U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# FY 2025 GDUFA Science & Research Report

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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 drugs.

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

The GDUFA funded research streamlines generic drug development and regulatory assessment. Through targeted research on bioequivalence, manufacturing standards, and quality assurance, the program reduces the time and resources required to bring high-quality, safe, and effective generic medications to market. This enhanced efficiency delivers two critical public health benefits. First, it makes generic drug development more economically viable for manufacturers, encouraging market competition that reduces drug shortage risks and helps to ensure medication availability. Second, it expands patient access to more affordable treatment options by facilitating availability of lower-cost generic alternatives, removing financial barriers that might otherwise prevent patients from accessing essential medications. The GDUFA science and research program

creates a sustainable pathway for generic drug availability, directly supporting FDA's mission to protect and promote public health through safe and effective medications.

### 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, and FDA's National Center for Toxicological Research.

### 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) 2025.

### How is the FY 2025 GDUFA Science & Research Report Organized?

This FY 2025 GDUFA Science and Research report describes active research projects and outcomes in eight chapters corresponding to those eight priority areas for FY 2025, 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:

- Summary of research ongoing or completed during FY 2025, typically highlighting one research project
- New, ongoing, and completed grants and contracts for research
- Active FDA research projects
- 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 advances research in areas where generic product development has been limited due to scientific knowledge gaps. GDUFA research outcomes help FDA establish new approaches that can be used by pharmaceutical manufacturers to develop generic drugs that were previously challenging or unfeasible to develop, and make these generic medicines available for patients.

Aligned with the GDUFA Science and Research Priority Initiatives for FY 2025, FDA continued to utilize ongoing external research collaborations and internal scientific excellence to conduct more than 50 research projects that facilitate generic product development and prepare FDA to assess information submitted in abbreviated new drug applications (ANDAs).

The outcomes from GDUFA-funded research expanded our understanding of drug products, including complex products, and contributed to the development of state-of-the-art analytical procedures to characterize product quality and performance. These new analytical procedures provided manufacturers more efficient approaches for developing generic products, and helped FDA better assess the bioequivalence (BE) and quality of complex generic products. FDA's recommendations related to BE and product quality are communicated to the generic drug industry largely through the continual publication of new and revised product-specific guidances (PSGs).

In FY 2025, FDA issued 925 PSGs (49 of which were for complex products), which provided recommendations for developing generic drugs and generating the evidence to support ANDA approval. This included the publication of over 800 PSGs that aligned FDA's BE recommendations with newly adopted international standards for immediate-release solid oral dosage forms under ICH M13A[1], which is the first ICH guideline specifically for generic drug BE. These revised PSGs were supported by extensive GDUFA-funded research on BE risk assessments and BCS classification.

In addition, GDUFA research allowed FDA to evaluate whether proposed BE approaches in pre-ANDA product development meetings are likely to be suitable. Following ANDA submission, the science and research knowledge gained in the program continued to support productive technical discussions in meetings between FDA and ANDA applicants on scientific matters.

During FY 2025, FDA approved the first generic liraglutide injection (referencing Victoza®) on December 23, 2024, marking a significant milestone as the first once-daily generic GLP-1 receptor agonist for type 2 diabetes. Subsequently, FDA approved additional generic liraglutide injections in April and July 2025, and the first generic liraglutide injection referencing Saxenda® on August 27, 2025. The GDUFA research that facilitated the regulatory assessment and approval of these generic products focused on developing

[1] 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.ich.org/page/multidisciplinary-guidelines#13-0%22.

analytical and in silico approaches to accurately characterize the molecular structure and impurity profiles of peptide drugs such as these.

For nanotechnology products, FDA advanced the understanding of the composition and critical quality attributes that modulate the performance of nanoparticles, developed improved characterization methods, and examined more efficient in vivo studies to support BE. This research supported the approval of multiple generic nanomaterial-containing products during FY 2025, including amphotericin B liposome injections, paclitaxel protein-bound particles, and iron sucrose injections.

The approval of these complex generic products demonstrates how FDA research creates the clarity and transparency that enables the generic drug industry to bring affordable medications to the American public. Through the GDUFA science and research program, FDA conducts targeted research in priority areas identified through early engagement with industry, generating the scientific insights needed to establish clear regulatory pathways. This research-driven transparency continues through pre-ANDA meetings during product development, where FDA shares research findings to guide industry efforts, and extends to post-submission technical discussions that leverage the program's accumulated scientific knowledge 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 2025. The CRCG hosted five scientific workshops during FY 2025, and played a central role in coordinating and enhancing generic drug industry engagement in the FY 2025 Generic Drug Science and Research Initiatives Public Workshop, which informed the 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 for the success of the GDUFA science and research program. By providing this research foundation and regulatory clarity, FDA enables generic manufacturers to successfully navigate the approval process, ultimately expanding American patients' access to cost-effective treatment options. We remain confident that our collaborative engagements to advance GDUFA science and research are effectively addressing these scientific challenges for generics. We look forward with optimism, as the outcomes of this research program, a key part of FDA's Drug Competition Action Plan continue to 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

**Dr. Michael Kopcha**
*Director*, Office of Pharmaceutical Quality

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# Impurities

A major GDUFA science and research priority area during GDUFA III[1] is to develop analytical procedures for generics to address impurities such as nitrosamines. The advancement of research in this area focuses on four key objectives: 1) understanding how ingredients in drug products may either contribute to or mitigate the formation of potentially harmful impurities such as nitrosamines, including nitrosamine drug substance-related impurities (NDSRIs), 2) evaluating the risk of human exposure to these impurities, and 3) developing analytical procedures for abbreviated new drug application (ANDA) applicants to efficiently address the potential risks, and 4) providing efficient bioequivalence (BE) approaches for reformulated products that mitigate nitrosamine risk. Research during fiscal year (FY) 2025 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 five years from FY 2023 through FY 2027 (GDUFA III).

## Summary of FY 2025 Activities

**During FY 2025, FDA's research related to nitrosamine impurities in drug products continued to expand across multiple scientific domains. This work involved numerous internal research projects with scientists from multiple offices collaborating across organizational boundaries.**

Among the internal research initiatives, CDER researchers investigated N-nitrosamine impurity formation and control strategies using secondary amine containing model drugs. Scientists evaluated various antioxidants and pH modifiers to mitigate N-nitroso-drug formation and studied how structural functional groups in a chemical structure affect the potential for formation of nitrosamine drug substance-related impurities (NDSRIs). Additional studies examined the role of commonly used excipients in bumetanide products on N-nitrosobumetanide formation during manufacturing or N-nitrosodimethylamine (NDMA) formation in metformin products. Building on these mitigation strategies, researchers also addressed safety concerns related to light-induced nitrosamine formation and steps in manufacturing drugs that used activated charcoal. A critical safety concern was addressed through research on N-nitroso-drug formation in secondary amine drug products when exposed to light, particularly important given that these products are often packaged in clear glass vials and may be exposed to light during clinical use without secondary packaging protection.

Another internal research project conducted by CDER scientists addressed nitrosamine impurity levels exceeding acceptable intake limits that have caused drug recalls and shortages. Using metformin as a model drug, scientists investigated NDMA formation risks and mitigation strategies. Three antioxidants (ascorbic acid, caffeic acid, and ferulic acid) effectively mitigated NDMA formation under long-term and accelerated storage conditions, with ferulic acid showing the highest inhibition. Higher antioxidant concentrations (≥ 0.1%) provided improved mitigation, while alkaline pH modification using sodium carbonate proved to be most effective at inhibiting NDMA formation. The research demonstrated that antioxidant effectiveness depends on compatibility with the drug substance, manufacturing approach, and formulation strategy, while alkaline pH adjustment suppresses nitrosation reactions that favor NDMA and NDSRI formation, in metformin and bumetanide, respectively[2,3].

While these studies addressed known nitrosamine formation pathways, researchers also turned their attention to emerging contamination patterns, including NDSRIs derived from active pharmaceutical ingredient (API) fragments. CDER researchers proposed a simplified approach to assess the risks of API fragment NDSRI by calculating a theoretical risk score and comparing it against a defined safety threshold. One input to this calculation, the extent of conversion from an API fragment to its corresponding NDSRI, was not well understood. To address this gap, scientists measured API fragments and their corresponding NDSRIs in 28 lots of selected drug products and calculated their conversion extents. They observed conversion extents ranging from 0.002% to 0.2% in the drug products within shelf life. Extrapolated stability data suggested a conversion extent of 0.3% at product expiry, providing an upper-limit estimate for risk score calculation and initial risk assessments[4]. Using this risk score calculation approach and

[2] Shakleya D, Alayoubi A, Brown D, Mokbel A, Abrigo N, Mohammad A, Wang J, Li D, Shaklah M, Alsharif F, Desai S, Essandoh M, Faustino P, Ashraf M, O'Connor T, Vera M, Raw A, Sayeed V, and Keire D. *Nitrosamine Mitigation: NDMA Impurity Formation and its Inhibition in Metformin Tablets*. Int J Pharm. (2024) 666:124832. https://doi.org/10.1016/j.ijpharm.2024.124832. PMID: 39414182.

[3] 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*. J Pharm Sci. (2023) 112(12):3075-3087. https://doi.org/10.1016/j.xphs.2023.06.013. PMID: 37364772.

[4] Yang J. *API Fragment NDSRI: Screening Results and Conversion Rate Assessment*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Sub-

FDA's Global Substance Registration System (GSRS), scientists conducted a simulation study to evaluate the risk of API fragment NDSRIs across all APIs at risk[5]. They identified more than 400 secondary amine-related impurities linked to over 200 APIs, predicted the corresponding NDSRI structures and calculated risk scores. The results suggest that a substantial proportion of these API fragment NDSRIs may exceed acceptable daily intake limits, posing a potential safety risk.

FDA developed new frameworks for BE assessment for reformulated products through two critical regulatory science initiatives that are described in more detail under **Research Highlight**. These research initiatives directly support the alternative BE approach outlined in FDA's revised September 2024 Guidance for Industry: *Control of Nitrosamine Impurities in Human Drugs*[6].

In the Guidance for Industry: *Control of Nitrosamine Impurities in Human Drugs*, the alternative BE approach for reformulated products outlined for Biopharmaceutics Classification System (BCS) Class I, II, or III drug products may not be appropriate for immediate release (IR) solid oral or IR oral suspension products containing BCS IV APIs, due to their poor solubility and permeability. Instead, the BE of the reformulated product containing BCS IV APIs can be supported with either a validated in vitro-in vivo correlation, physiologically based pharmacokinetic (PBPK) modeling, or in vivo BE studies. Using representative model compounds with varying BCS classifications, researchers successfully demonstrated that validated PBPK models can perform virtual BE studies and conduct sensitivity analyses to establish acceptable parameter safe space for formulation modifications. The research established that PBPK modeling represents a viable alternative approach to support BE assessment for the reformulated nitrosamine impacted BCS IV drug products[7].

In addition to the PBPK efforts mentioned above, to support the implementation of FDA's revised September 2024 nitrosamine guidance, which emphasizes the critical role of BCS classification in determining appropriate BE approaches for reformulated products, FDA has developed comprehensive internal capabilities for BCS classification and quantitative biopharmaceutics assessment. For example, FDA has established robust frameworks for systematically establishing BCS categories for nitrosamine-impacted drug products. The work conducted under Contract 75F40124P00142 with Drexel University, which explores the utilization of large language models to extract BCS relevant information from various data sources, has been adapted to help extract critical information and support classification efforts for applications of nitrosamine-impacted products. For more detailed information on this artificial intelligence (AI)-driven approach and other data analytics initiatives, see the **Chapter 8 "Data Analytics and Artificial Intelligence"**. This collaborative approach enhances FDA's internal expertise in quantitative biopharmaceutics with advanced information extraction methods to support efficient and consistent BCS class determinations.

Beyond these computational and database development efforts, FDA's research program also focused on improving safety assessment methodologies. CDER scientists from multiple offices are collaborating with the National Center for Toxicological Research (NCTR) to develop improved methods for evaluating the mutagenicity and carcinogenicity of N-nitrosamine drug impurities. Due to limitations of standard Ames testing for nitrosamines, which often produces weak or negative responses for known potent carcinogens, the team developed an Enhanced Ames Test (EAT) through comprehensive studies of 12 small molecule N-nitrosamines and 17 NDSRIs. The EAT was validated through Health and

stance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

[5] Yu X. *Fragment Nitrosamine Risks Based on Quantity, Extent of Conversion Rate and CPCA Calculations (Automated)*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Rockville, MD, Nov. 6-7, 2024.

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

[7] Wu F. *Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Example*. Presentation at: FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Rockville, MD, Nov. 7, 2024.

Environmental Sciences Institute (HESI) ring trials and found to be extremely sensitive and moderately specific for identifying carcinogenic nitrosamines, contributing to FDA guidance development.

Although extensive progress has been made developing the EAT, concerns remain about how EAT results relate to carcinogenicity, particularly for NDSRIs where limited cancer data exist for validation. FDA continues to require follow-up metabolism and in vitro mammalian cell data to support claims that negative EAT findings indicate non-carcinogenicity. FDA is developing complementary in vitro mammalian cell assays using human TK6 cell lines expressing different cytochrome P450 enzymes and human hepatic HepaRG cells. These systems confirmed mutagenicity of EAT-positive compounds while revealing that some EAT-negative nitrosamines and NDSRIs may still be mutagenic.

To address these limitations, FDA initiated specialized metabolic studies. A pilot study of in vitro nitrosamine metabolism, collaborating with NCTR and partially funded by FDA Critical Path, used N-nitroso-sertraline to investigate metabolic activation of complex nitrosamines. The study identified major metabolites and DNA adduct formation, demonstrating α-hydroxylation as the dominant pathway and highlighting key differences between complex and small molecule nitrosamines that likely contribute to different mutagenicity/carcinogenicity potencies. These efforts aim to better understand nitrosamine mutagenicity mechanisms and contribute to evidence-based carcinogenicity risk assessment, particularly for complex nitrosamines.

To help the generic drug industry implement valuable research outcomes from FDA's research program, and to engage with global experts about ongoing scientific challenges and research needs, FDA and the Center for Research on Complex Generics (CRCG) co-hosted a public workshop titled *Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products* on November 6 to 7, 2024[8]. This hybrid workshop built upon the success of the first FDA-CRCG workshop on nitrosamine impurities held in June 2023, facilitating meaningful dialogue among FDA, industry, and academia on safety assessment methods, recommendations on acceptable intake limits, risk factors and mitigation strategies for NDSRI formation, and bioequivalence approaches for reformulated products.

Additionally, CDER scientists are represented in the International Council for Harmonisation (ICH) efforts on nitrosamines. A concept paper[9] for nitrosamine risk assessment and control was published as an addendum to ICH M7(R2). This international harmonization effort will help establish global standards for nitrosamine risk assessment and control, facilitating more consistent and efficient regulatory processes for generic drug developers.

[8] All presentation files and recordings of this workshop are available on the CRCG website to the following link: https://www.complexgenerics.org/education-training/updates-on-approaches-to-acceptable-intakes-of-nitrosamine-drug-substance-related-impurities-ndsris-and-bioequivalence-assessment-for-reformulated-drug-products.

[9] *Final Concept Paper - Addendum to ICH M7 on Risk Assessment and Control of N-Nitrosamine Impurities*. Available at: https://database.ich.org/sites/default/files/ICH_M7SubGroup_Final_Concept_Paper_2024_0424.pdf.

## Research Highlight

The nitrosamine impurity issue has had a broad and significant impact on the pharmaceutical industry, requiring risk assessments and regulatory actions across numerous new drug and abbreviated new drug applications. In response to FDA's September 2024 revised guidance on *Control of Nitrosamine Impurities in Human Drugs*, which introduced an alternative BE approach for reformulated products, two critical research initiatives were undertaken to support consistent and efficient regulatory review processes.

### 1. Provisional BCS Classification Development

A critical need emerged for consistent BCS classification of affected drug substances to support the alternative BE approach outlined in the revised guidance. A cross-functional working group was established to develop a provisional BCS classification system specifically for nitrosamine-impacted products as illustrated in **Figure 1**. The working group successfully developed comprehensive scientific principles, standards, and working tools, including standardized flow charts for solubility and permeability classification and a review template. Through this systematic approach, the working group completed provisional BCS classifications for drug substances involved in applications of nitrosamine-impacted products, providing reviewers with a centralized resource accessible through a designated platform. This initiative enhances review consistency and efficiency by eliminating the need for individual BCS assessments across different offices, thereby reducing variability in review timelines and ensuring uniform application of bioequivalence testing requirements.

### 2. BCS Class IV Risk-Based Evaluation Framework

While the FDA guidance indicates that comparative dissolution testing may suffice for BCS Class I, II, and III drug products to demonstrate bioavailability or bioequivalence after reformulation for nitrosamine mitigation, BCS IV drug substances present unique challenges due to their low solubility and permeability characteristics and unpredictable absorption profiles. To address this gap, comprehensive research was conducted to investigate nitrosamine-impacted drug products containing BCS IV drug substances. A four-tier risk-based evaluation framework was developed considering the primary limitations for BCS IV drugs, approaches for low permeable drugs, rigorous dissolution testing for low soluble drugs and absorption predication methods, such as PBPK modeling.

