effects of oxycodone, and (3) evaluate the safety and tolerability of the manipulated products via the IN route. The study design included a single-dose, randomized, double-blind, active controlled, five-way crossover study. The 39 study subjects who completed the study were non-dependent recreational opioid users who underwent a naloxone challenge and discrimination test to ensure they could discriminate between the positive drug effects of the active control and placebo and also tolerate the study products. The active control used in the study (Treatment D) was a milled oxycodone HCl immediate-release (IR) tablet (oxycodone HCl 40 mg dose) and the placebo (Treatment E) was microcrystalline cellulose powder. The three other treatments the subject received were different manipulated products of oxycodone HCl 40 mg; naloxone HCl 20 mg ER tablets where Treatment A contained fine particles [106–300 µm], Treatment B contained medium particles [300–600 µm], and Treatment C contained coarse particles [600–1000 µm]. The PK findings of the study showed that the rates and extents (except of early extent) of absorption of oxycodone and oxymorphone were comparable between the three manipulated products despite different particle size ranges (90% confidence intervals of peak concentration [Cmax] and area under curve from zero to infinity [AUCinf] were within acceptance range of 80.00-125.00%, Figure 1). For oxycodone, as particle size increased (A < B < C), the earlier extent of absorption (AUC 0-0.5, 0-1, and 0-2) decreased while for naloxone, a lower rate and extent of absorption were observed as the particle size increased (Figure 1). Results of the study indicate that the PD endpoints of Drug Liking and Take Drug Again (maximum effect, Emax) measured by visual analog scale (VAS) of all three treatments of manipulated products have significant AD potential ($p<0.0001$) as compared with milled oxycodone HCl IR tablets (Treatment D) (Table 1). The results also indicated an overall comparable AD potential between the manipulated products with different particle sizes, Table 1. All study treatments were well tolerated without unexpected or serious adverse events. In conclusion, the change of the nasal bioavailability of naloxone compared to oxycodone did not impact the AD properties of the product as measured by the similar low scores for Drug Liking and Take Drug Again. The AD properties of this product via the IN route were not impacted by the particle size of the insufflated manipulated product.