The research methodology involved analyzing a database of nitrosamine-impacted drug products for provisional BCS classification, with key parameters including solubility, permeability, fraction absorbed, and food effects. Subcategories of BCS II and BCS IV drug products were established based on solubility characteristics. The research resulted in a comprehensive database and the development of a preliminary four-tier risk evaluation framework to guide assessments for reformulated BCS IV drug products, as illustrated in **Figure 2**. The frame-

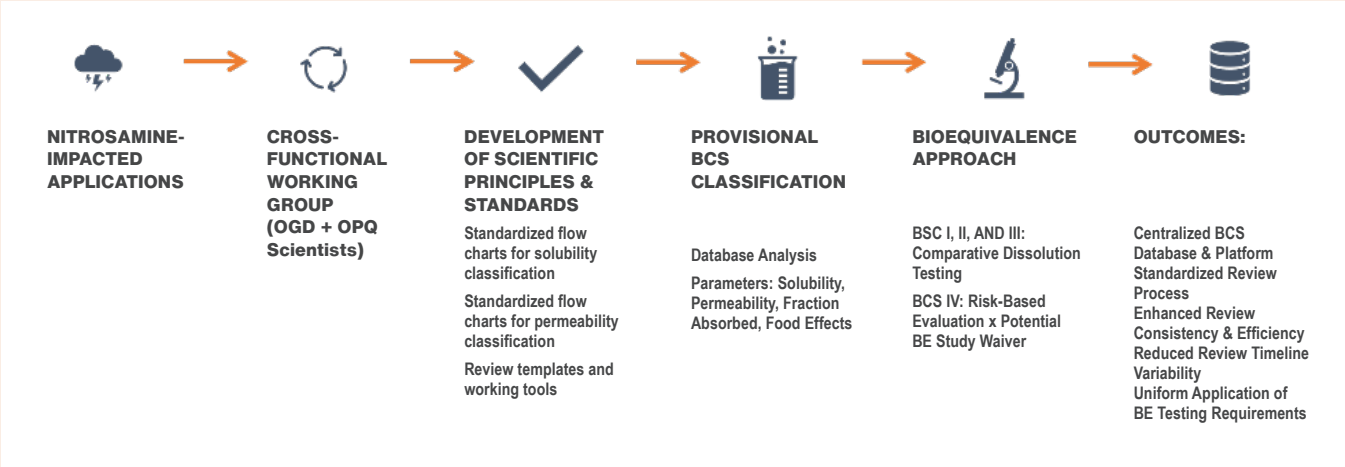


**Figure 1.** Integrated BCS Classification and Risk Assessment Workflow for Nitrosamine-Impacted Drug Products

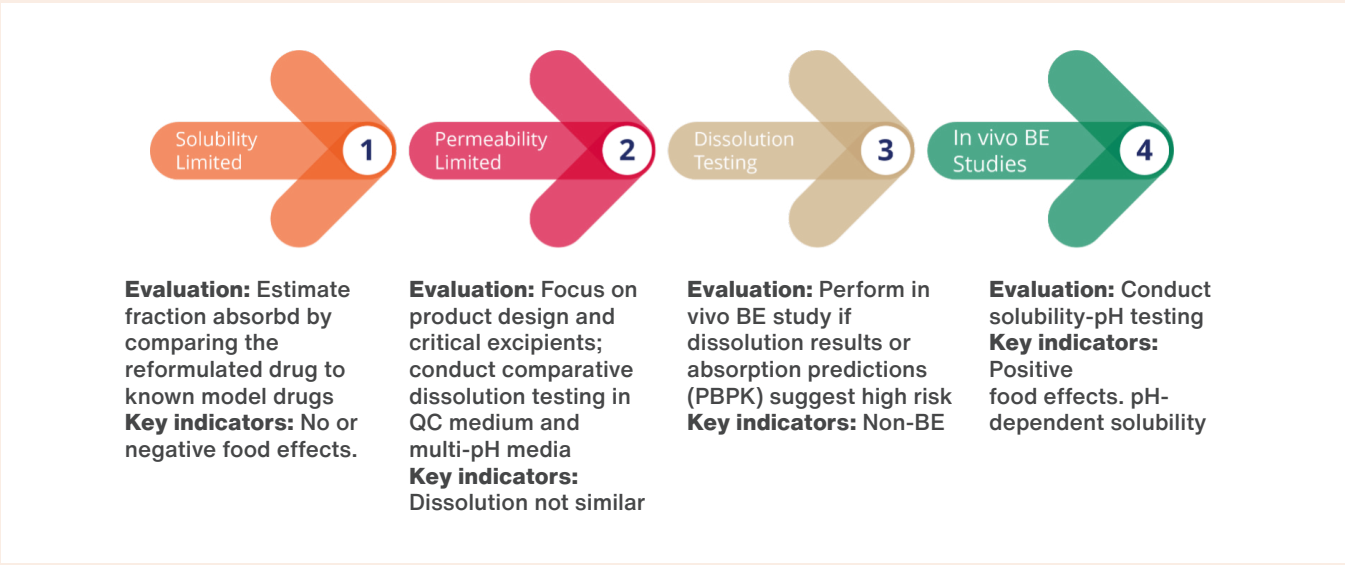


**Figure 2.** Four-tier risk evaluation framework for nitrosamine-impacted reformulated drug products containing BCS Class IV drug substances[10]

work provides a potential pathway for establishing BE without in vivo studies for nitrosamine-impacted BCS IV drugs when reformulations involve antioxidants or pH modifiers with limited absorption impact.

## Research Projects and Collaborations

### Completed Grants and Contracts

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

### Active FDA Research

- *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*
- *Establishment of an In Vivo Mutation Test Pipeline for Evaluating the Mutagenicity of N-Nitrosamines*
- *Genetic Toxicology Evaluations in Support of FDA Centers for Evaluating Substances for the Genotoxic Potential*
- *Investigation of N-Nitroso-Ketamine Formation Following a Photostability Stress Study*
- *Investigation of N-Nitroso-Ketamine Formation during the Ketamine API Manufacturing Process due to Contact with Activated Carbon*
- *In Vitro and In Silico Modeling Approaches for Supporting Biowaiver for Non Q1/Q2 BCS Class 3 Drug Products*
- *Pilot Investigation of Nitrosamine Drug Substance-Related Impurity (NDSRI) Metabolic*

[10] Zhang Q. *Managing Bioequivalence Risks for Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

*Activation and its Potential Impacts on NDSRI Mutagenicity and Carcinogenicity (CDER Intramural Funding Program, Critical Path)*

- *Managing Risks for BCS IV Drugs: Current Approach and Future Direction*
- *Mitigation Studies of NDSRI Formation in Model Drug Containing Secondary Amine*
- *Mitigation Studies of Nitrosamine Formation in Quinapril Drug Product*
- *Metformin Excipient Studies to Determine Mechanistic Route of NDMA Formation in Extended-Release Formulations*
- *Mutagenicity of N-Nitroso Drug-Substance-Related Impurities in Bacterial and Mammalian Cell Genotoxicity Assays Optimized for Evaluating the Mutagenicity of N-Nitrosamines*
- *Suppressing Nitrosamine Drug Substance Related Impurities by Solid Dispersion (CDER Intramural Funding Program, Critical Path)*

# Outcomes

### General Guidance

FDA Guidance for Industry. *Control of Nitrosamine Impurities in Human Drugs* (September 2024, Rev.2)[11]: Updates on Timeline and Other Emerging Scientific and Technical Issues:

- *Recommended Implementation Timelines* (Jun 23, 2025) Link to Posting
- *Emerging Scientific and Technical Information on Ritonavir* (Oct 28, 2024) Link to Posting
- *Emerging Scientific and Technical Information on Leachable NDBA and Other Small-Molecule Nitrosamines in Infusion Bags* (Aug 18, 2025) Link to Posting

### International Guidance

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). *ICH M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Carcinogenic Risk - Scientific Guideline* (September 30, 2023)[12]: Addendum: Risk Assessment and Control of *N*-Nitrosamine Impurities:

- *Final Concept Paper. Addendum to ICH M7 on Risk Assessment and Control of N-Nitrosamine Impurities.* (Apr 24, 2025) Link to Posting

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

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Seo J-E. *Application of HepaRG Cells for Genetic Toxicity Testing as an In Vitro New Approach Methodology (NAM)*. Presentation at the 2025 Korea Institute of Toxicology Workshop. Daejeon, South Korea, Sept. 19, 2025.

Shakleya D. *Nitrosamine Mitigation in Metformin: NDMA Impurity Formation and its Inhibition in Metformin ER Tablets*. Presentation at the American Chemical Society (ACS) Fall Meeting 2025. Hybrid Meeting, Washington, DC, Aug. 21, 2025.

Chen H. *Pre- and/or Post-approval Case Studies for New Drug Application*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Essandoh M, and Shakleya D. *Effect of Excipients on N-nitroso-dimethylamine (NDMA) Formation in Metformin HCl Drug Products*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

Shakleya D. *Mitigation Strategies to Reduce the Risk of Nitrosamine Impurities in Pharmaceutical Drug Products*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for

Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

Wang R. *Bridging Pre- and Post-Change Drug Products in Generic Drug Applications Impacted by Nitrosamine Drug Substance-Related Impurities (NDSRIs): Case Studies*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Wu F. *Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Example*. Presentation at: FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Yang J. *API Fragment NDSRI: Screening Results and Conversion Rate Assessment*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Yu X. *Fragment Nitrosamine Risks Based on Quantity, Extent of Conversion Rate and CPCA Calculations (Automated)*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Zhang Q. *Managing Bioequivalence Risks for Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Zou G. *Extraction and Quantification of N-Nitroso-Ketamine Impurity in Ketamine Drug Products Using Mixed-Mode Solid Phase Extraction and LC-MS/MS*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

Zuk S and Lu D. *FDA Nitrosamine Guidance 2024: Implementation of Control Strategies and Bioequivalence Approaches*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 7, 2024.

Berger D. *Multiple Nitrosamines in a Single Drug Product: Root Causes and Determination of Acceptable Intakes*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 6, 2024.

Kruhlak N. *Development and Regulatory Application of the Carcinogenic Potency Categorization Approach (CPCA)*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 6, 2024.

Heflich R. *FDA Nitrosamine Drug Impurity Research: Mutagenicity and Genotoxicity Evaluation of NDSRIs*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 6, 2024.

Sierra-Vega N. *Advanced Manufacturing: Mechanistic Understanding and Optimization of a Twin-Screw Wet Granulation Process for Manufacturing of Extended-Release Tablets*. Presentation at the 2024 American Institute of Chemical Engineers (AIChE) Annual Meeting. San Diego, CA, October 29, 2024.

Raney S. *Takeaways from Translational Science Sharpshooters - Simple Strategies for Accuracy, Efficiency, and Impact*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

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) 2025 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 five years from FY 2023 through FY 2027 (GDUFA III).

## Summary of FY 2025 Activities

**In FY 2025, research on complex active ingredients continued to advance in two key areas: analytical method development and complex active ingredient characterization. We have also achieved significant progress in understanding complex iron carbohydrate products and in conducting immunogenicity risk assessments for peptides and oligonucleotides. Notably, our work has focused on evaluating innate immune response modulating impurities (IIRMIs) through in vitro assays.**

Our internal and external research on complex parenteral iron carbohydrate injection products has enhanced our understanding of the complex ferric oxyhydroxide core and surrounding carbohydrate structures that constitute the active ingredient. Research conducted at Purdue University (Contract 75F40121C00189) analyzed the carbohydrate component of Injectafer (ferric carboxymaltose, NDA 203565) and elucidated both the composition of this complex carbohydrate component and the interaction between the iron core and the carbohydrate. Additionally, a grant with the University of Maryland, Baltimore (U01FD007363) to develop advanced analytical methods for the characterization and analysis of ferric derisomaltose was recently completed. This research analyzed both the iron core structure and carbohydrate composition. The research on complex iron carbohydrate products directly contributed to the recent approval of three first generic iron sucrose products.

The development of quantitative nuclear magnetic resonance (qNMR) continues to expand its application in regulatory science. Due to chemical modifications and higher-order structure formation in complex oligonucleotide drugs, classic UV absorbance-based assays may be less reliable for therapeutic RNAs. To address this challenge, a new $^{31}$P quantitative NMR (qNMR) method was developed for accurate assay of oligonucleotides in as-is drug products. Beyond solution-state qNMR, solid-state NMR (SSNMR) has recently been applied to study challenging issues of microstructure state and API distribution. A mini-review was published discussing recent improvements in quantitative SSNMR (qSSNMR)[2].

Despite significant advances in analytical characterization of active ingredients and impurities in complex peptide and oligonucleotide products, gaps remain in understanding how product- and process-related impurities contribute to immunomodulatory and immunogenic activity. This includes activities mediated by pattern recognition receptor activation. The application of in silico and in vitro methods to assess comparative risk between products with the same API but different impurity profiles—without needing clinical trials—has been discussed in several manuscripts and presentations. These include the 2024 FDA and the Center for Research on Complex Generics (CRCG) workshop on *Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products*, the Workshops on Recent Issues in Bioanalysis, and the European Immunogenicity Platform.

Another peptide mixture product, glatiramer acetate, is an immunomodulator therapeutic used to treat multiple sclerosis (MS). This complex drug consists of a mixture of synthetic peptides composed of four amino acids: glutamate, alanine, tyrosine, and lysine, with an average molecular weight of 5-9 kDa. Recent research[3] identified ultrafiltration as a critical process step that affects glatiramer acetate molecular weight distribution and subse-

[2] Zheng Z, Chen K, Liu Y, Munson E, and Su Y. *Quantitative Solid-State NMR Spectroscopy (qSSNMR) in Pharmaceutical Analysis*. Magnetic Resonance in Chemistry. (2025) 63:585-592. https://doi.org/10.1002/mrc.5536. PMID: 40417854. PMCID: PMC12379110.

[3] Campos-García VR, Herrera-Fernández D, Espinosa-de la Garza CE, González G, Vallejo-Castillo L, Avila S, Muñoz-García L, Medina-Rivero E, Pérez NO, Gracia-Mora I, Pérez-Tapia SM, Salazar-Ceballos R, Pavón L, Flores-Ortiz LF. *Process Signatures in Glatiramer Acetate Synthesis: Structural and Functional Relationships*. Scientific Reports. (2017) 7(1):12125. https://doi.org/10.1038/s41598-017-12416-1. PMID: 28935954. PMCID: PMC5608765.

quently influences other structural features essential for demonstrating API sameness. This scientific insight, which links process variation to final complex drug quality, has supported complex generic approvals and led to the glatiramer acetate product-specific guidance (PSG) revision in 2025[4] and two additional generic approvals since 2024.

The impact of FDA's research into peptide higher-order structure, impurities, and immunogenicity has facilitated timely scientific advice to generic drug developers, greater clarity about regulatory expectations, and increased patient access to generic drugs with complex APIs. For example, during FY 2025 FDA approved the first generic versions of liraglutide (3 approvals), exenatide (1 approval), and glucagon (2 approvals), in addition to recent approvals of generic teriparatide and calcitonin salmon products.

## Research Highlight

### 1. Characterization of Immunomodulatory Activity as Part of Peptide and Oligonucleotide Similarity Assessment

Currently, only 25% of complex peptide products have approved generic counterparts, while no generic oligonucleotide products have received approval. Both product classes share the complexity of potentially triggering unwanted immune responses, including immunomodulation, hypersensitivity reactions, and anti-drug antibody (ADA) that can compromise therapeutic efficacy and patient safety. To enable in vitro assays for detecting and assessing impurity-related risks between generic and reference listed drugs, the Office of Pharmaceutical Quality Research focused on identifying and validating critical assay parameters essential for generating reliable and reproducible data, including: 1) cell source selection and processing protocol optimization, 2) comprehensive evaluation of formulation matrix effects on assay performance, 3) identification of appropriate immune activation biomarkers, and 4) implementation of robust positive and negative controls to ensure assay suitability and data integrity. Our studies demonstrate that functional assays designed to assess whether impurities can activate innate immune responses can detect a wide range of model pattern recognition receptor (PRR) agonists in the presence of peptides ranging from 8-39 amino acids with sensitivity up to 0.001% of total product mass (for example, 100 ng of zymosan can be detected in 10 mg of semaglutide drug substance), though excipients such as phenol, m-cresol, and polysorbates can mask the presence of some impurities in a concentration-dependent manner.

For nucleic acid-based therapeutics both the API and any product- or process-related impurities can activate PRR to trigger downstream inflammatory responses. Proof of concept studies using an antisense oligonucleotide demonstrated high sensitivity to PRR engaging impurities, however certain backbone modifications and base substitutions significantly reduced assay sensitivity. These findings indicate that assay fitness for purpose must be established for the specific sequence composition and chemical modifications of each oligonucleotide therapeutic.

Our studies, presented at the 2024 FDA-CRCG workshop, facilitate the implementation of specialized functional assays to characterize the immunomodulatory effects of impurities underscoring the value of employing orthogonal analytical approaches in comparative immunogenicity assessments.

### 2. qNMR for Oligonucleotide Drugs

A rapid and accurate $^{31}$P qNMR method was established for direct assay of oligonucleotide drug products in formulation using external references. Compared to conventional UV absorbance at 260 nm, this approach offers improved accuracy and flexibility for complex generic oligonucleotide drug development, supporting process monitoring, assay, and quality control applications. As a primary ratio method for phosphorus quantification, $^{31}$P qNMR demonstrated superior accuracy over UV methods, particularly for phosphorodiamidate morpholino oligomers (PMOs) such as eteplirsen. Through the $^{31}$P NMR chemical shift analysis, the approach also enables assessment of critical quality attributes including impurity profiling and diastereoisomer distribution analysis (**Figure 2**), which are important for regulatory evaluation. Overall, the $^{31}$P qNMR method provides a robust analytical tool for characterizing oligonucleotide therapeutics.

[4] The revised *Draft Guidance on Glatiramer Acetate* was published on October 1, 2025.

# Research Projects and Collaborations

### Continuing Grants and Contracts

- Grant (1U01FD008322) *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.