RESEARCH HIGHLIGHT *continued*

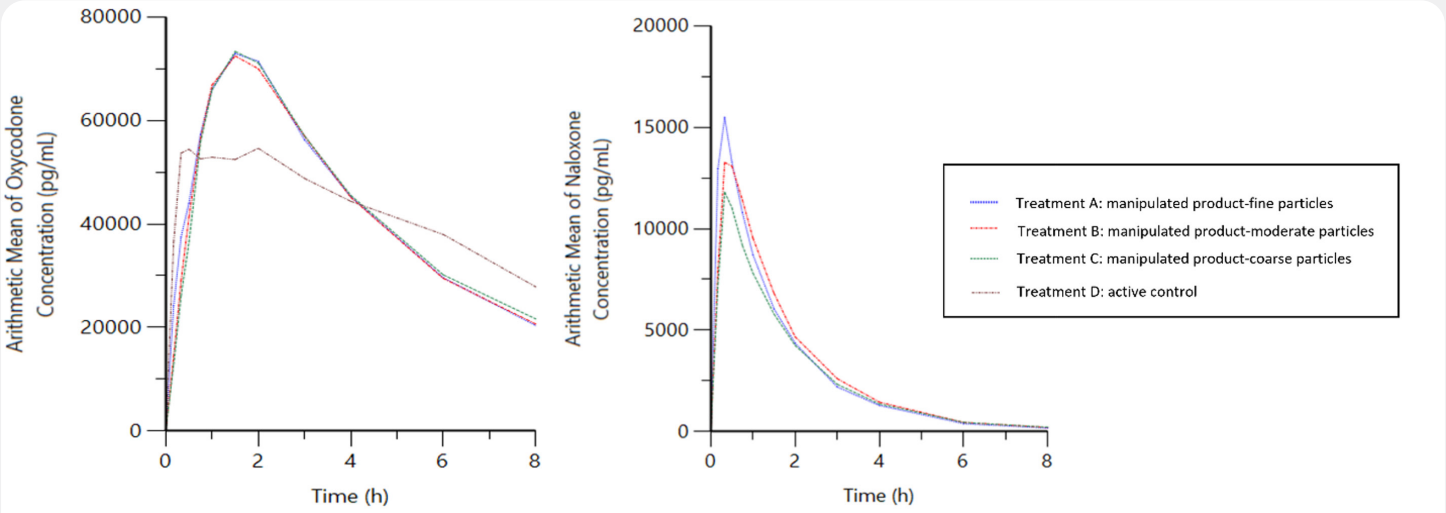


Figure 1. The Pharmacokinetic Profiles of Oxycodone (left) and Naloxone (right) After the IN Administration of Three Manipulated Products (Treatments A, B, and C) of Oxycodone HCl and Naloxone HCl ER Tables and Active Control (Treatment D) (N= 39).

Table 1. Pharmacodynamic endpoints (Drug Liking Emax and Take Drug Again) After the IN Administration of Three Manipulated Products (Treatments A, B, and C) of Oxycodone HCl and Naloxone HCl ER Tables Compared to Active Control (Treatment D) AND Placebo (N= 37).

Endpoint Statistic	Treatment A: Manipulated Product - Fine Particles (N=37)	Treatment B: Manipulated Product - Medium Particles (N=37)	Treatment C: Manipulated Product - Coarse Particles (N=37)	Treatment D: Active Control (N=37)	Treatment E: Placebo (N=37)
Drug Liking VAS E_{max}					
Mean (SD)	63.8 (18.03)	65.5 (21.00)	63.5 (17.36)	90.2 (11.28)	50.4 (9.12)
Median	55.0	62.0	60.0	93	50
Range	23 – 100	0 – 100	28 – 100	60 – 100	4 – 75
Take Drug Again VAS E_{max}					
Mean (SD)	57.8 (22.17)	59.4 (25.03)	55.5 (22.87)	80.2 (18.74)	49.5 (17.42)
Median	50.0	50.0	50.0	86.0	50.0
Range	0 – 100	0 – 100	0 – 100	50 – 100	0 – 99

Range=minimum – maximum; SD=standard deviation

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 the University of Auckland

Completed Grants and Contracts

- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Artan Markollari at Biopharma Services USA Inc.

Active FDA Research

- *Development of In Vitro Methods for Nasal ADF Opioids*
- *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists*

OUTCOMES

Product-Specific Guidances

There were one revised and two new and PSGs published in FY2024 related to *Opioid* Products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *Revised Draft Guidance for Naloxone Hydrochloride, Spray, Metered.* (NDA 208411) (Aug. 22, 2024). Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride, Spray, Metered.* (NDA 217722) (Aug. 22, 2024). Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride, Spray, Metered.* (NDA 208969) (Feb. 15, 2024). Link to Posting

Articles

- Chen B, Zhang F, Dhupia J, Morgenstern M, Costello M, Boyce H, Sun W, Raofi S, Tian L, and Xu W. *A Chewing Study of Abuse-Deterrent Tablets Containing Polyethylene Oxide Using a Robotic Simulator.* AAPS PharmSciTech. (2023) 24(8): 245. https://doi.org/10.1208/s12249-023-02706-5. PMID: 38030835.
- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Respiratory Drug Delivery (RDD) 2024. (2024) 1: 440-443.
- Mcguire M, Mostofa A, Shon J, Frost M, Kim M, and Li K. *Designs of Clinical Swallowability Assessments of Solid Oral Dosage Forms in Regulatory Submissions.* International Journal of Pharmaceutics. (2024) 659: 124229. https://doi.org/10.1016/j.ijpharm.2024.124229. PMID: 38762166.