### Completed Grants and Contracts

- Grant (U01FD007363) *Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex* - Ferric Derisomaltose with Sarah L. Michel at University of Maryland, Baltimore
- 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 (75F40121C00189) *Characterization of Carboxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes* with Eric J. Munson at Purdue University
- 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

- *Adaptive Immune Assay Development and Standardization*
- *Advancing Quality and Safety Assessment of Synthetic Oligonucleotides with Precision Analytics and New Alternative In-Vitro Methods*

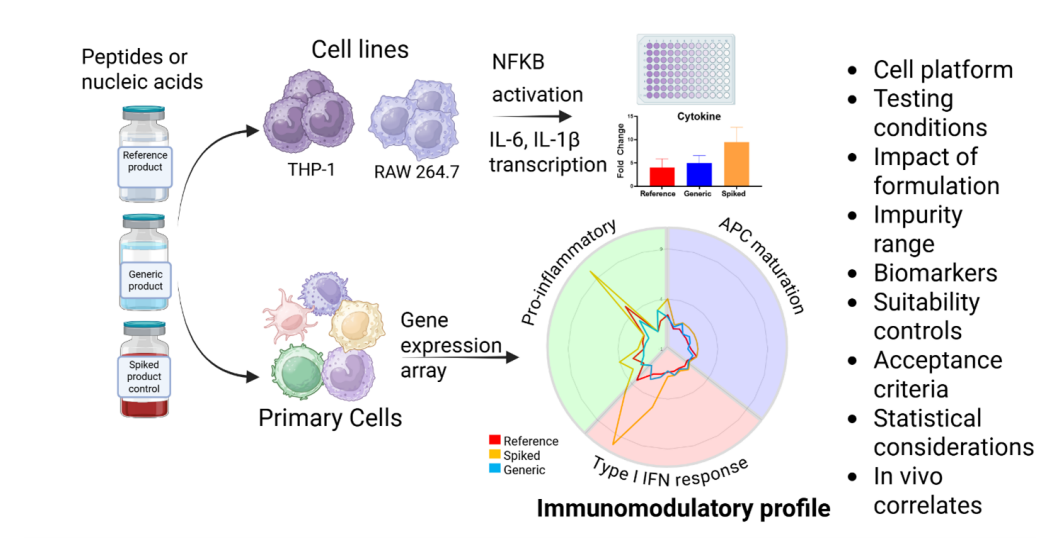


**Figure 1.** Schematics of assay systems to compare the immunomodulatory effects of impurities in generic peptide and oligonucleotide therapeutic products using cell lines or primary cells expressing pattern recognition receptors. Strategies include cell lines expressing defined sets of innate immune receptors with single biomarker readouts, or primary cells such as whole blood, peripheral blood mononuclear cells (PBMC), or dendritic cells expressing a broad array of receptors with multiple biomarker readouts. Our studies explored the critical assay attributes needed to ensure that assays are fit for purpose, as well as product attributes that may require further assay development.

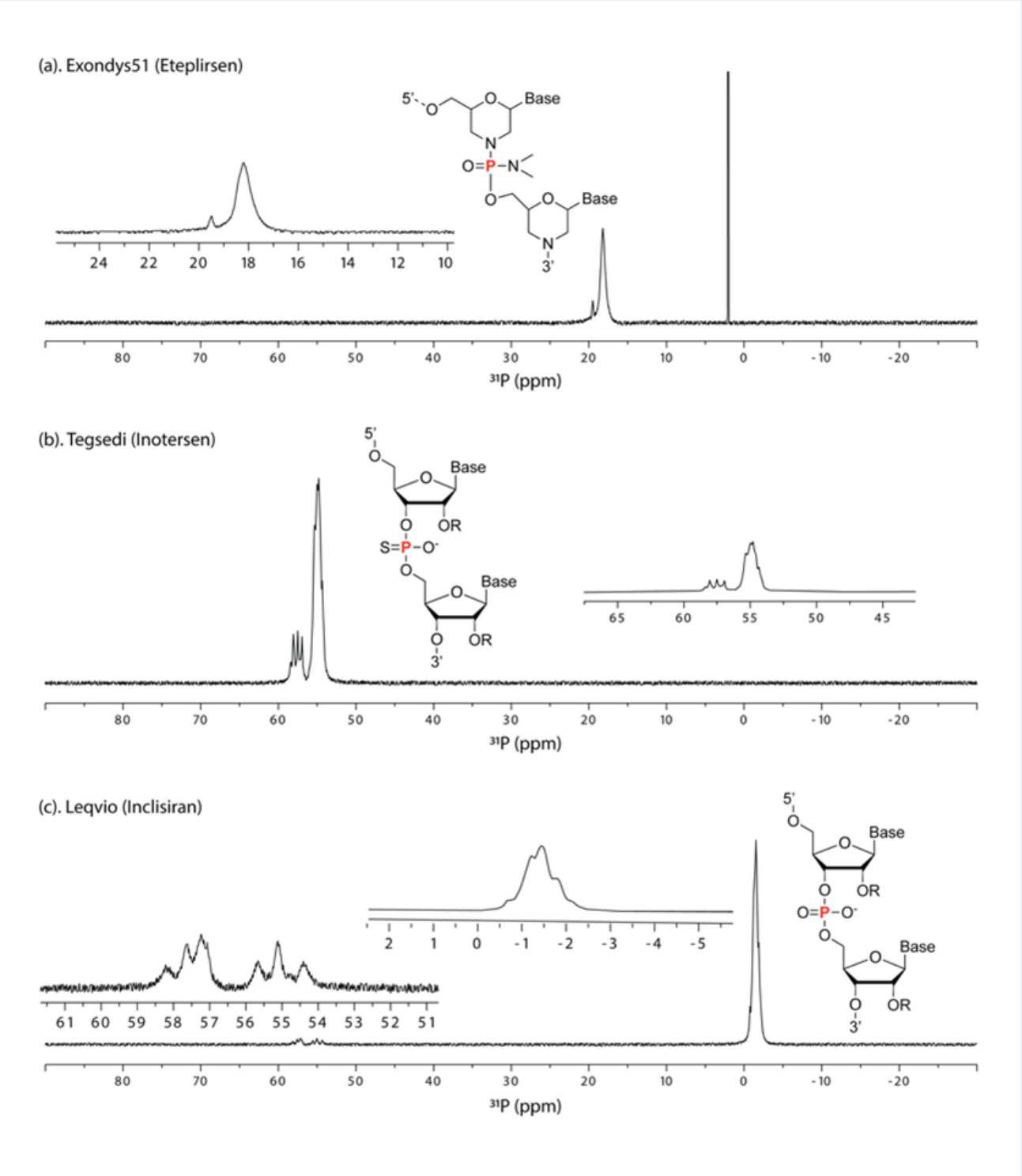


**Figure 2.** The $^{31}$P qNMR spectra of drug products of (a) eteplirsen, (b) inotersen, and (c) inclisiran. The backbone structures are shown for linkages of phosphorodiamidate morpholino oligomer (PMO) in (a), phosphorothioate (PS) in (b) and small interfering RNA (siRNA) in (c). The $^{31}$P chemical shift and peak area directly report chemical structure and assay, respectively. (Li et al. https://pubs.acs.org/doi/full/10.1021/acs.analchem.4c03693)

- *Assessing Feasibility of In Vitro Immunogenicity Assays for Newly Approved Peptide Products*
- *Characterization of PEGylated Peptide Drug Products to Support PSG Development*
- *Characterizing Diastereomeric Compositions of Phosphorothioated Oligonucleotides by High-Resolution Precision Analytics*
- *Compare Peptide Structures in Different Formulation*
- *Detection of Innate Immune Response Modulating Impurities in Generics and Biosimilars: a New Tool to Inform Immunogenicity Risk*
- *Development of Alternative Techniques to Assess IIRMI*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Immunogenicity Risk Studies to Support the PSG for Oligonucleotide*
- *Peptide Higher Order Structure Analysis by NMR*
- *Oligonucleotide Lipid Nanoparticles*

# Outcomes

### Product-Specific Guidances

There were six new PSGs published in FY 2025[5] related to *Complex API* products. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Enfuvirtide, Injectable* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Eplontersen Sodium, Solution* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Estrogens, Conjugated, Cream* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Icatibant Acetate, Injectable* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Motixafortide Acetate, Powder* (May 20, 2025) Link to Posting
- *New Draft Guidance for Zilucoplan Sodium, Solution* (May 20, 2025) Link to Posting

### Articles

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[5] The revised *Draft Guidance on Glatiramer Acetate* was published on October 1, 2025, which is the first day of FY 2026, and is therefore not included among the list of PSGs published in FY 2025 that were impacted by GDUFA-funded research.

and Thacker S. *2024 White Paper on Recent Issues in Bioanalysis: Evolution of Immunogenicity Assessment Beyond ADA/NAb; Regulated Genomic/NGS Assays; Hypersensitivity Reactions; Minimum Noise Reduction; False Positive Range; Modernized Vaccine Approaches; NAb/TAb Correlation*. Bioanalysis. (2025) 17(3):105-149. https://doi.org/10.1080/17576180.2024.2439229. PMID: 39862111. PMCID: PMC11863570.

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### Posters

Ranjbar S, Beringhs AO, Bin Q, Wang Y, and Lu X. *Effect of Process Parameters and Buffer Exchange on the Critical Quality Attributes of siRNA Loaded Lipid Nanoparticles*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Lee JK, Manangeeswaran M, Verthelyi D, and Pang E. *In Vitro Assays for the Evaluation of Innate Immunogenicity in Generic Peptide Drug Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

### Presentations

Pang E. *Immunogenicity Assessment in Peptides: Progress and Remaining Challenges*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, Jun. 3, 2025.

Liang L. *Generic Oligonucleotides – Challenges and Opportunities*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, Jun. 3, 2025.

Verthelyi D. *Considerations Regarding the Assessment and Mitigation Strategies of Immunogenicity-Related Risks for Generic Oligonucleotide Therapeutics*. Presentation at the Workshops for Recent Issues in Bioanalysis (WRIB). New Orleans, LA, Apr. 09, 2025.

Zhang D. *Comparability in Generic Oligonucleotide Drug Development: Regulatory Considerations and Case Studies*. Presentation at the DIA/FDA Oligonucleotide-Based Therapeutics Conference. Washington, DC, Oct. 28, 2024.

Verthelyi D. *Innate Immune Response Modulating Impurities Testing for Immunogenicity Risk Assessments*. Presentation at the Immunogenicity and Bioassay Summit. Hybrid Meeting, Washington, DC, Oct. 18, 2024.

Pang E. *Regulations, Guidances, and Sameness Assessment for Generic GLP-1 Products*. Presentation at the Chinese Biopharmaceutical Association. Rockville, MD, Oct. 12, 2024.

Howard K. *Alternative Models: From Humanized Mice to Microphysiological Systems and Beyond*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 08, 2024.

Luke M. *Opportunities and Challenges: Generic Oligonucleotide Drugs*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide

and Oligonucleotide Drug Products. Hybrid Meeting, Rockville, MD, Oct. 08, 2024.

Lee H-N. *Assessment of IIRMI for Oligonucleotide Therapeutics*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 08, 2024.

Rogers H. *Regulatory Oversight of the Immunogenicity Risks of Oligonucleotide Therapeutics*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 08, 2024.

Shubow S. *Recombinant Peptides: Role of In Vitro Data in Immunogenicity Risk Mitigation*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 08, 2024.

Yang K. *Comprehensive Impurity Characterization and Profiling in Synthetic Oligonucleotides through Precision Analytics*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 08, 2024.

Lionberger R. *Closing Remarks*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 07, 2024.

Manangeeswaran M. *In Vitro Tools and Assays: Review, Challenges, Suitability Standards*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products. Hybrid Meeting. Rockville, MD. Oct. 07, 2024.

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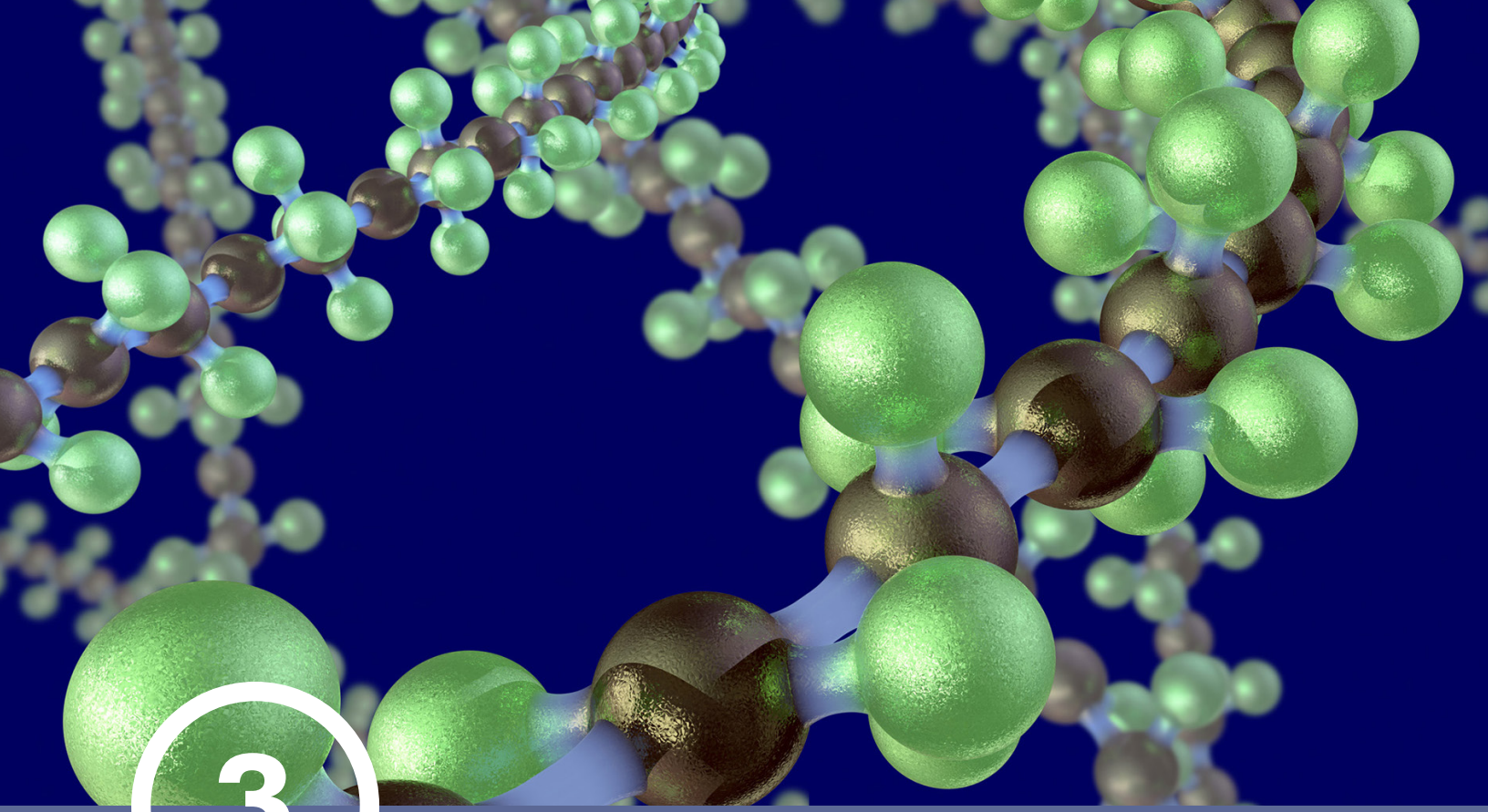

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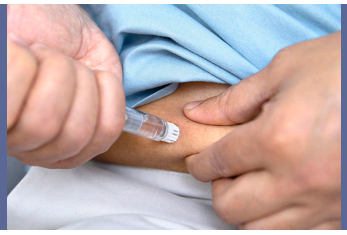
# Complex Dosage Forms & Formulations

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) 2025 that was aligned with this GDUFA science and research priority area is described below, highlighting LAI products and nanotechnology products independently in separate subsections.

[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 2025 Activities

**In FY 2025, the research activities on LAI products focused on (1) developing in vitro release testing (IVRT); (2) developing analytical tools to characterize complex polymeric excipients; (3) formulation characterization using advanced analytical and imaging tools; (4) exploring In Vitro-In Vivo Correlations (IVIVCs); and (5) structure-performance modeling.**

The GDUFA research program continues to play an important role in facilitating the development and approval of generic LAI products. The research insights have enabled FDA to continually develop and revise product-specific guidances (PSGs) for these complex products, prepared FDA to provide timely scientific advice to generic drug developers, and facilitated greater patient access to these important generic medicines. For example, in FY 2025, FDA published two revised PSGs and five new PSGs for LAI products, and approved a second generic poly(lactic-co-glycolic acid) (PLGA)-based risperidone long-acting injection.

Contract 75F40122C00019 investigated the effect of material properties, manufacturing process, and structural properties on the quality attributes of long-acting ethylene vinyl acetate (EVA)-based solid implants. Through enhanced understanding of drug release mechanisms, researchers developed a predictive semi-empirical model showing promising preliminary results. Current data demonstrate the model's potential to predict real-time drug release profiles for up to 3.5 years using only three-month in vitro drug release data. The study also evaluated how accelerated release conditions, including addition of ethanol and elevated temperatures, affect microstructure and transport properties of EVA based implants. These findings provide valuable insights for developing accelerated in vitro release testing as a reliable surrogate for comprehensive real-time assessments in generic drug development, where extended-release of up to three or more years present significant testing challenges.

Grant U01FD005443 focused on identification of critical processing parameters (CPPs) and CQAs for prepared levonorgestrel intrauterine systems (IUSs). This work included investigating how these parameters and attributes impact the in vitro release profile of levonorgestrel. The researchers continued to conduct long-term IVRT of commercial and in-house manufactured IUSs. Comprehensive IVRT of polydimethylsiloxane (PDMS)-based IUSs over their intended duration is challenging. While organic solvents can accelerate drug release testing, improper solvent selection may compromise IUS structure and alter release mechanisms, invalidating test results. The FDA laboratory is developing a guiding principle for solvent selection based on Hansen solubility parameters of the solvent, drug, and polymer matrix. This guiding principle will help identify solvents that accelerate release while preserving IUS integrity and original release mechanisms.

Contract 75F40123C00142 focuses on investigating how active pharmaceutical ingredient (API) properties affect the performance of suspension-based in situ forming implant products, with particular emphasis on IVIVC development. Pharmacokinetic studies in rabbits are being conducted to assess the impact of API particle size on in vivo drug release and systemic exposure patterns. The research under Contract 75F40123C00196 conducted comprehensive reverse engineering on buprenorphine in situ forming implant to support the development of compositionally equivalent formulations. This work also developed and validated an in vitro drug release method using a new custom-designed adapter and USP Apparatus 2 system, which will be used to evaluate how PLGA polymer characteristics influence product performance and to explore possible IVIVCs. The integrated research approach provides insights into

both formulation composition and API property effects on in situ forming implant performance.

Contract 75F40124F19001 focused on three-dimensional correlative imaging, quantitative image analysis of critical quality attributes, and image-based in silico modeling for LAI and inhaler products. This work structurally characterized commercial and in-house LAI products and developed models correlating structural characteristics with formulation performance to enhance understanding of how formulation and manufacturing parameters impact product performance.

Under Contract 75F40123C00192, researchers developed a novel assay method to quantify acid end groups in PLGA mixtures containing polymers with varying end groups (acid end group vs. ester end group). The approach uses UV dye conjugation to measure the total acid number of PLGA, which is then converted to determine the quantity of acid-terminated PLGA relative to the total PLGA content. This method represents a significant analytical advancement for characterizing PLGA polymers in formulations containing sub-milligram quantities of material.