OUTCOME *continued*

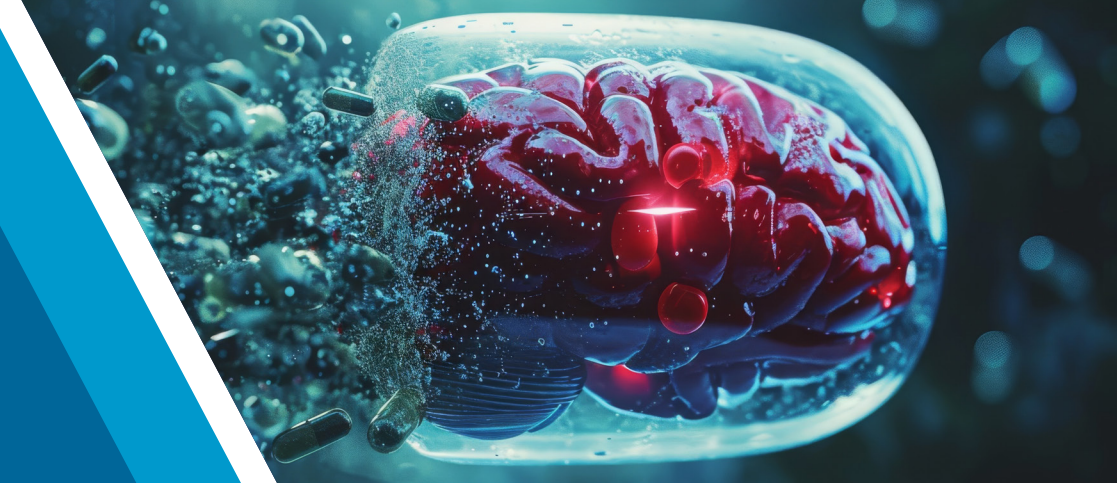
Posters

- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Chopski S, Al-Ghabeish M, Babiskin A, Zhao L, and Walenga R. *Identifying Critical Parameters for Physiological Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.
- Sultana T, Quarterman J, Newman B, Al-Ghabeish M, Chopski S, Walenga R, Pavuluri V, Shakleya D, Li M, Ashraf M, and Zidan A. *Critical Formulation Attributes of Naloxone Nasal Spray Products Affecting Nasal Permeation.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

Presentations

- Holtgrewe N, Walenga R, Bielski E, and Guo C. *Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders.* Presentation at the Respiratory Drug Delivery (RDD) 2024. Tucson, AZ, May 06, 2024.
- Chopski S, Al Ghabeish M, Babiskin A, Zhao L, and Walenga R. *Physiologically Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 25, 2023.

OTHER ACTIVITIES



Summary of FY 2024 Activities

In FY 2024, 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.

RESEARCH PROJECTS AND COLLABORATIONS

New Grants and Contracts

- Contract (75F40123D00041-75F40124F19002) *Labor for Scientific/Clinical Support for Human Subject Monitoring* at Realm Research LLC

Continuing Grants and Contracts

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

Active FDA Research

- *Global Manufacturing Sites for Complex Drug Products*
- *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - M13A*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

OUTCOMES

Articles

- Hastedt J, Backman P, Cabal A, Clark A, Ehrhardt C, Forbes B, Hickey A, Hochhaus G, Jiang W, Kassinos S, Kuehl P, Prime D, Son Y, Teague S, Tehler U, and Wylie J. *iBCS: 3. A Biopharmaceutics Classification System for Orally Inhaled Drug Products.* Molecular Pharmaceutics. (2024) 21: 164-172. https://doi.org/10.1021/acs.molpharmaceut.3c00685. PMID: 38059771.
- Kotsybar J, Hakeem S, Zhang L, and Jiang W. *Global Harmonization of Immediate-Release Solid Oral Drug Product Bioequivalence Recommendations and the Impact on Generic Drug Development.* Clinical and Translational Science (2023) 16 (12): 2756-2764. https://doi.org/10.1111/cts.13670. PMID: 37904315.

OUTCOME *continued*

Posters

- Bae J, Tran T, Shon J, Kim M, Borges S, and Li K. *A Survey on Recommendation of Food Conditions in Bioequivalence Studies with Pharmacokinetic Endpoints for Generic Oral Antineoplastic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Mina M, Amin Anno K, Zhang Z, Sun W, Zhang L, and Jiang W. *Deep Dive into Generic Drug Applications to Seek Data-Driven Harmonization of Bioequivalence Criteria for Narrow Therapeutic Index Drugs.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Park S, Nguyen D, Tran T, Li K, Kim M, Borges S, and Shon J. *Assessment of Male Infertility Risks to Support Product-Specific Guidance Development for Generic Oral Products.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Tran T, Bae J, Nguyen D, Shon J, Kim M, Borges S, and Li K. *Safety Considerations of Subject Population Selection in Bioequivalence Studies for Generic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Wang J, Tong A, Sun W, Hu M, Fang L, Kim M, and Zhao L. *A Quantitative Modeling Approach to Predict Availability of Generic Orphan Drug Products.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 28, 2024.
- Sun W, Mahjabeen S, Kinjo M, Thomas S, Wu F, Ni Z, Frost M, Markollari A, Best R, Le S, Kim M, and Zhao L. *A Generic Tacrolimus Capsule Shown Not to Be Bioequivalent to the Brand Tacrolimus Capsule in a Post-approval Pharmacokinetic Bioequivalence Study in Healthy Subjects.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting. Colorado Springs, CO, Mar. 27, 2024.
- Zhang P, Donnelly M, Feng K, Gong Y, Liu X, Babiskin A, Yoon M, Zhao L, and Fang L. *Assessment of Repeated Crossover Bioequivalence Design Under Steady State Conditions.* Poster Presentation at the American Conference on Pharmacometrics (ACoP) 2023. National Harbor, MD, Nov. 06, 2023.
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- Yu C, Jiang W, Matta M, Wang R, Haidar S, and Seo H. *Regulatory Perspective of Considerations in Endogenous Therapeutic Analyte Bioanalysis.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 22, 2023.

OUTCOME *continued*

Presentations

- Gong Y. *Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs: First-Year Review.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Bethesda, MD, Sep. 25, 2024.
- Zhang L. *ICH M13A: First ICH Guideline for Bioequivalence.* Presentation at the Small Business and Industry Assistance (SBIA) Workshop: Advancing Generic Drug Development: Translating Science to Approval 2024. Hybrid Meeting. Bethesda, MD, Sep. 24, 2024.
- Fang L. *Narrow Therapeutic Index Drug Classification: US FDA Current Process.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Jiang W. *Data-driven & Science-based Recommendation on Harmonization of Bioequivalence Standards for Narrow Therapeutic Index Drugs.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Zhang L. *Introduction & Overview: Current Regulatory Horizon of Narrow Therapeutic Index Drugs & ICH Guideline Development for Bioequivalence Assessment.* Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Bethesda, MD, Sep. 09, 2024.
- Lionberger R. *Overview of the Generic Drug Approval Process.* Presentation at the American Association of Colleges of Pharmacy (AACP) Annual Meeting - Pharmaceutics Section Programming: Generic Drugs and Bioequivalence: What Every Pharmacy Student Should Know! Boston, MA, Jul. 21, 2024.
- Lionberger R. *Overview of the GDUFA Research Portfolio.* Presentation at the Fiscal Year (FY) 2024 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, May 20, 2024.
- Jiang W. *Deep Dive into Generic Drug Applications to Seek Data-Driven Harmonization of Bioequivalence Criteria for Narrow Therapeutic Index Drugs.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 16, 2024.
- Zhang L. *Opening Remarks - Global Bioequivalence Harmonization: Enhancing Access to Affordable Medicines.* Presentation at the Product Quality Research Institute (PQRI)/European Federation for Pharmaceutical Sciences (EUFEPS) Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024. Rockville, MD, Apr. 16, 2024.
- Kotsybar J. *Overview of the FDA Product-Specific Guidance (PSG) Program.* Presentation at the Generic Drugs Forum (GDF) 2024: Regulatory Considerations to Enhance Generic Drug Access. Silver Spring, MD, Apr. 10, 2024.
- Monroy-Osorio M. *Overview and Considerations of Pre-ANDA Scientific Meetings Under GDUFA III.* Presentation at the Generic Drugs Forum (GDF) 2024: Regulatory Considerations to Enhance Generic Drug Access. Silver Spring, MD, Apr. 10, 2024.
- Tsakalozou E. *Considerations and Expectations when Meeting with the FDA under the Industry Meeting Pilot MIE program.* Presentation at the Small Business and Industry Assistance (SBIA) 2024 Webinar: A Deep Dive: FDA's Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs. Virtual Meeting, Jan. 18, 2024.
- Zhang L. *FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Expanding Generic Drug Access Through International Engagements. Virtual Meeting, Feb. 28, 2024.