Through Contract 75F40121C00133, the University of Connecticut created physiologically-based pharmacokinetic (PBPK) model-guided mechanistic IVIVCs for three long-acting suspension products: medroxyprogesterone acetate, paliperidone palmitate, and aripiprazole lauroxil. These established mechanistic IVIVCs have the potential to enable in vitro BE approaches in lieu of costly and lengthy in vivo BE studies. Current research under Grant U01FD008304 focuses on investigating the complex interactions between the physicochemical properties of qualitatively and quantitatively (Q1/Q2) equivalent LAI formulations and local tissue physiology. Research conducted to date has evaluated the impact of API particle size distribution and agglomeration patterns on in vitro drug release characteristics, as well as effects of various manufacturing processes on drug release behavior, including particle size reduction methods such as jet milling, wet media milling, and antisolvent recrystallization. Detailed analysis of Q1/Q2 variants of Depo Provera 150 demonstrated that agglomeration patterns and surface area serve as key factors controlling drug release kinetics, with certain formulations containing larger API particles exhibiting unexpectedly accelerated drug release rates due to the presence of loosely associated agglomerates. Research conducted under Grant U01FD008303 involved extensive in vitro evaluation of selected PLGA injectable implants, providing novel understanding of how formulation quality attributes influence both local and systemic drug exposure in animal studies. These findings have strengthened the PLGA implant computational model currently under development, which can now simulate both in vitro experimental conditions and in vivo environments, including local tissue metabolic processes.

## Research Highlight

IVRT often serves as a pivotal performance test in in vitro-BE approaches or as a quality control tool. To better simulate and predict in vivo drug release processes, IVRT methods commonly try to imitate relevant biological fluids and physiological environments. A previous study assessing compositionally equivalent dexamethasone intravitreal implants manufactured from different polymer sources demonstrated similar drug release profiles in saline-based IVRT but divergent release profiles in more biologically relevant phosphate-buffered saline (PBS)-based IVRT. To better understand which IVRT method more accurately reflects in vivo drug release behavior and underlying mechanisms, a study under Contract 75F40120C00198 evaluated and compared the drug release behavior of two implant formulations (E2 and A1) using saline-based IVRT, PBS-based IVRT, and an in vivo rabbit model. Formulation E2 exhibited a comparable shape of release profile in the PBS-based IVRT compared to saline-based IVRT, but the lag phase and erosional phase were substantially prolonged in the PBS-based IVRT due to neutralization of acidic PLGA degradation products (**Figure 1**). In vivo release profile of Formulations E2 and A1 were similar (**Figure 2**), as confirmed by f2 similarity testing and a matched pairs analysis. Further investigation of PLGA matrix degradation during both in vitro and in vivo release revealed that the PBS-based IVRT provided a better simulation of the implant's surface erosion processes, whereas the saline-based IVRT provided a better simulation of bulk erosion mechanisms. This study demonstrated that saline-based IVRT accurately predicted rabbit in vivo release profiles of dexamethasone intravitreal implant formulations, despite the buffered nature of rabbit vitreous compared to the unbuffered saline medium. Therefore, saline-based IVRT may prove valuable for in vitro release testing applications where "biopredictiveness" is prioritized. Conversely, PBS-based IVRT demonstrated strong

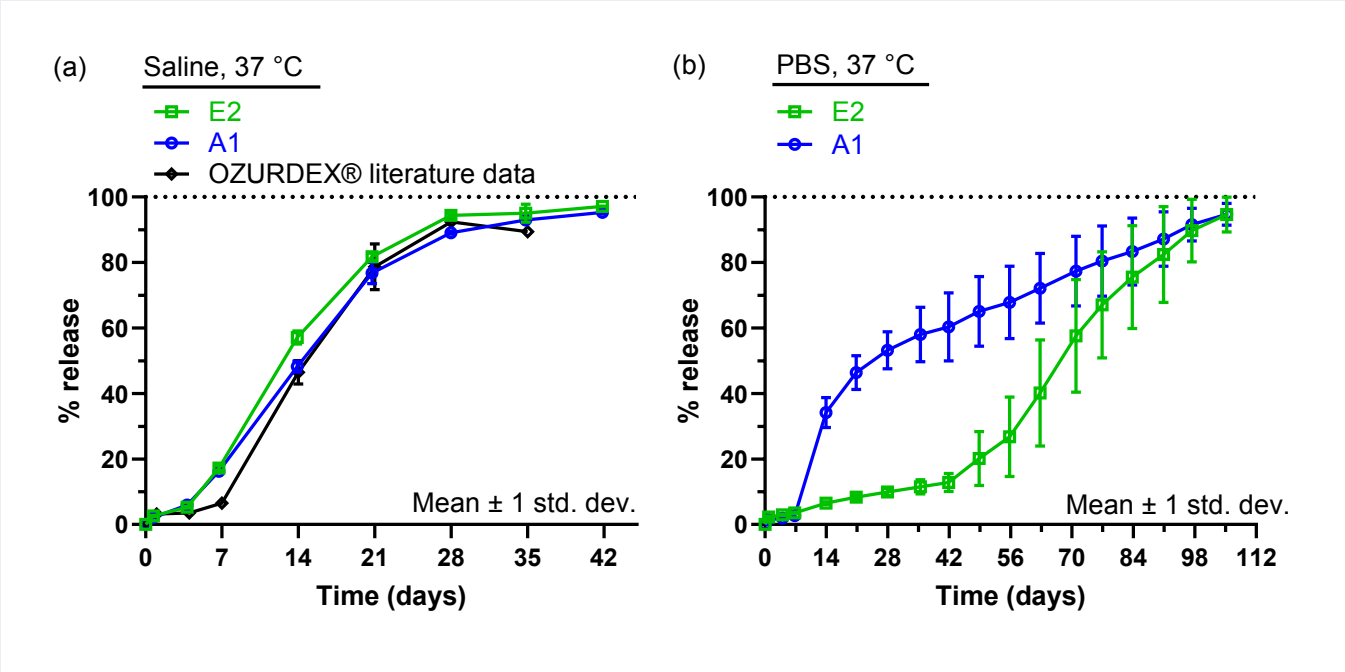



**Figure 1.** In vitro release tests of Formulation E2 an A1 in two different IVRTs. (a) Saline-based IVRT. (b) PBS-based IVRT.

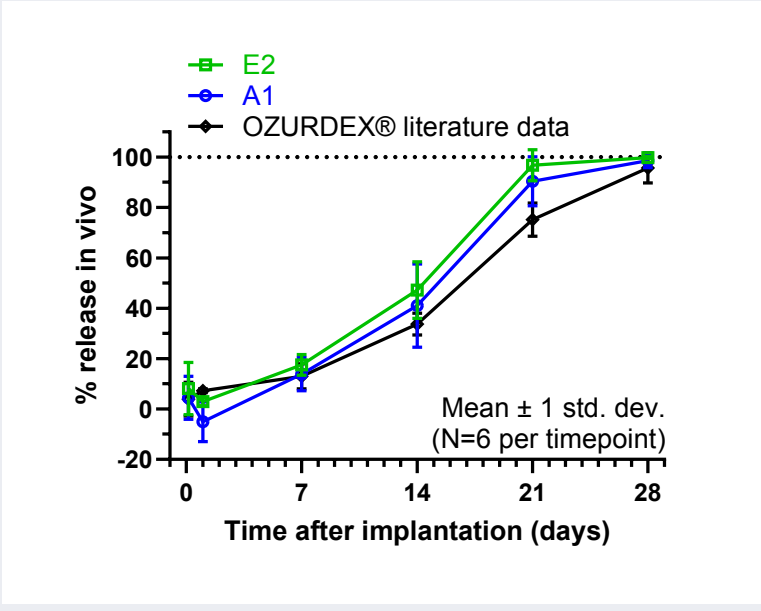



**Figure 2.** In vivo release test of Formulations E2, A1 and OZURDEX dexamethasone intravitreal implant.

discriminatory capability, which may be advantageous for other in vitro release testing applications needing enhanced sensitivity to formulation differences.

## Research Projects and Collaborations

### Continuing 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 (1U01FD005443) *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 (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina
- 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 (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 (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

### Completed Grants and Contracts

- 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 (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 (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at Regents of the University of Michigan, College of Pharmacy

### Active FDA Research

- *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations*
- *An Innovative Alternative Approach for Assessing Drug Release from Levonorgestrel Intrauterine Systems (IUSs) for Supporting Bioequivalence: In Vitro Drug Release Model in Combination with Advanced Morphological Characterization with Micro-Imaging*
- *Assessing New Analytical Methods for Characterization of Complex Excipients in Long Acting Drug Products*
- *Development of Biorelevant Subcutaneous Interstitial Fluid (ScIF) Media and Characterization of the Behavior of a Long-Acting Injectable (LAI) In Situ Implant in ScIFs*
- *Development of PBPK Modeling and Simulation Approaches for LAI Suspension Drug Products*
- *Evaluation of Impact of Excipients and Manufacturing Process on the Quality of DEXTENZA (NDA208742) to Support Development of PSG*
- *Internal research identified via SME Triage Process to support LAI PSG development*
- *Mechanistic evaluation of formulation design and performance of estradiol intravaginal ring products*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

## Outcomes

### Product-Specific Guidances

There were five new and two revised PSGs published in FY 2025 related to *Long-Acting Injectable, Insertable, or Implantable products*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance on Aripiprazole Intramuscular Suspension, Extended Release* (NDA 217006). (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance on Aripiprazole Intramuscular for Suspension, Extended Release* (NDA 202971). (May 20, 2025) Link to Posting
- *New Draft Guidance on Aripiprazole Lauroxil Intramuscular Suspension, Extended Release*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance on Levonorgestrel Intrauterine System* (NDA 203159). (Nov. 19, 2024) Link to Posting
- *New Draft Guidance on Levonorgestrel Intrauterine System* (NDA 208224). (May 20, 2025) Link to Posting
- *New Draft Guidance on Risperidone Intramuscular for Suspension, Extended Release*. (May 20, 2025) Link to Posting
- *New Draft Guidance on Risperidone Subcutaneous Suspension, Extended Release*. (Nov. 19, 2024) Link to Posting

### Publications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Silva DA, Lukacova V, Alam K, Tsakalozou E, Al Abdullah S. *Physiologically Based Pharmacokinetic Modeling and Mechanistic In Vitro-In Vivo Correlation for Long-Acting Injectable Suspension*. Poster Presentation at the Controlled Release Society (CRS) Annual meeting and Exposition. Philadelphia, PA. Jul. 18, 2025.

Garner J, Hadar J, Skidmore S, Park H, Park K, Wang Y, Jhou Y, Smith W, Zhang D, Zou Y. *Microstructural and Compositional Analysis of Dexamethasone-Loaded Poly(Lactide-Co-Glycolide) Rods*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA, Jul. 14, 2025.

Poudel S, Pangeni R, Zhang Q, Wang Y, Qin B, Halquist M, Xu Q. *In Vitro Release Testing System Development for Buprenorphine In Situ Forming Implant*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA, Jul. 14, 2025.

Poudel S, Pangeni R, Huo Z, Farkas D, Zhang Q, Wang Y, Qin B, Longest W, Tong R, Halquist M, and Xu Q. *Reverse Engineering of the Sublocade® Buprenorphine In Situ Forming Implant*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Clark A, Wang R, Gautreau J, Wang Y, Qin B, Burgess D, and Zhang S. *Untangling the Interplay of Drug Solubility, Microstructure, and Polymer Behavior on the Performance of Commercial Controlled Release Microsphere Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

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Zhong Z, Ren A, Doluisio N, Smith W, Qin B, Wang Y, and Zhang F. *Reverse Engineering of Nexplanon® Contraceptive Implant: Physicochemical Properties and In Vitro Drug Release*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

Zhong Z, Ren A, Qin B, Wang Y, and Zhang F. *Development of a Coextrusion Process to Prepare Etonogestrel Long-Acting Implant*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

### Presentations

Zu Z. *Impact of Cream Composition on Critical Quality Attributes of Miconazole Nitrate Vaginal Creams*. Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA, Jul. 15, 2025.

Gong Y. *Considerations of Bioequivalence Studies for Long-Acting Injectables and the Application of Model-Integrated Evidence Approaches*. Presentation at the Scientists Advancing Affordable Medicines, Inc. (SAAMnow) Spring Workshop. Virtual Meeting, Jun. 10, 2025.

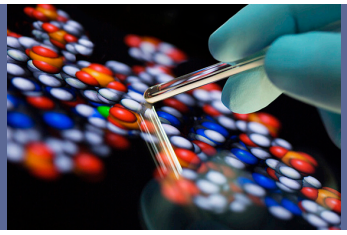
Zhang Q. *Navigating Formulation Assessment: Considerations when Preparing the Q1/Q2 Sameness Inquiry*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Navigating Controlled Correspondences to Support Generic Drug Development. Virtual Meeting, Feb. 27, 2025.

Fang L. *Regulatory Considerations in Development of Generic Long-Acting Injectable (LAI) Formulations for HIV Treatment and Prevention*. Presentation at the Advancing Access Planning for Long-Acting HIV Treatment in LMICs. Washington, DC, Oct. 24, 2024.

Wang Y. *Role of GDUFA Research on Resolving Technical and Regulatory Challenges for Complex Generic Drug Development and Approval*. Presentation at the 2024 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 22, 2024.

Kamal N. *Evaluate Qualitative Sameness of Collagens Impacting CQAs of Collagen Implants*. Presentation at 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

Raney S. *Takeaways from Translational Science Sharpshooters - Simple Strategies for Accuracy, Efficiency, and Impact*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.



# Nanotechnology Products

## Summary of FY 2025 Activities

**Since the initiation of GDUFA I in 2012, FDA has conducted a broad portfolio of research on nanotechnology products. These efforts have advanced regulatory science and enabled the development of product-specific guidances (PSGs) and abbreviated new drug application (ANDA) assessment strategies. In FY 2025, an increasing number of generic nanotechnology products were approved, including two generic amphotericin B liposome for injection products, three generic paclitaxel protein-bound particles for injectable suspension products.**

FY 2025 internal and external research continued to enhance the efficiency of bioequivalence (BE) approaches for nanotechnology products by 1) improving the understanding of critical quality attributes (CQAs) that determine the product performance, and 2) advancing analytical methods to support characterization and product development.

To facilitate the development and assessment of generic nanotechnology products, research was conducted to examine how differences in formulation or manufacturing processes may influence the quality, performance, or in vivo behavior of nanotechnology products. FDA continued to support efforts to advance the understanding in this area. There are ongoing efforts in collaboration with the University of Connecticut (Contract 75F40123C00118) to evaluate how siRNA-related impurities, lipid source variability, and manufacturing processes impact product quality and BE. In addition, under IAA-75F40123S30031, the behavior of nanoparticles in various biological environments is being investigated, with the goal of predicting in vivo performance and facilitating BE assessment. In parallel, the Institute of Quantitative Systems Pharmacology developed a multi-scale, systems-based model for liposomal doxorubicin nanoparticle drug delivery under Contract 75F40119C10139. This model may potentially be used to evaluate bioavailability at target sites by incorporating distinct nanoparticle properties and characteristics.

FDA has also invested in analytical method development to support the characterization of nanotechnology products. Contract 75F40124C00132, initiated in FY 2024 with the University of Maryland, is exploring the use of water proton nuclear magnetic resonance (wNMR) as a real-time, noninvasive tool to characterize albumin-bound nanoparticle drugs with minimal sample preparation. In addition, significant progress has been made through ongoing internal research projects focused on developing in vitro release testing (IVRT) methods for liposomal drug products. These efforts include: 1) the use of compendial methods for multivesicular liposomal drug products; and 2) the application of an adaptive perfusion IVRT method to better understand and evaluate nanomaterial release kinetics.

Research efforts continued to address the scientific and regulatory challenges associated with iron carbohydrate complex products. This included an ongoing contract with Purdue University (75F40121C00189) and a recently completed grant with the University of Maryland, Baltimore (U01FD007363) to develop advanced analytical methods. In parallel, FDA launched an internal research initiative to improve recommendations in product-specific guidances (PSGs) and support more efficient development and assessment of generic nanotechnology products.

During FY 2025, FDA also co-hosted a workshop with the Center for Research on Complex Generics (CRCG), titled *Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices*. This workshop provided critical considerations for robust particle size measurement across a diverse range of materials, including emulsions, suspensions, iron colloids, and micelles, along with step-by-step demonstrations of

measurement procedures and hands-on activities using seven dynamic light scattering instruments and four laser diffraction instruments.

## Research Highlight

The regulatory assessment of nanomaterial-containing drug products presents unique challenges that can benefit from rigorous analytical methodologies and standardized data processing protocols. Complex pharmaceutical formulations such as liposomes, emulsions, lipid nanoparticles, and iron sucrose injections often exist as heterogeneous mixtures, which can complicate accurate measurement of particle size distribution (PSD). For generic drug development, characterization of these nanomaterial subpopulations can be critical for the demonstration of equivalence to the appropriate reference listed drugs. These assessments rely on the certainty derived from the degree of precision and reproducibility of the methodologies used.

Asymmetrical flow field-flow fractionation coupled with multi-angle light scattering (AF4-MALS) has emerged as a sophisticated analytical platform capable of separating and characterizing nanomaterial subpopulations with multiple physicochemical properties. This technique provides orthogonal analytical capabilities that complement traditional ensemble particle sizing methods, offering detailed assessment of particle size distributions, molecular weight determinations, apparent density measurements, and morphological characteristics. The growing adoption of AF4-MALS in pharmaceutical development and regulatory submissions reflects its value in addressing the analytical complexity of modern nanomaterial-containing formulations.

The goal of the study was to understand data processing-based variability in PSD reporting and help mitigate the impact on regulatory decision making. The current research demonstrates the variability associated with the AF4-MALS data processing workflow (**Figure 1**), particularly when transitioning from analyzing well-characterized particle standards to analyzing commercial complex drug products. While monodisperse polystyrene latex standards displayed minimal variation between the investigated data processing approaches consistent with published literature, nanomaterial-containing drug products exhibit differences between applied models which could impact the reported particle size distribution and overall measurement uncertainty. Factors such as compositional heterogeneity, particle fill states, drug distribution profiles, and surfactant localization create additional analytical complexities that affect light scattering signals and concentration measurements, which are the topic of further investigation.

Data processing variability represents a fundamental regulatory challenge which can complicate generic product development and assessment. The lack of standardized analytical protocols for data processing

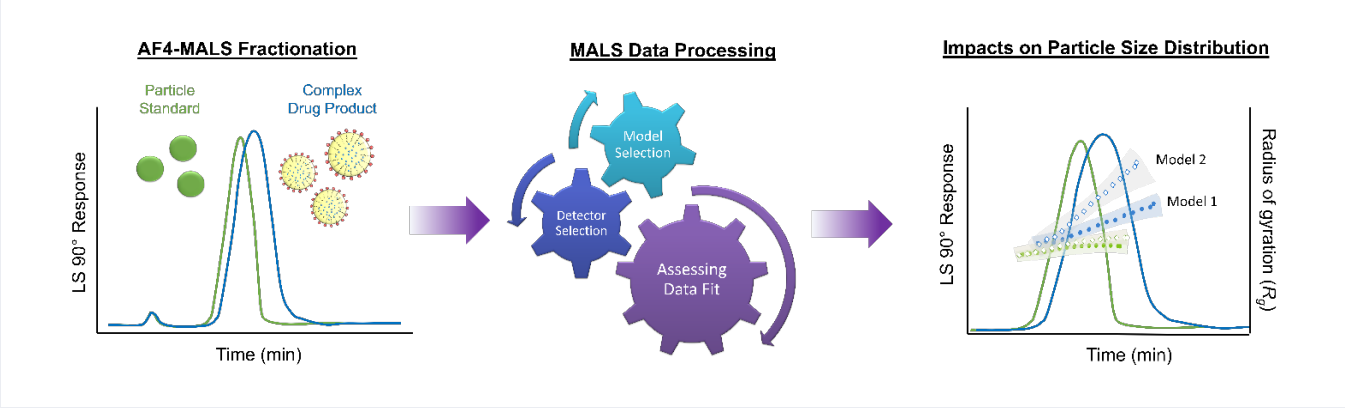



**Figure 1.** Schematic of the multi-angle light scattering data analysis workflow for comparing particle standards and complex drug products of similar sizes.

approaches can yield divergent size determinations with differing degrees of reported variability for identical samples. The research described here highlights the importance of developing and implementing standardized processing guidelines and validation criteria for AF4-MALS data to address data processing as well as fundamental analytical parameters (including peak integration approaches, baseline selection criteria, and overall method optimization strategies). The results of this research also indicate that greater standardization and transparency in data processing and reporting protocols can have a substantial impact by facilitating the development and regulatory assessment of an expanding landscape of nanomaterial-containing drug products. These efforts help minimize analytical variability while maximizing assessment confidence, ultimately supporting the development and approval of complex nanomaterial-containing generic drug products.

## Research Projects and Collaborations

### Continuing Grants and Contracts

- Contract (75F40124C00132) *Characterizing Albumin-Bound Nanoparticle Drugs using wNMR* with Yihua Bruce Yu 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

### Completed Grants and Contracts

- Grant (1U01FD007363) *Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex - Ferric Derisomaltose* with Sarah L. Michel at 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 National Institute of Standard Tech
- 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

### Active FDA Research

- *Application of Adaptive Perfusion In Vitro Release Testing Method to Improve Understanding and Assessment of Nanomaterials*
- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Bupivicaine Multivesicle Liposomes.*
- *Characterization of Ferric Derisomaltose*
- *Characterization of the Carbohydrate Components in Ferric Carboxymaltose*
- *Complex Iron Carbohydrate Drugs: Data Mining and Deficiency Analysis of Pending ANDAs*
- *Evaluation of In Vivo Pharmacokinetics of Sirolimus Oral and Protein-bound Formulations and Doxorubicin HCl Liposome Injection*
- *Improving In Vitro Drug Release Testing of Multivesicular Liposome Using a Compendial USP 2 Apparatus*
- *In Vitro Characterization of Disintegration and Release Kinetics of Albumin-Bound Nanoparticles.*
- *Novel Imaging and Spectroscopy Methods for Characterizing Size, Chemical Composition, and Morphology of Nanomaterials.*
- *Oligonucleotide Lipid Nanoparticles*
- *PBPK Models for Complex Injectables*
- *Assessment of Continuous Manufacturing Processes for Nanomaterials*

# Outcomes

### Product-Specific Guidances

There were five new and three revised PSGs published in FY 2025 related to *Nanotechnology* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Clobetasol Propionate, Suspension/Drops*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Ferric Carboxymaltose, Solution*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Ferumoxytol, Solution*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Paclitaxel Intravenous, Powder* (NDA 211875). (May 20, 2025) Link to Posting
- *New Draft Guidance for Paclitaxel Intravenous, Powder* (NDA 216338). (Nov. 19, 2024) Link to posting
- *Revised Draft Guidance for Phytonadione, Injectable* (NDA 012223). (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Phytonadione, Injection, Injectable* (ANDA 083722). (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Phytonadione, Injection, Injectable* (ANDA 087955, 087954). (Nov. 19, 2024) Link to Posting

### Publications

FDA. *Modern Intact NMR Approach Reveals Synchronized Microstructural Changes in Nanoemulsion Drug Formulations*. Regulatory Science Impact Stories. (2025). Available at: https://www.fda.gov/drugs/regulatory-science-action/modern-intact-nmr-approach-reveals-synchronized-microstructural-changes-nanoemulsion-drug.

Gan J, Juang V, Wang K, Xia Z, Ackermann R, Yu M, Dorsey K H, Lin W, Wang X, Wang Y, Liang J, Zheng J, Xu X, Park J H, and Schwendeman A. *Reverse Engineering of Onivyde® - Irinotecan Liposome Injection*. International Journal of Pharmaceutics. (2025) 669:125000. https://doi.org/10.1016/j.ijpharm.2024.125000. PMID: 39608586.

Li J, Juang V, Lu Z, Wang Y, and Schwendeman A. *In Vitro Release Method Development for Onivyde® using Agilent NanoDis® System*. International Journal of Pharmaceutics. (2025) 682:125903. https://doi.org/10.1016/j.ijpharm.2025.125903. PMID: 40578462.

Plavchak C, Liu J, Wang Y, Xu X, Faustino P, Qu H, and Smith W. *Utilization of AF4 for Characterizing Complex Nanomaterial Drug Products: Reexamining Sample Recovery and its Impact on Particle Size Distribution as a Quality Attribute*. Journal of Chromatography A. (2025) 1743: 465703. https://doi.org/10.1016/j.chroma.2025.465703. PMID: 39874741.

Siriwardane D, Shakiba S, Jiang W, and Mudalige T. *Evaluation of Size-Based Distribution of Components in VYXEOS® Liposomal Formulation using Asymmetric Flow Field-Flow Fractionation*. Journal of Chromatography A. (2024) 1738: 465488. https://doi.org/10.1016/j.chroma.2024.465488. PMID: 39515205.

Xia Z, Liu Y, Lu Z, Gan J, Yu M, Olsen K, Wang Y, Xu X, Schwendeman S, and Schwendeman A. *The Impact of Product Quality Attributes on In Vivo Performance of Bupivacaine Multivesicular Liposomes*. Drug Delivery and Translational Research. (2025) 15(9):3268-3280. https://doi.org/10.1007/s13346-025-01806-y. PMID: 40035967.

Juang V, Gan J, Xia Z, Wang Y, and Schwendeman A. *Development and Optimization of an In Vitro Release Assay for Evaluation of Liposomal Irinotecan Formulation*. International Journal of Pharmaceutics. (2024) 667(Pt A):124854. https://doi.org/10.1016/j.ijpharm.2024.124854. PMID: 39442767.

### Posters

Ranjbar S, Shih K, Beringhs AO, Qin B, Wang Y, and Lu X. *Effect of Ionizable Lipid Source on the Quality Attributes of siRNA Lipid Nanoparticle Therapeutics*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA, Jul. 14, 2025.

Gamage P, Jiang W, and Mudalige T. Quantitative and *Qualitative Analysis of Lipids and Cholesterol Derivatives in SMOF Lipids 20% Intravenous Lipid Emulsion*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Jayaraj S, Jiang W, and Mudalige T. *Elevating Liposomal Formulation Analysis: An Advanced CE-C4D Method for Quantification of Ionic Excipients in Liposomal Doxorubicin*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Ranjbar S, Beringhs AO, Bin Q, Wang Y, and Lu X. *Effect of Process Parameters and Buffer Exchange on the Critical Quality Attributes of siRNA Loaded Lipid Nanoparticles*. Poster Presentation at American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Wijewantha N, Gamage P, Jiang W, and Mudalige T. *Comprehensive Composition Analysis of Doxorubicin HCl Liposomes*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

### Presentations

Smith W. *Regulatory Perspective: Method Validation and Common Deficiencies*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices. Hybrid Meeting. Rockville, MD, Sept. 23, 2025.

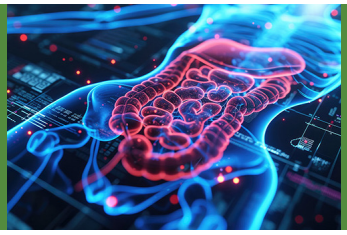
Xu X. *One Size Does Not Fit All: Challenges of Particle Size Measurement in Pharmaceutical Applications and Opportunities through Advanced Manufacturing*. Presentation at AAPS Bay Area Discussion Group, San Francisco, CA, November 6, 2024.

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 including gastrointestinal locally acting drug products, and buccal and sublingual drug products. The advancement of research in this area focuses on understanding how inactive ingredients and other aspects of a formulation influence drug absorption via complex routes of delivery, building physiologically based pharmacokinetic (PBPK) models, and identifying biopredictive dissolution conditions and predicting failure situations for BE. The goal of this research is to support the development of efficient BE approaches for these products. Research during fiscal year (FY) 2025 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 five years from FY 2023 through FY 2027 (GDUFA III).



# Locally Acting GI Products and Buccal/Sublingual Products

## Summary of FY 2025 Activities

**In FY 2025, research efforts for locally acting gastrointestinal (GI), buccal, and sublingual drug products were designed to continue improving in vitro bioequivalence (BE) methods and developing biopredictive in silico models. The research funded by Grants U01FD007660 and U01FD007662 (see Research Highlight) focused on developing and validating PBPK models to support BE evaluations of locally acting GI drug products. Both grants employ in vitro dissolution testing under physiologically relevant conditions with in silico physiologically based pharmacokinetic (PBPK) modeling to establish in vitro-in vivo relationships. Independently, the research funded by Contract 75F40120C00150 aims to advance PBPK modeling capabilities for predicting drug absorption from buccal and sublingual delivery systems by developing a comprehensive in silico platform that integrates human-derived tissue models with mechanistic computational tools. Collectively, this research is intended to facilitate more efficient generic product development and assessment, thereby expanding patient access to important medicines that uses these complex routes of delivery.**

Grant U01FD007660 aims to develop a validated PBPK model to provide supportive evidence (e.g., PBPK model-based virtual BE trial simulations) when evaluating the BE of locally acting GI drug products. This objective is achieved through integrated in vitro and in silico components. In vitro release and dissolution studies of marketed locally acting GI drug products (brand and generic), specifically budesonide, sulfasalazine, and mesalamine products, were performed under physiologically relevant conditions that mimic the gut physiologies of healthy subjects and patients with ulcerative colitis or Crohn's disease. Subsequently, PBPK models were developed to describe budesonide, sulfasalazine, and mesalamine PK in healthy subjects. The measured in vitro release profiles were integrated into the corresponding PBPK models, and different methods for their integration were assessed. In vitro-in vivo relationships were established for budesonide and mesalamine in healthy subjects. In addition, disease physiologies accounting for physiological differences in the disease state were developed and implemented in GastroPlus. PBPK models for mesalamine and sulfasalazine in patients with irritable bowel disease were subsequently developed and able to describe observed plasma concentrations. These efforts provide a comprehensive investigation into the correlation between product quality or performance attributes (e.g., release and dissolution) and in vivo active pharmaceutical ingredient (API) release in both healthy subjects and patients, thereby supporting BE assessment for locally acting GI drug products.

The objective of Contract 75F40120C00150 is advancing PBPK modeling capabilities for predicting drug absorption from buccal and sublingual delivery systems. This was accomplished by developing a comprehensive in silico platform using human-derived tissue models and mechanistic computational models in MembranePlus™. The key innovation was the Dynamic In Vitro Dissolution and Absorption Model (DIVDAM), which uses a three-compartment system to assess formulation excipient influence on drug permeation under physiological conditions and enables mechanistic in vitro-in vivo extrapolation (IVIVE) of oral cavity permeability. This research successfully integrated laboratory data with clinical pharmacokinetic information through GastroPlus® PBPK modeling, validated using five commercial products (buprenorphine, fentanyl, rizatriptan, sufentanil, and zolpidem), establishing a robust

framework that provides FDA with enhanced regulatory evaluation tools and supports generic developers with model-integrated evidence approaches to optimize BE study design and mitigate failure risks.

## Research Highlight

One of the most challenging BE issues for drug products that may deliver drugs both locally and systemically is deconvoluting the relationship between local and systemic drug exposure. Grant U01FD007662, specifically focused on mesalamine (5-ASA) and sulfasalazine formulations used to treat inflammatory bowel diseases like ulcerative colitis and Crohn's disease. The research encompasses four main aims: generating biopharmaceutic data through in vitro dissolution studies, model-based analysis of this data, PBPK model-based in vitro-in vivo extrapolation, and virtual BE studies in healthy adults and disease patients. The workflow used to develop and validate the IVIVE-PBPK models is illustrated in **Figure 1**. In FY 2025, extensive dissolution testing of various commercial formulations (Pentasa, Apriso, Mesacol MMX, Lialda, Azulfidine) under different pH conditions and biorelevant media was conducted. The data were used to develop and validate IVIVE-PBPK models that can recapitulate intraluminal, intracellular (enterocytes) and plasma concentration profiles well. Preliminary virtual BE assessments for these GI locally acting products indicate that model-integrated approaches using biopredictive in vitro dissolution data can be extended to GI locally acting drug products. These models have the potential to identify the biopredictive in vitro dissolution/in vivo release through the interpretation/deconvoluation of PK data from locally acting drugs and predict local drug exposure to provide the totality of evidence for BE evaluations.

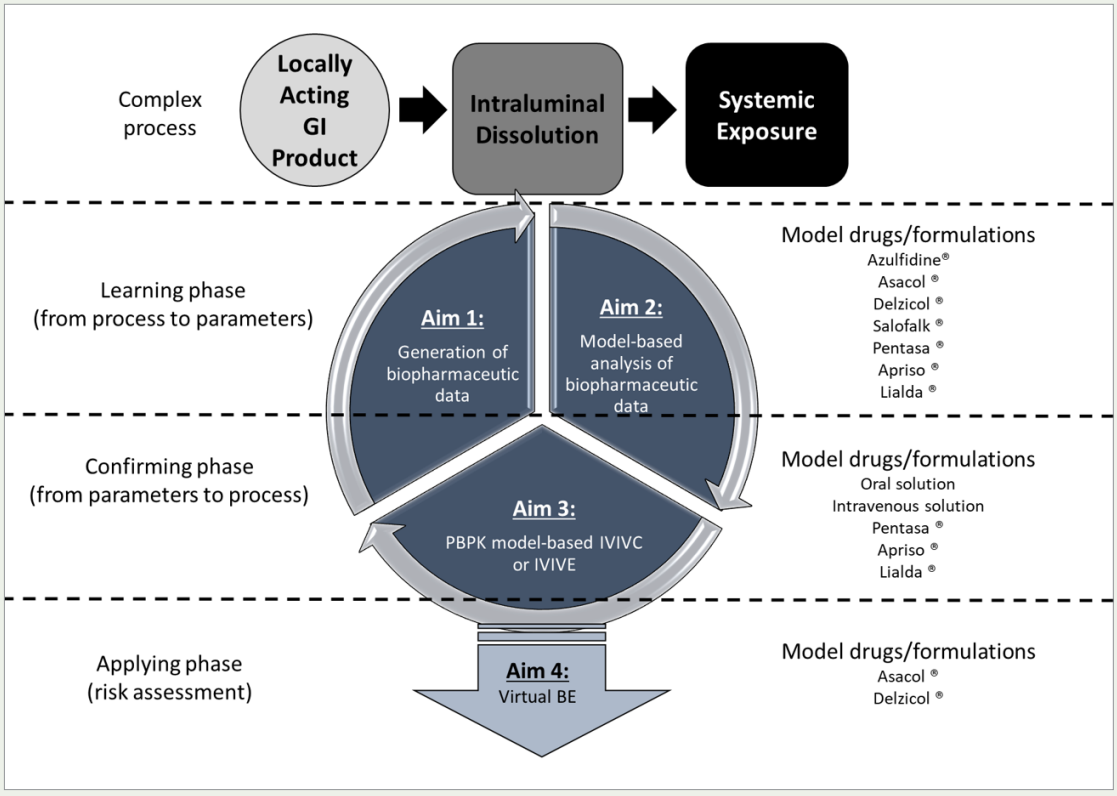



**Figure 1.** This diagram shows the stepwise modeling workflow that is applied to develop and validate the IVIVE-PBPK models for the selected model formulations.

## Research Projects and Collaborations

### Continuing Grants and Contracts

- 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
- 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 (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
- 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

### Completed Grants and Contracts

- 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 Products*
- *Using Physiologically Based Pharmacokinetic (PBPK) Modeling for Bioequivalence Assessment for Gastrointestinal (GI)-Locally Act*

## Outcomes

### Product-Specific Guidances

There was one new PSG published in FY 2025 related to *Locally Acting GI Products and Buccal/Sublingual* products.

- *New Draft Guidance for Diazepam, Film.* (May 20, 2025) Link to Posting

## Publications


Cheng Y, Thomas S, Tsang Y, Almeida S, Ashraf M, Fotaki N, Heimbach T, Patel N, Shah H, Jiang X, Kim M, Moody R, Rostami-Hodjegan A, Singh R, Zhao L, Babiskin A, and Wu F. *Advances in Physiologically Based Pharmacokinetic (PBPK) Modeling and its Regulatory Utility to Support Oral Drug Product Development and Harmonization*. Pharmaceutical Research. (2025) 42(5): 819–833. https://doi.org/10.1007/s11095-025-03849-9. PMID: 40155500. PMCID: PMC12158835.