OUTCOME *continued*

- Sarago C. *International Engagement with OGD Parallel Scientific Advice (PSA) Process.* Presentation at the Small Business and Industry Assistance (SBIA) Webinar: Expanding Generic Drug Access Through International Engagements. Virtual Meeting, Feb. 28, 2024.
- Luke M. *Considerations for Medical Scientists: Product Development, Career Development and Regulatory Science.* Presentation at the Johns Hopkins University School of Medicine. Baltimore, MD, Dec. 14, 2023.
- Raney S. *Generic Drug Science & Research Priorities for FY 2024.* Presentation at the BAA Industry Day 2023. Virtual Meeting, Oct. 25, 2023.
- Zhao L. *When Modeling & Simulation Meets AI.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 24, 2023.
- Lionberger R. *Predicting Formulation Performance: Learning from Generic Drugs.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Lionberger R. *FDA's Role in Drug Delivery Technology Innovation.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2023. Orlando, FL, Oct. 23, 2023.
- Ibrahim S, Tampal N, and Zhang L. *Advancing Toward Harmonized Global Scientific and Technical Standards for Generic Drugs.* Presentation at the 2023 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 02, 2023.
- Zhang L. *ICH M13 Guideline Series.* Presentation at the Medicines for Europe - 2nd Workshop on Bioequivalence. Brussels, Belgium, Apr. 26, 2023.

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APPENDIX

GDUFA Science and Research Outcomes for Fiscal Year 2024

As part of the enhanced accountability and reporting commitments in the Generic Drug User Fee Amendments of 2022 (GDUFA III), FDA prepares annual outcome reports on the extent to which GDUFA science and research-funded projects support:

1. Development of generic drug products
2. Generation of evidence needed to support efficient review and timely approval of Abbreviated New Drug Applications (ANDAs)
3. Evaluation of generic drug equivalence

Aggregate metrics of research outcomes are reported for each of the three categories listed above within summary tables in this outcomes report (and in outcomes reports for other fiscal years in GDUFA II and GDUFA III). A separate GDUFA Science and Research Report for each fiscal year during GDUFA II and GDUFA III includes more details about the outcomes in each category, including lists of publications, presentations, and posters, links to Product-Specific Guidances (PSGs), and information about workshops at which scientific advancements and regulatory advice were communicated to the generic drug industry.

1. GDUFA research supporting the development of generic drug products

This category describes research outcomes that support the development of generic drug products (prior to abbreviated new drug application [ANDA] submission or re-submission). Examples of research in this category include the development of a new analytical method for improved product characterization or the development of an in vitro-in vivo correlation that informs formulation optimization.

Aggregate metrics of research outcomes under this category include:

a. Number of pre-ANDA meetings impacted by research
b. Number of Controlled Correspondences impacted by research
c. Number of product-specific guidances (PSGs) impacted by research
d. Number of post-complete response letters (CRL) Scientific Meetings
e. Number of PSG Teleconferences
f. Number of publications, presentations, and posters that are relevant to this category
g. Number of workshops that communicate scientific advancements and regulatory advice to the generic drug industry
h. Number of other items that fall in this category (e.g., general guidances for industry)

APPENDIX *continued*

2. GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs

This category describes research outcomes that support the generation or review of data included in an ANDA. Examples of research in this category include the development of an analytical method that demonstrates active pharmaceutical ingredient sameness or the development of a new bioequivalence study design.