Cheng Y, Pal A, Moody R, Heimbach T, Lukacova V, Patel N, Rullo G, Xu Y, Ahmed T, Kerwash E, Fang L, and Wu F. *Using Model Master Files to Support Oral Drug Product Development and Regulatory Submissions*. Pharmaceutical Research. (2025) 42(5): 753–763. https://doi.org/10.1007/s11095-025-03865-9. PMID: 40437347.

Dwivedi P, Kalra P, Zhou H, Alam K, Tsakalozou E, Al-Ghabeish M, Kelchen M, and Pauletti G. *In Vitro Oral Cavity Permeability Assessment to Enable Simulation of Drug Absorption*. Pharmaceutics. (2025) 17(7): 924. https://doi.org/10.3390/pharmaceutics17070924. PMID: 40733132.

Li T, Felton J, Lewis J, Cheng Q, Meredith R, Lu HT, Benken A, Dutta PP, Liao J, Zhao XD, Matvekas A, Baker J, Hasler WL, Babiskin A, Walenga R, Fang L, Lionberger R, Pal MP, Sun D, and Gianchandani YB. *An Ingestible Device for Automated Sampling and Location Tracing in Gastrointestinal Tract*. PLoS One. (2025) 20(7):e0327667. https://doi.org/10.1371/journal.pone.0327667. PMID: 40644523.

### Posters

Amaral Silva D, Zhou H, Wu F, Fotaki N, Pereira Garrastazu G, and Lukacova V. *Using PBPK to Establish In Vitro-In Vivo Relationship for Budesonide Delayed Release Oral Drug Product*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Badge S, Hossain M, Boyce H, Kim M, and Al-Ghabeish M. *Ethanol Solubility of Rate Controlling Polymer in Modified Release Formulation Can Impact Alcohol Dose Dumping: An Assessment Through Principal Component Analysis*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Kalra P, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Pauletti G, and Zhou H. *Mechanistic Model of In Vitro Intraoral Absorption of Buprenorphine for the Buccal and Gingival Mucosa*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Kalra P, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Pauletti G, and Zhou H. *Mechanistic In Vitro Oral Absorption Model to Predict Mucosal Permeability of Oral Cavity Drug Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Zhao G, Wei K, Nguyen D, Lim H, Rege B, Lu D, and Zhang Q. *FDA Perspective on Dissolution Testing for Development of High-Risk Oral Drug Products Containing Amorphous Solid Dispersions*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Dwivedi P, Alam K, Tsakalozou E, Al Ghabeish M, and Pauletti G. *Formulation Effects of Marketed Oral Cavity Products on In Vitro Buccal Permeability*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

Dwivedi P, Alam K, Tsakalozou E, Kelchen M, and Pauletti G. *Oral Cavity Permeation of Buprenorphine Across In Vitro Models of the Buccal and Gingival Mucosa*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

# Inhalation and Nasal Products

## Summary of FY 2025 Activities

**FDA research in FY 2025 focused on the continuing effort to refine product-specific guidance (PSG) recommendations for generic development of orally inhaled and nasal drug products (OINDPs). The substantial scientific advances brought about by the FDA's generic drug research on OINDPs are the reason that most PSGs on OINDPs now include recommendation for an option to demonstrate bioequivalence (BE) that is more efficient than conducting a comparative clinical endpoint (CCEP) BE study. FY 2025 research focused on further optimizing the efficiency of BE approaches by evaluating additional in vitro characterization methods to assess product performance, and by further developing modeling methods that have the potential to support more efficient BE approaches.**

Research exploring additional in vitro characterization methods for dry powder inhaler (DPI) products included evaluation of high-speed imaging and optical coherence tomography techniques with optically accessible DPI devices to determine their potential in particle sizing and deposition measurements across various drug formulations (Contract 75F40123C00201 with The University of Sydney). In addition, research on optical photothermal infrared and atomic force microscopy infrared spectroscopy techniques for identification, particle sizing, and characterization of morphological and agglomeration assessment of inhalation powders at the sub-micron scale were conducted by The University of Sydney (Contract 75F40122C00202).

In relation to dissolution studies, for both DPI and metered dose inhaler (MDI) products, efforts were made to better understand the need for more biopredictive/biorelevant study design parameters and to determine the best approaches for demonstrating sensitivity (Contract 75F40122C00197 with Inhalation Sciences Sweden AB).

Other focus areas included research on understanding formulation complexities and challenges with the transition to next generation propellants (NGPs) for MDI drug products (Contract 75F40123C00186), which also provided insights into conducting realistic aerodynamic particle size distribution (APSD) tests as well as spray pattern and plume geometry studies. In December 2024, the FDA and the Center for Research on Complex Generics (CRCG) co-hosted a two-day workshop bringing together experts from academia, brand name and generic pharmaceutical industries, and health and regulatory agencies. Presentations and discussions focused on three key areas: the current scientific understanding of NGPs, existing regulatory frameworks for transition programs, and the challenges encountered by the pharmaceutical industry in advancing their transition development programs.

Quantitative methods and modeling research for OINDPs concentrated on method development, model credibility, and model efficiency for physiologically based pharmacokinetic (PBPK), computational fluid dynamics (CFD), and population pharmacokinetics (PK) modeling approaches. The results of these research projects are summarized in the **"Mechanistic Modeling for Non-Orally Administered Drug Products"** and **"Quantitative Clinical Pharmacology"** subsections, respectively, found in **Chapter 7**. Overall, results showed progress toward improvement of regional deposition CFD models for MDIs and PBPK models for putative nose-to-brain nasal products.

## Research Highlight

As part of the FDA's efforts to provide more efficient BE approaches, alternative techniques (e.g., in vitro dissolution and morphology-directed Raman spectroscopy [MDRS]) were evaluated to assess their utility as in vitro characterization methods to support BE determination (Contract HHSF223201710116C with the University of Bath, completed in FY 2022). The outcome of this research was published in FY 2025.[2] In this research, the impactor-sized mass (ISM) dose of commercial DPIs (marketed in the United States (US) or Europe (EU)) containing different strengths of fluticasone propionate (FP) and salmeterol xinafoate (SX) as monotherapy and combination products were evaluated to determine the relationship between the extent of agglomeration and dissolution kinetics.

Following compendial methods, the APSD of all studied DPI batches were found to have no statistical differences ($p<0.05$) for the ISM fraction. For dissolution, the FP component in the aerosolized dose was observed to be inversely proportional to drug loading, where the low strength had the fastest rate of dissolution, and the high strength product had the slowest rate of dissolution (**Figure 1a**). The dissolution rate of the FP component was similar in the monotherapy products from different regions; however, the FP component was observed to have a slower dissolution rate in the EU combination therapy product (Seretide Accuhaler 100/50) compared to the US product (Advair Diskus 100/50) even though these products are manufactured by the same company and contain qualitatively (Q1) and quantitatively (Q2) the same formulations (**Figure 1b**). The same trend was observed whether the aerosolized sample was collected with a USP inlet or a medium-sized Oropharyngeal Consortium throat model.

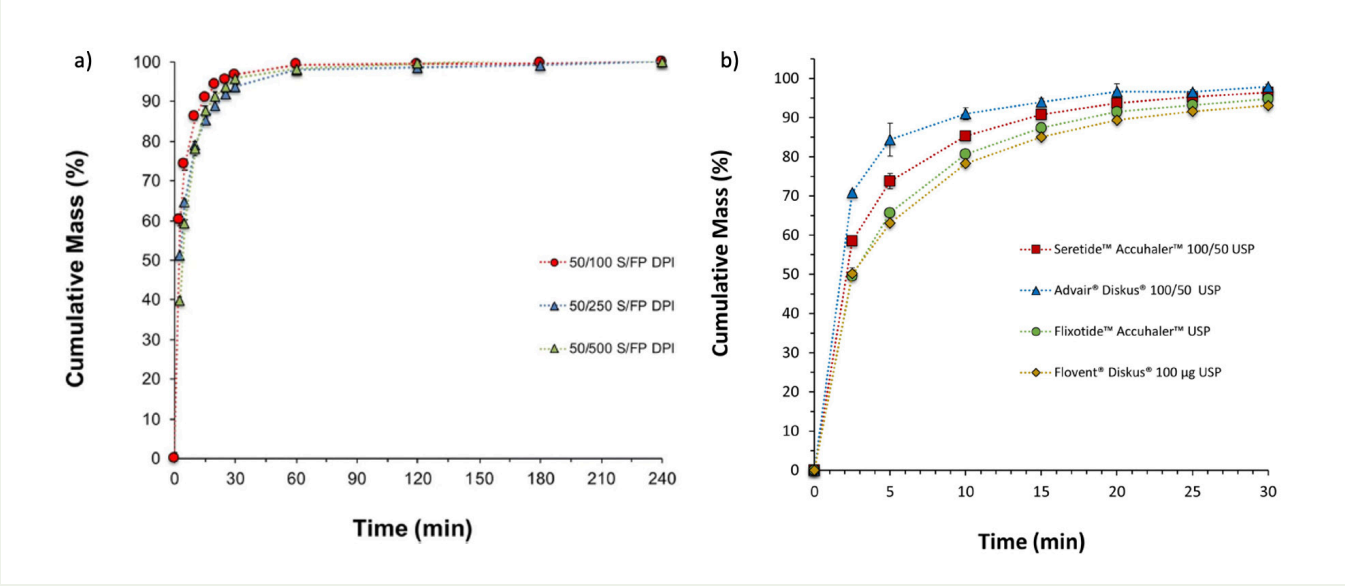



**Figure 1.** Mean cumulative mass (%) dissolution profiles of the aerosolized dose of FP formulated powder collected at 60 L/min with a USP inlet and preseparator from commercial DPIs with a) different FP strengths, and b) same FP strength in combination and monotherapy products from different regions. Error bars show standard deviations, n=3. S: Salmeterol xinafoate, FP: Fluticasone propionate.

[2] Farias G, Ganley W, Price R, Conti D, Mangal S, Bielski E, Newman B, Shur J. Microstructural Characterization of Dry Powder Inhaler Formulations Using Orthogonal Analytical Techniques. Pharmaceutical Research. (2024) 41(10):2015-2029. https://doi.org/10.1007/s11095-024-03776-1. PMID: 39375241. PMCID: 11530509.

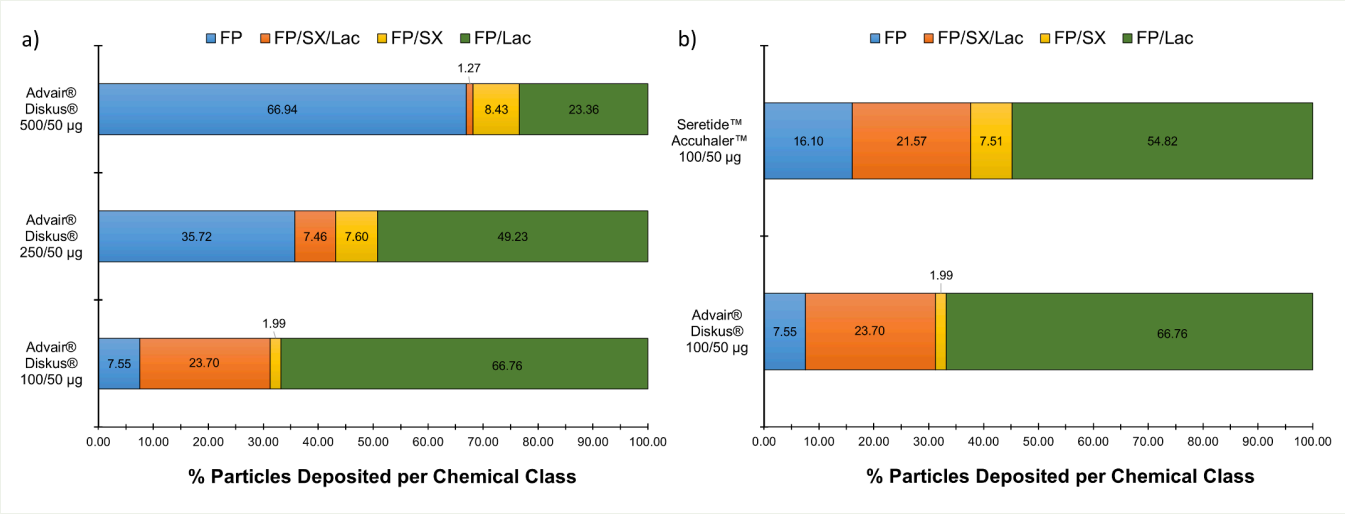



**Figure 2.** Chemical classification of FP agglomerates of the ISM dose collected at 60 L/min with a USP inlet and preseparator of combination therapy DPIs a) with different strengths of FP, and b) from different regions. Quantities are percentage by number and an average of 6 independent measurements of at least 3000 particles. FP: Fluticasone propionate, SX: Salmeterol xinafoate, Lac: Lactose monohydrate.

MDRS was used to determine the state of agglomeration post-aerosolization of FP in the combination therapy products (**Figure 2**). The agglomeration profiles explained the observed dissolution profiles – a higher percentage of free-standing FP corresponded to a slower dissolution rate. For the monotherapy products, MDRS determined the percentage of free-standing FP to be similar in both products, aligning with the dissolution profiles.

The results from this research helped inform recommendations for particle morphology characterization studies as part of a more efficient BE approach (in lieu of conducting a CCEP BE study) for generic DPIs that are formulated Q1 and Q2 the same as the reference standard. Indeed, such scientific advances and insights from FDA's generic drug research on OINDPs has directly supported the development of five new PSGs and nine revised PSGs in FY 2025. This research is a critical component of FDA's work to expand patient access to important generic OINDPs by ensuring that FDA is ready to provide timely scientific advice to generic drug developers, ensuring the clarity of regulatory expectations, and continually enhancing the efficiency of generic OINDP development and assessment.

## Research Projects and Collaborations

### Continuing Grants and Contracts

- 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 (U01FD007936) *Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic Data of Generic OIDPs via Population Pharmacokinetic Modeling and Non-Compartmental Approaches* with Jürgen Bernd 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

- 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
- 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 (75F40122C00202) *Identification of Drug Distribution in Aerosols: a Nanospectroscopy and Nanothermal Analysis* with Hak-Kim Chan at The University of Sydney
- Contract (75F40123C00186) *Research Challenges Related to Environmentally Friendly Propellants in Metered Dose Inhalers* with Jag Shur at AptarGroup, Inc.

### Completed 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
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London
- 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 (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

### 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*
- *Nasal PBPK Modeling of Suspension-based Nasal Sprays*
- *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*
- *Morphological and Performance Evaluation of Spray-dried Phospholipid Porous Particles*
- *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 five new and nine revised PSGs published in FY 2025 related to *Inhalation and Nasal Drug Products*. All, as listed below, were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Albuterol Sulfate; Budesonide Aerosol, Metered*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Budesonide; Formoterol Fumarate Aerosol, Metered*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Budesonide; Formoterol Fumarate Dihydrate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Epinephrine Aerosol, Metered*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Epinephrine Spray*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate Powder*. (Nov. 19, 2024) Link to Posting

- *New Draft Guidance for Fluticasone Propionate Spray*. (May 20, 2025) Link to posting
- *Revised Draft Guidance for Fluticasone Propionate; Salmeterol Xinafoate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Formoterol Fumarate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Formoterol Fumarate; Mometasone Furoate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Mometasone Furoate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Salmeterol Xinafoate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Tiotropium Bromide Powder*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Treprostinil Powder*. (Nov. 19, 2024) Link to Posting

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Chopski S, Walenga RL, Tan ML, Alam K, Babiskin A, Fang L, and Tsakalozou E. *Impact of Mechanistic Modeling and Simulation Methodologies on Product Specific Guidance Development for Non-Orally Administered Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2025) 14(9):1421-1430. https://doi.org/10.1002/psp4.70078. PMID: 40704493.

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Zapata Del Bano A, Silva L, Ulc F, Hegrova' V, Deraime G, Paul A, Han L, Bielski E, Newman B, and Shur J. *Investigation of Surface Characteristics of Micronized Salbutamol Sulphate Particles Formulated in Different Propellants Using Integrated Scanning Electron Microscopy & Atomic Force Microscopy*. Poster Presentation at the Drug Delivery to the Lungs Conference. Edinburgh, Scotland, Dec. 13, 2024.

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Hejazi M, Owen X, Wilkins J, Schuman T, Hindle M, Longest W, Walenga R, Kaviratna A, Newman B, and Golshahi L. *Understanding the Impact of Disease on Pediatric Regional Intranasal Drug Delivery with Nasal Sprays*. Poster Presentation at the Fourth Aerosol Dosimetry Conference. Irvine, CA, Oct. 16, 2024.

Schroeter J, Garcia G, Rose M, Kimbell J, and Walenga R. *A Hybrid CFD-PBPK Approach to Simulate Deposition, Absorption, and Bioavailability of Corticosteroid Nasal Sprays*. Poster Presentation at the Fourth Aerosol Dosimetry Conference. Irvine, CA, Oct. 16, 2024.

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Holl M B. *Materials for Inhaled Aerosol Treatment of Disease: Optical Photothermal Infrared Microscopy (O-PTIR) as an Advanced Characterization Method for Assessing the Emitted Dose of Complex Dry Powder Inhaler Formulations*. Presentation at the University of Wisconsin Pharmacy 2025. Madison, WI, Sep. 26, 2025.

Boc S. *Recommendations for Demonstrating Bioequivalence of Nasal Sprays: Scientific Thinking and Regulatory Research*. Presentation at the IPAC-RS Nasal Innovation Forum. West Trenton, NJ, Sep. 19, 2025.

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Newman B. *FDA Perspective on MDI Propellant Transitions - from Generic Drug Perspective*. Presentation at the International Society for Aerosols in Medicine (ISAM) Congress 2025. College Park, MD, Jun. 22, 2025.

Walenga R. *Model Integrated Evidence and Model Master File for Developing Orally Inhaled Drug Products*. Presentation at the International Society for Aerosols in Medicine (ISAM) Congress 2025. College Park, MD, Jun. 22, 2025.

Bielski E. *FDA's Option-Based BE Approach Recommendations for Locally Acting Metered Dose Inhalers and Dry Powder Inhalers*. Presentation at the Pulmonary Drug Delivery (PDD) Conference. Istanbul, Turkey, Jun. 13, 2025.