Aggregate metrics of research outcomes under this category include:

a. Number of pre-ANDA meetings impacted by research
b. Number of ANDA submissions impacted by research
c. Number of ANDA reviews impacted by research
d. Number of ANDA approvals impacted by research
e. Number of PSGs impacted by research
f. Number of post-CRL Scientific Meetings
g. Number of publications, presentations, and posters that are relevant to this category

3. GDUFA research supporting the evaluation of generic drug equivalence

This category describes research outcomes that support changes to equivalence standards for ANDA review or the re-evaluation of equivalence of approved products. Examples of research in this category include alternative methods to demonstrate equivalence.

Aggregate metrics of research outcomes under this category include:

a. Number of pre-ANDA meetings impacted by research
b. Number of ANDA submissions impacted by research
c. Number of ANDA approvals impacted by research
d. Number of controlled correspondences discussing alternative bioequivalence approaches
e. Number of PSGs that provided new approaches to equivalence
f. Number of post-CRL Scientific Meetings
g. Number of publications, presentations, and posters that are relevant to this category

APPENDIX *continued*

The following are research outcomes from fiscal years 2018[1], 2019, 2020, 2021, 2022, 2023.

GDUFA research supporting the development of generic drug products

Outcome type	Number FY2018	Number FY2019	Number FY2020	Number FY2021	Number FY2022	Number FY2023	Number FY2024
Number of pre-ANDA meetings impacted by research	62	93	92	113	92	89	116
Number of Controlled Correspondences impacted by research	113	178	291	97[2]	137	309	400
Number of PSGs impacted by research	86	82	86	40	73	19	18
Number of Post-CRL Scientific Meetings	NA	NA	NA	NA	NA	2	0
Number of PSG Teleconferences	NA[3]	NA	NA	NA	NA	NA	1
Number of publications, presentations, and posters that are relevant to this category	244	162	156	233	169	301	268
Number of workshops that communicate scientific advances and regulatory advice to the generic drug industry	8	5	5	14	17	19	15
Number of other items that fall in this category (e.g., general guidances for industry)	2	2	3	5	1	10	5

APPENDIX *continued*

GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs

Outcome type	Number FY2018	Number FY2019	Number FY2020	Number FY2021	Number FY2022	Number FY2023	Number FY2024
Number of pre-ANDA meetings impacted by research	16	39	59	33	22	46	57
Number of ANDA submissions impacted by research	138	167	166	81	65	183	175
Number of ANDA reviews impacted by research	44	36	62	50	65	80	96
Number of ANDA approvals impacted by research	63	102	152	161	126	167	161
Number of PSGs impacted by research	29	35	48	11	65	33	32
Number of Post-CRL Scientific Meetings	NA	NA	NA	NA	NA	1	6
Number of publications, presentations, and posters that are relevant to this category	82	92	100	102	68	212	268

APPENDIX *continued*

GDUFA research supporting the evaluation of generic drug equivalence

Outcome type	Number FY2018	Number FY2019	Number FY2020	Number FY2021	Number FY2022	Number FY2023	Number FY2024
Number of pre-ANDA meetings impacted by research	32	52	24	28	50	33	32
Number of ANDA submissions impacted by research[4]	NA	NA	NA	NA	NA	NA	288
Number of ANDA approvals impacted by research[5]	NA	NA	NA	NA	NA	NA	67
Number of controlled correspondences discussing alternative BE approaches[6]	NA	NA	NA	NA	NA	32	32
Number of PSGs that provided new approaches to equivalence	36	27	30	21	78	67	31
Number of Post-CRL Scientific Meetings	NA	NA	NA	NA	NA	2	2
Number of publications, presentations, and posters that are relevant to this category	37	36	21	58	140	118	154

[1] FY2018 numbers were recalculated with the FY2019 methodology and thus differ from those originally reported for FY2018

[2] FY2021 numbers differ from those originally reported for FY2021 due to the correction of an administrative error in FY2021 data

[3] NA: not available. These meeting types did not exist prior to GDUFA III. Such metrics are now as part of the enhanced accountability and reporting commitments under GDUFA III

[4,5] These two additional metrics were added in this category in FY24

[6] This additional metric was added in this category in FY23