Boc S. *Challenges with Method Standardization for Inhalation and Nasal Drug Products*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, Jun. 3, 2025.

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Bielski E. *FDA's Current Perspectives on the Propellant Transition: Work Towards Global Harmonization*. Presentation at the Respiratory Drug Delivery (RDD) Europe. Lisbon, Portugal, May 8, 2025.

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Silva L. *Alternative In Vitro Bioequivalence Approaches for the Low GWP Propellant Transition*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Navigating the Transition to Low Global Warming Potential Propellants. Hybrid Meeting. Rockville, MD, Dec. 05, 2024.

Dhapare S. *Clinical Pharmacology Considerations for Low Global Warming Potential (LGWP) Propellant*

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Luke M. *Navigating the Transition to Low Global Warming Potential Propellants*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Navigating the Transition to Low Global Warming Potential Propellants. Hybrid Meeting. Rockville, MD. Dec. 04, 2024.

Cristofoletti R. *Organoid and Bioengineered Tissue Models: Exploiting Potential to the Fullest*. Presentation at the Baltic Conference. Virtual Meeting, Oct. 30, 2024.

Yang Y. *Spray-Dried Phospholipid Porous Particles for Inhalation: Effect of Manufacturing Process Parameters on Drug Product Quality*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

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Walenga R. *In Silico Modeling to Support Development and Approval of Generic Orally Inhaled Drug Products in the United States*. Presentation at the Fourth Aerosol Dosimetry Conference – Inhaled Aerosol Dosimetry: Advances, Applications, and Impacts on Risk Assessments and Therapeutics. Irvine, CA, Oct. 16, 2024.

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# Ophthalmic Products

## Summary of FY 2025 Activities

**FDA's GDUFA research for ophthalmic products in FY 2025 focused on two complementary research initiatives that are critical to enhancing the efficiency of generic product development and assessment: (1) identifying, characterizing, and correlating formulation-dependent critical quality attributes (CQAs) that influence in vitro, ex vivo, and in vivo product performance; and (2) advancing mechanistic, model informed approaches to assess the influence of those attributes on physiologically relevant bioequivalence (BE) considerations for complex, locally acting products. These priorities are consistent with the research program's emphasis in recent years on tear film-relevant characterization, interspecies physiologically based pharmacokinetic (PBPK) translation, and in vitro-based assessments for complex ophthalmic dosage forms. The ocular PBPK modeling research activities are summarized in the "Mechanistic Modeling for Non-Orally Administered Drug Products" subsection, found in Chapter 7.**

A focal effort this year was an internal case study on dexamethasone intracanalicular inserts. Using an array of analytical methods, GDUFA research linked excipient source and architecture to crosslinking capacity and microstructure, and in turn to swelling kinetics and drug release. Faster-swelling networks released drug more rapidly; non-micronized active pharmaceutical ingredient (API) slowed release relative to micronized API; and data supported a diffusion-with-transient-swelling mechanism. The resulting information-rich package identified practical CQAs and surrogate indicators of network-forming potential that can support physicochemical and structural (Q3) characterization-based BE approaches for hydrogel inserts when direct compositional sameness after curing cannot be reliably demonstrated. Further details on this important work are included in the Research Highlight below.

## Research Highlight

Sustained-release intracanalicular inserts offer a practical alternative to topical drops, but assessing equivalence can be challenging because the performance of these products depends on the network that forms in situ when the hydrogel precursor crosslinks, rather than on the uncured components alone. To facilitate generic drug development for this class of products, internal research at the FDA built upon prior GDUFA research and examined how source-to-source variability in a key hydrogel-forming excipient affects structure and in vitro performance of ophthalmic inserts. This work was used as a case-study to develop advanced characterization approaches for this class of products.

The inserts were prepared from polyethylene glycol N-hydroxysuccinimidyl-glutarate (PEG-SG) that undergoes irreversible amidation with trilysine acetate (TLA), forming a crosslinked hydrogel that retains the drug and swells while releasing dexamethasone. The study compared multiple PEG-SG precursors: 4-arm PEG-SG, 20 kDa from three vendors (V1, V2, V3), an 8-arm 20 kDa PEG-SG (8a), and a 4-arm 40 kDa PEG-SG (40k). Inserts were manufactured under common conditions to isolate the impact of excipient characteristics on the finished insert. Orthogonal analytics, rheology, thermal/mechanical testing, X-ray microscopy (XRM) with Artificial Intelligence (AI) segmentation, swelling, and in vitro release testing (IVRT) were integrated to relate excipient quality to hydrogel structure and performance.

Precursor characterization demonstrated meaningful differences in end-group functionalization, molecu-

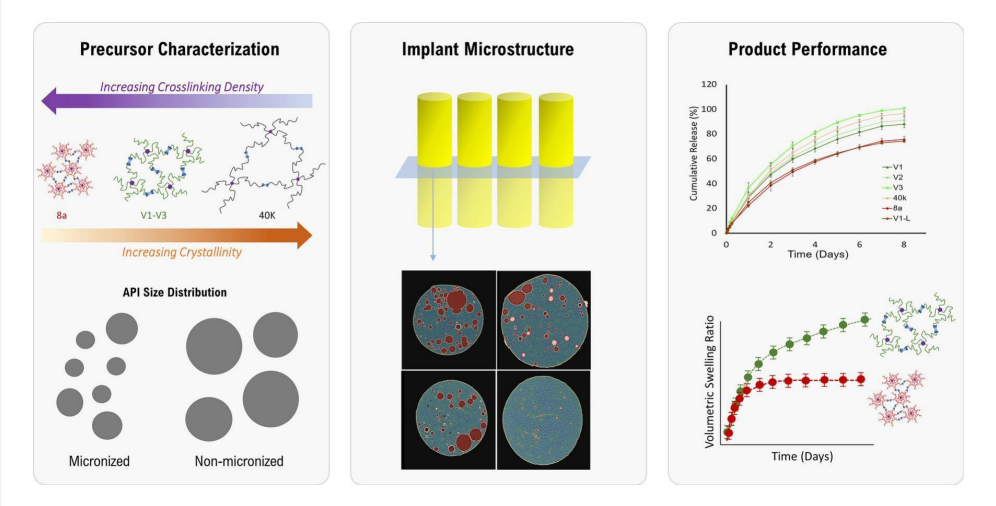


**Figure 1.** Graphical abstract illustrating the interplay between precursor characteristics, implant structure, and product performance in polymer-based drug delivery systems. Precursor characterization highlights the impact of crosslinking density, crystallinity, and drug particle size distribution on matrix properties. Implant microstructure is represented by polymer matrices containing dispersed drug domains, reflecting how formulation parameters influence internal architecture. Product performance is evaluated through cumulative drug release profiles and volumetric swelling behavior across multiple formulations, linking material design to function. Adapted from VandenBerg et al. (2025).

lar-weight distribution, and impurity content across PEG-SG materials. For example, $^{1}$H NMR showed higher functionalization for the 8-arm polymer (~96%) and lower functionalization for 40k and V3 (~76%), consistent with FTIR carbonyl signals; combining functionalization with Size-Exclusion Chromatography–Multi-Angle Light Scattering/Matrix-Assisted Laser Desorption/Ionization provided a quantitative indicator of theoretical chemical crosslinks per mass. The noted differences foreshadowed the network that forms after curing and, in turn, the swelling and release behavior of the finished inserts.

Direct imaging of the dry inserts by X-ray microscopy with AI segmentation revealed systematic shifts in microstructure. Porosity increased from V1-L (prepared with non-micronized API) and V1 through the commercial comparator, V3, 8a, and was highest for 40k; average pore size followed a similar rank order. Within-insert dexamethasone particle-size distributions were comparable for micronized formulations (D50 ≈ 9 - 10 µm), whereas the non-micronized formulation (V1L) showed larger particles (D50 ≈ 13.4 µm).

Swelling studies corroborated the structure-function link. Inserts produced with the lower-functionalization material (V3) swelled faster than inserts made with V1 or V2, while the more highly crosslinked or more crystalline systems (8a and 40k) exhibited slower swelling kinetics and lower equilibrium swelling. A strain-memory experiment, relevant to clinical handling, showed that pre-stretching to approximately 100% in the dry state gave the desired radial expansion with minimal axial growth during hydration; cross-sectional area increased ~6 to 9-fold.

The results of IVRT demonstrated that all inserts displayed discriminating release profiles that aligned with the swelling trends: faster-swelling networks released dexamethasone more rapidly. Formulations prepared with non-micronized API released drug more slowly than otherwise similar inserts containing micronized dexamethasone, underscoring the role of API particle-size distribution on insert performance. Across formulations, the Korsmeyer–Peppas model provided the best fit to the cumulative release data, consistent with coupled diffusion and transient swelling as the governing mechanism. Mesh-size calculations based on Flory–Rehner theory supported this interpretation: early in the test, API particulates greatly exceeded the network mesh dimensions by >10fold, indicating that release is mediated by solubilization-driven diffusion rather than particle migration.

Taken together, the results illustrate that compositionally-same PEG-SG inserts can differ in ways that materially affect the crosslinked network and performance after curing. Several aspects were determined to be relevant for insert performance: (i) precursor end-group functionalization, molecular-weight distribution, and theoretical crosslinks per mass as indicators of network-forming potential; (ii) insert microstructure/porosity and density by XRM-AI and supportive thermal/mechanical assessments; (iii) swelling kinetics and equilibrium swelling that track with in vitro drug release; and (iv) drug particle size distribution. This can support a practical, information-rich approach to establishing insert performance similarity even when direct compositional analysis of an irreversibly crosslinked network is not feasible.

In conclusion, this work shows that modest differences in the hydrogel-forming PEG excipient, across vendors and architectures, translate into measurable changes in crosslink density, microstructure, swelling, and dexamethasone release, providing a coherent structure-to-performance framework for PEG-SG based intracanalicular inserts. An integrated set of analytical methods spanning polymer chemistry, microstructure imaging, swelling measurements, and IVRT with appropriate model fitting identified practical CQAs and surrogate measures of crosslink density that can support Q3 characterization focused approaches to assess equivalence when direct compositional analysis of the cured network is not feasible or impractical. The scientific insights gleaned from this research elucidated how critical material attributes may influence the BE of this class of products, implicated the importance of suitable controls and relevant product characterizations, and suggested ways that FDA could provide recommendations to help streamline the development and assessment of safe and effective generic intracanalicular inserts.

# Research Projects and Collaborations

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

### Completed Grants and Contracts

- Contract (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina

### Active FDA Research

- *Assessing New Analytical Methods for Characterization of Complex Excipients in Long Acting Drug Products*
- *Development of PBPK/PD Modeling Approaches for Ophthalmic Drug Products*

# Outcomes

### Product-Specific Guidances

There were five new and two revised PSGs published in FY 2025 related to *Ophthalmic* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Brimonidine Tartrate, Solution/Drops*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Clobetasol Propionate, Suspension/Drops*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Cyclosporine, Solution*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Nepafenac, Suspension/Drops* (NDA 021862). (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Nepafenac, Suspension/Drops* (NDA 203491). (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Phentolamine Mesylate, Solution*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Pilocarpine Hydrochloride, Solution*. (May 20, 2025) Link to Posting

### Publications


Chen B, Costello M, Kuehster L, Lynd N, Qin B, Wang Y, and Zhang F. *Investigation of the Thermal Stability and Hydrolytic Degradation Kinetics of Poly(lactide-co-glycolide) Melts*. AAPS PharmSciTech. (2025) 26/1:24. https://doi.org/10.1016/j.ejpb.2025.114805. PMID: 39779655.

Chopski S, Walenga RL, Tan M-L, Alam K, Babiskin A, Fang L, and Tsakalozou E. *Impact of Mechanistic Modeling and Simulation Methodologies on Product Specific Guidance Development for Non-Orally Administered Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2025) 14(9):1421-1430. https://doi.org/10.1002/psp4.70078. PMID: 40704493. PMCID: PMC12439276.

Garimella H, Norris C, German C, Przekwas A, Walenga R, Babiskin A, and Tan M-L. *Quasi-3D Mechanistic Model for Predicting Eye Drop Distribution in the Human Tear Film*. Bioengineering. (2025) 12(8):825. https://doi.org/10.3390/bioengineering12080825. PMID: 40868337. PMCID: 12383929.

Garner J, Skidmore S, Overdorf G, Hadar J, Park H, Park K, Wang Y, Jhon Y, Smith W, Zhang D, and Zou Y. *A New Analytical Method for Quantifying Acid-End-Cap PLGA inSub-Milligram Quantities*. Molecular Pharmaceutics. (2024) 22/1:446–458. https://doi.org/10.1021/acs.molpharmaceut.4c01057. PMID: 39566092.

Kuehster L, Bingham M, Dai J, Jhon Y, Wang Y, Qin B, Smith W, Xu X, Zhang F, and Lynd N. *Characterization of the Repeat Unit Sequence of Poly(lactide-co-glycolide)*. Macromolecules. (2025) 58(8), 3886–3897. https://doi.org/10.1021/acs.macromol.4c02895.

Le Merdy M, Tan M-L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for an Ophthalmic Ointment Using PBPK Modeling and Simulation*. AAPS Journal. (2025) 27:150. https://doi.org/10.1208/s12248-025-01138-2. PMID: 39065612.

Ren A, Zhong Z, Magaw M, Wang Y, Qin B, Smith W, Xu X, Listro T, and Zhang F. *Understanding the Impact of Accelerated Release Testing Conditions on Physicochemical Properties and Drug Release Mechanisms from Etonogestrel Implants based on Ethylene Vinyl Acetate*. European Journal of Pharmaceutics and Biopharmaceutics. (2025) 214: 114805. https://doi.org/10.1016/j.ejpb.2025.114805. PMID: 40639446.

Walenga R, Alam K, Clarke J, De Backer J, Friden M, Hamadeh A, Mowli J, Sonti S, Spires J, Tan M-L, Musuamba F, and Tsakalozou E. *Regulatory and Industry Perspective on the Model Master File Framework for Locally Acting Drug Products*. Pharmaceutical Research. (2025) 42: 773-784. https://doi.org/10.1007/s11095-025-03823-5. PMID: 40011371.

VandenBerg MA, Zaman RU, Plavchak CL, Smith WC, Nejad HB, Beringhs AO, Wang Y and Xu X. *Impact of Polymer Source Variations on Hydrogel Structure and Product Performance in Dexamethasone-Loaded Ophthalmic Inserts*. International Journal of Pharmaceutics (2025) 682: 125959. https://doi.org/10.1016/j.ijpharm.2025.125959. PMID: 40645309.


### Posters

Johnson C, Maier E, Bhalla A, Crowell E, Wang Y, Qin B, and Zhang F. *In-Vivo and Biopredictive In-Vitro Dissolution Testing of Dexamethasone Intravitreal Implants in Rabbits*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Le Merdy M, Mullin J, Tan M-L, and Lukacova V. *Predicting Brinzolamide Ocular Response in Humans Using an Ocular PBPK-PD Modeling and Simulation*. Poster Presentation at the American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting. Washington, DC, May 28, 2025.

### Presentations

Zhang Q. *Navigating Formulation Assessment: Considerations when Preparing the Q1/Q2 Sameness Inquiry*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Navigating Controlled Correspondences to Support Generic Drug Development. Virtual Meeting, Feb. 27, 2025.

Smith W. *Regulatory Perspectives: Method Validation and Common Deficiencies*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices. Hybrid Meeting. Rockville, MD, Sept. 23, 2025.

## Topical Products

# Summary of FY 2025 Activities

**During fiscal year (FY) 2025, FDA's GDUFA-funded research continued to support the development of efficient bioequivalence (BE) approaches for topical drug products that can expedite generic drug development and assessment, and thus improve patient access to these essential medications. This research encompasses products applied to the skin as well as those administered through vaginal and rectal routes.**

The research program continued to develop and implement efficient characterization-based BE approaches for prospective generic products when the formulation composition is well matched to that of the reference standard (RS). Continuing Grants U01FD007954, and U01FD007957 and completed Grant U01FD007323 focused on validating enhanced in silico tools using physicochemical and structural (Q3) characterization and in vitro permeation testing (IVPT) data for formulation variants of marketed products. The goal of these research efforts was to quantitatively describe formulation metamorphosis and elucidate the impact of certain inactive ingredients in a mechanistic skin absorption model that can be applied towards bioavailability predictions and bioequivalence assessments. Research completed under Grant U01FD007323 provided several case studies on model-guided optimization of IVPT study design[3] and a semi-mechanistic model capturing the impact of co-permeation of the inactive ingredient propylene glycol on clobetasol propionate (CbP) permeation from a CbP cream product[4]. Noteworthy research under Grant U01FD006522 funded by FDA's generic drug research program is provided under **Research Highlight 1**. Internally in the FDA, dermal PBPK modeling has been used to support product-specific guidance (PSG) development and lifecycle management for products applied on the skin. 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"**.

The GDUFA research program also supported the development of IVPT methods to facilitate the inclusion and implementation of efficient characterization-based BE approaches for topical product PSGs. During FY 2025, internal FDA research demonstrated the feasbility of developing IVPT methods to assess the rate and extent to which tapinarof[5], ruxolitinib[6], and roflumilast[7] permeate

[3] Zhang Y, Murthy N, Rangappa S, Paterson D, Polak S, Dancik Y, Tsakalozou E, Ghosh P, and Clarke J. *Application of PBPK Modelling to Optimize IVPT Study Design and Predict the Impact of Formulation Changes on Skin Permeation*. Poster Presentation at the Skin Forum 2025. Berlin, Germany. Jun. 23, 2025.

[4] Maciel Tabosa A, Dancik Y, Thakur K, Zhang Y, Rangappa S, Murthy N, Tsakalozou E, Ghosh P, Polak S, and Clarke J. *Mechanistic Physiologically-Based Pharmacokinetic Modelling of Skin Permeation of Propylene Glycol from Clobetasol Propionate Cream Formulations with variable Propylene Glycol Content*. Poster Presentation at the Barrier Function of Mammalian Skin Gordon Research Conference (GRC). Waterville Valley, NH, Aug. 10, 2025.

[5] Roy K. and Yang Y. *Method Development and Validation for the Evaluation of In Vitro Skin Permeation (IVPT) of Tapinarof from VTAMA Topical Cream, 1% (w/w)*. Presentation at the 2025 American Chemical Society (ACS) Fall Meeting. Washington, DC., Feb. 23, 2025.

[6] Kamal N, Ali M, Sultana T, Srinivasan P, Russo J, Jiang Y, Ghosh P, Ashraf M, and Zidan A. *Assessment of In Vitro Skin Permeation of Ruxolitinib of OPZELURA (Ruxolitinib Phosphate) Topical Cream, EQ 1.5% Base to Support a Demonstration of Bioequivalence*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

[7] Kamal N, Sultana T, Ali M, Russo J, Jiang Y, Ghosh P, Zidan A, and Ashraf M. *Development of In Vitro Skin Permeation Testing*

across the skin from their respective topical products. The internal research on ZORYVE (roflumilast) topical cream, 3% also used polarized light microscopy and morphologically directed Raman spectroscopy to investigate crystals in the formulation. FDA also co-hosted a workshop with the Center for Research on Complex Generics (CRCG), titled *Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration*. This workshop provided critical considerations for IVPT method development and validation studies, along with step-by-step demonstrations of IVPT procedures aligned with FDA guidance and hands-on activities with diffusion cell systems.

FDA's internal research also focused on expanding characterization-based BE approached for complex topical foam products. Dynamic foam analysis with live imaging successfully characterized the microstructure of several model topical foam and shampoo products. The rheological behavior of these products was also assessed using optimized measurement conditions. These analytical advances provide the foundation for comprehensive foam characterization that may inform future PSG development for complex topical foam formulations. Additionally, artificial intelligence (AI)-enhanced analytical approaches were developed for characterizing microstructure of complex semisolid formulations complementing traditional approaches for the particle size distribution and oil globules characterization. External GDUFA-funded research at the Northeastern University (Grant U01FD007656) is ongoing to develop characterization-based BE approaches for complex vaginal and rectal products, such as gelatin-encapsulated suppositories and creams, including evaluation of methodologies for assessing local bioavailability for such products.

Another goal of this research program was to develop efficient BE approaches for prospective generic products that have differences in the formulation compared to the RS product. As part of this effort, FDA prioritized research to understand and elucidate the underlying mechanisms that enable BE between generic products and RS 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 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 Q3 properties, release and subsequently bioavailability of drug from the formulations. 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 creams may be perceived by human subjects and whether some changes in the amount of different types of inactive ingredients can lead to significant differences in the sensorial properties in vivo. Further details on this work are included in the **Research Highlight 2** below. 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 2025, the research continued at Joanneum Research (Grant U01FD007669) to address the remaining challenges associated with the use of dermal open flow microperfusion as a tool for efficient cutaneous PK-based BE approach. 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[8].

## Research Highlight 1

Research from Grant U01FD006522 (completed in FY2021) and continuing knowledge acquired through funded research (Grants U01FD007323 and U01FD007954) resulted in the development and validation of a mechanistic skin absorption model for lidocaine/prilocaine topical drug products. The model predicted the absorption of lidocaine and prilocaine following topical application of EMLA® cream (lidocaine/prilocaine topical cream, 2.5%/2.5%) and other formulation variants in virtual subjects by leveraging

*Method to Assess Bioequivalence of Topical Roflumilast Cream Formulations*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

[8] Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Belsey N, Rantou E, Ghosh P, Bunge A, Woodman T, Delgado-Charro M, and Guy R. *Raman Spectroscopy as a Tool to Accelerate Development of Complex Medicinal Products*. Journal of Controlled Release. (2025) 387. https://doi.org/10.1016/j.jconrel.2025.114190. PMID: 40907794.

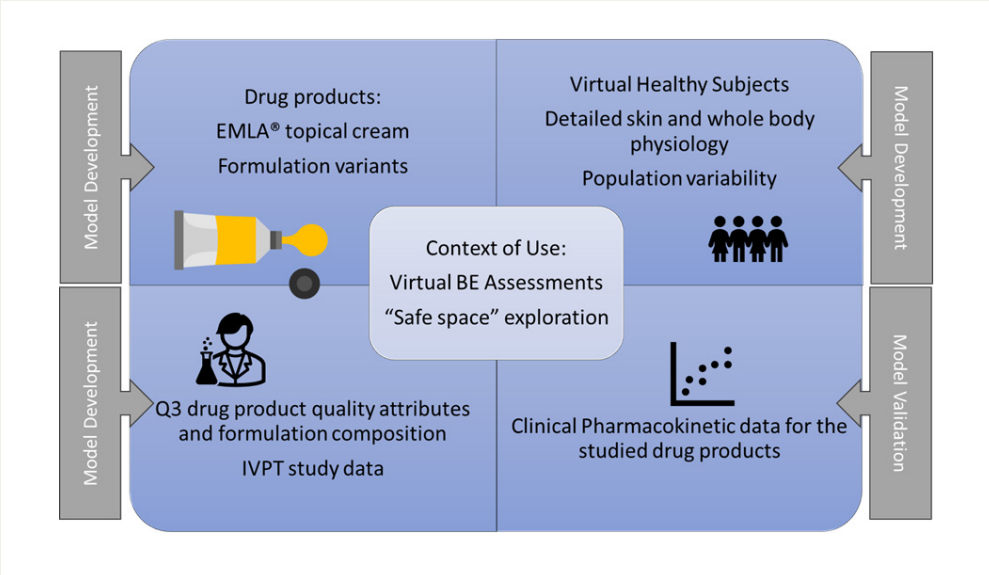


**Figure 1.** Schematic representation of the "building blocks" and workflow related to the development and validation of a dermal PBPK model for lidocaine/prilocaine topical cream products. The mechanistic skin absorption model was able to predict permeation through the skin and absorption into the systemic circulation of lidocaine and prilocaine following their application on the skin of virtual subjects. This research project was supported by U01FD006522. IVPT: in vitro permeation testing; Q3: physicochemical and structural.

information on Q3 product attributes and IVPT study data (**Figure 1**). Model validation demonstrated sensitivity to microstructural characteristics of these formulation variants that were different from the EMLA® cream. Virtual BE assessments performed using the validated dermal PBPK model highlighted the capability of the model to identify potential BE failure modes related to drug product quality attributes for prospective generic topical creams. The developed model can be used to identify a BE "safe space" for the EMLA® cream, perform risk-based assessments, and support decision making in drug development and lifecycle management for the product of interest. These results illustrate the capability of this dermal PBPK model, which has been systematically developed and improved by FDA's generic drug research program, to streamline both the development and assessment of complex generic topical products, thereby facilitating patient access to this important class of drug products.

## Research Highlight 2

The sensory perception of topical products during and following application on the skin may impact patient compliance and adherence to a treatment regime. Compositional differences in the formulation of semisolid topical products, in general, has the potential to significantly impact their Q3 properties as well as patient's perception of look and feel of the products. Therefore, as part of Grant U01FD006700 we explored the influence of inactive ingredient concentration (Q2) on Q3 properties, to understand and predict how similar a patient's sensorial perceptions of a prospective generic product may be compared to a reference standard.

Series of formulations were prepared with Q2 differences in the gelling agent (e.g., Carbopol® 980P (CBP)) and alcohol for gels and in the oil phase (e.g., mineral oil) and emulsifier (e.g., ammonium lauryl sulphate (ALS)) for creams. The topical formulations were extensively characterized for rheology, tribology and texture, the drying rate and globule size distribution (as applicable) were measured for each formulation (**Figure 2**). Following

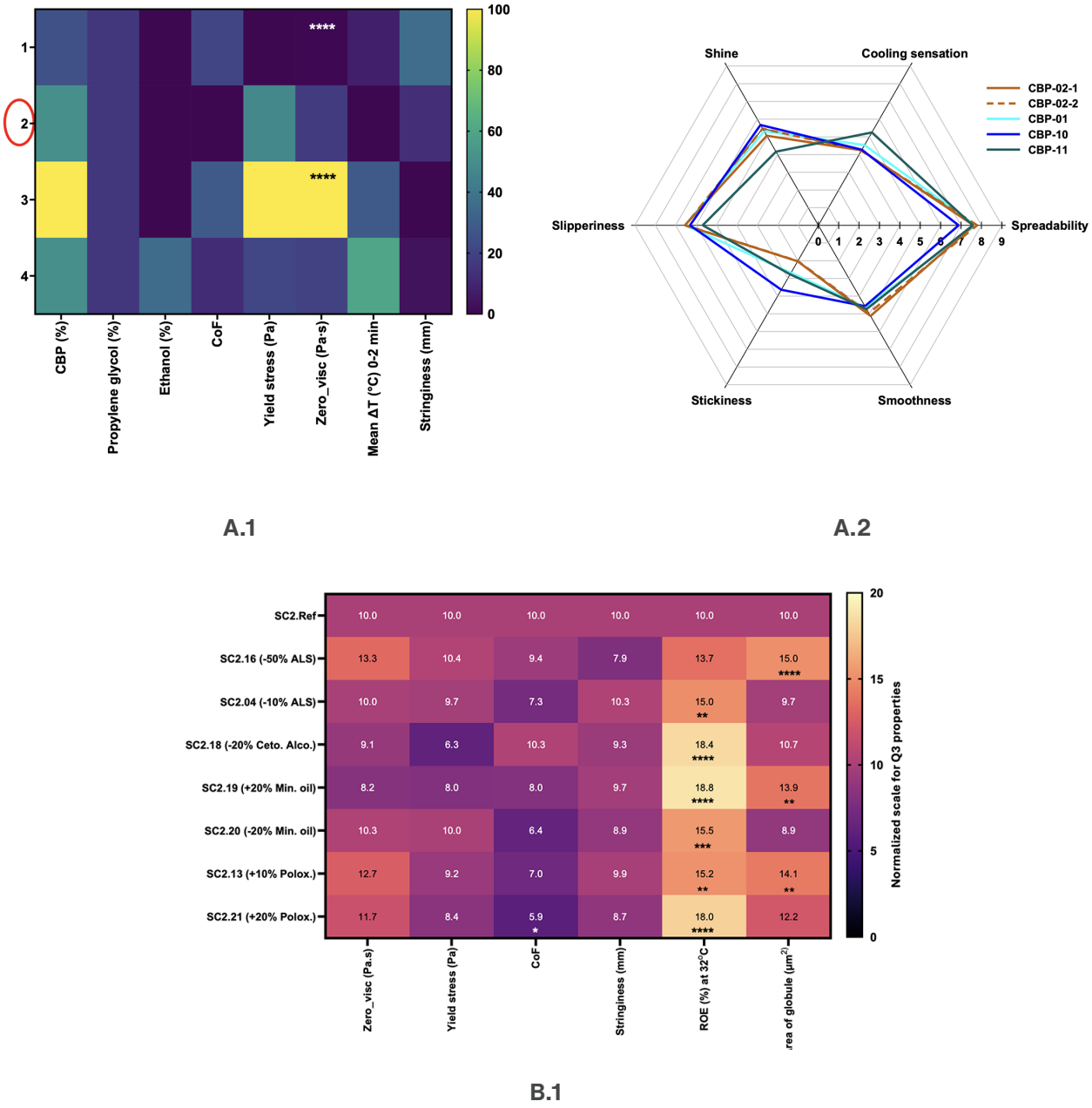


**Figure 2.** Ingredient concentration (Q2) changes for A.1) Carbopol® 980P (CBP), propylene glycol and ethanol in the gels and B.1) ammonium lauryl sulphate (ALS), cetostearyl alcohol (Ceto.Alco),mineral oil (Min.Oil), and poloxamer 404 (Polox) in the creams, in relation to the reference formulation (circled in red); a subset of Q3 properties including zero shear viscosity (Zero_visc), coefficient of friction (CoF), yield stress, mean temperature different from 0 to 2 min (Mean ΔT (oC) 0-2 min), rate of evaporation (ROE)%, stringiness, and area of globules are normalized for different units. The number of "*" summarizes the p values/significant levels: without "*" meaning p>0.05 or no significant difference, with "*" significant difference at p<0.05, "**" significant difference at p<0.01, "***" significant difference at p<0.0005, and "****" significant difference at p<0.0001 between the reference and composition variant formulations. Spider diagram of sensory scores for different sensory attributes evaluated for A.2) gel formulations (CBP-01, CBP-02, CBP-10, and CBP-11 are the same as formulation 1, 2, 3, 4).

statistical analysis of the Q3 data, a subset of topical formulations was selected for human sensory panel test. For this study, the subjects were trained on concepts and assessment criteria of the multiple sensory attributes. These visual and touch attributes that can be perceived immediately after rubbing the formulation on the skin or evaluated 1-2 minutes after application (after feel sensation). The intensity of each formulation sensorial attribute was rated using a continuous 1-9 scale, representing from very low (1) to very high (9) intensity.

The results of multiple sensory panel tests for gels and creams suggest that in general Q3 properties are more sensitive to changes in the formulation composition compared to the sensorial properties Additionally, we were able to observe some degree of correlation between some of the Q3 attributes and sensory attributes. For example, in the gel formulations by increasing the concentration of CBP, the zero sheer viscosity increased and subsequently the formulations with higher amounts of CBP were perceived to be less spreadable and stickier. For the cream formulations, the participants perceived notable differences in several sensory attributes including spreadability, immediate shine, and stickiness among formulations with Q2 differences in ALS and mineral oil. The obtained data demonstrate that when differences in some of Q3 attributes are substantial, they are likely to be perceptible by human subjects; also it may be possible to predict some potential differences in sensorial attributes between two topical formulations from their Q3 characteristics assessed in vitro.

## Research Projects and Collaborations

### Continuing Grants and Contracts

- Grant (U18FD007054-04S1) *Center for Research on Complex Generics – Supplement on In Vitro Approaches to Evaluate and Compare the Adhesion Performance of Transdermal and Topical Delivery Systems* with Yousuf Mohammed at The University of Queensland.
- 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
- 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
- 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

### Completed 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 (U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- 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 (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

### Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *Laboratory-Based Experimental Methodologies to Support in Vitro-Based BE Approaches*
- *Research to Support Development of In Vitro-Based BE Approaches for Topical Products*
- *Topical Dermatological Corticosteroids Dose S election Using Model-based Approach*

## Outcomes

### Product-Specific Guidances

There were seven new and five revised PSGs published in FY 2025 related to *Topical* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Adapalene; Benzoyl Peroxide; Clindamycin Phosphate, Gel.* (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Azelaic Acid, Gel.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Cantharidin, Solution.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Estrogens, Conjugated, Cream.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Mitomycin, Powder.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Roflumilast, Cream.* (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Ruxolitinib Phosphate, Cream.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Selenium Sulfide, Lotion/ Shampoo.* (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Tacrolimus, Ointment.* (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Tazarotene, Cream.* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Terbinafine, Gel.* (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Terbinafine Hydrochloride, Cream.* (May 20, 2025) Link to Posting
- *New Draft Guidance for Terbinafine Hydrochloride, Solution & Spray.* (May 20, 2025) Link to Posting

### Publications

Chopski S, Walenga RL, Tan M-L, Alam K, Babiskin A, Fang L, and Tsakalozou E. *Impact of Mechanistic Modeling and Simulation Methodologies on Product Specific Guidance Development for Non-Orally Administered Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2025) 14(9):1421-1430. https://doi.org/10.1002/psp4.70078. PMID: 40704493.

Kim D, Ahn J, Kim D, Kim J, Yoo S, Lee J, Ghosh P, Luke M, and Kim C. *Quantitative Volumetric Photoacoustic Assessment of Vasoconstriction by Topical Corticosteroid Application in Mice Skin*. Photoacoustics. (2024) 40:100658. https://doi.org/10.1016/j.pacs.2024.100658. PMID: 39553383. PMCID: PMC11563941.

Namjoshi S, Telaprolu K, Grice J, Benson H, Raney S, Roberts M, and Mohammed Y. *Effect of "In Use" Administration on Topical Product Metamorphosis and Skin Permeation of Acyclovir Creams: Implications for Bioequivalence*. Pharmaceutical Research. (2024) 41/12:2391–2401. https://doi.org/10.1007/s11095-024-03797-w. PMID: 39654002.

Tu D, Lemberger N, Wallmeier K, Riseman J, Kuzma B, Wei Y, Khoo T, Ghosh P, Luke M, Raney S, Fallnich C, and Evans C. *Improved Dual-Modality Bioequivalence Evaluation of Topical Formulations Within Human Skin Using Stimulated Raman Scattering Microscopy*. Pharmaceutics. (2025) 17(9): 1193. https://doi.org/10.3390/pharmaceutics17091193. PMID: 41012529. PMCID: PMC12473907.

Walenga R, Alam K, Clarke J, De Backer J, Friden M, Hamadeh A, Mowli J, Sonti S, Spires J, Tan M, Musuamba F, and Tsakalozou E. *Regulatory and Industry Perspective on the Model Master File Frame-*

*work for Locally Acting Drug Products*. Pharmaceutical Research. (2025) 42(5):773-784. https://doi.org/10.1007/s11095-025-03823-5. PMID: 40011371. PMCID: PMC12158826.

Zarmpi P, Tsikritsis D, Watson A, Vorng J, Tyagi V, Belsey N, Rantou E, Ghosh P, Bunge A, Woodman T, Delgado-Charro M, Guy R. *Raman Spectroscopy as a Tool to Accelerate Development of Complex Medicinal Products*. Journal of Controlled Release. (2025) 387 :114190. https://doi.org/10.1016/j.jconrel.2025.114190. PMID: 40907794.

### Posters

Rath S, Abdulhafid K, Niu M, Ghosh P, and Michniak-Kohn B. *Impact of Quantitative Differences in Carbomer on Drug Release from Diclofenac Sodium Topical Gels*. Poster Presentation at the Innovations in Dermatological Sciences Conference. Piscataway, NJ, Sept. 16, 2025.

Sharkawy A, Jamaledin R, Williams A, Bunge A, Guy R, Pettarin M, Spires J, Ghosh P, Tsakalozou E, and Delgado-Charro M. *Impact of Topical Product Metamorphosis on Absorption of Metronidazole*. Poster Presentation at the Barrier Function of Mammalian Skin Gordon Research Conference (GRC). Waterville Valley, NH, Aug. 11, 2025.

Zarmpi P, Tsikritsis D, Belsey N, Rantou E, Ghosh P, Bunge A, Delgado-Charro M, and Guy R. *Raman-Assessed Microstructure, Dermatopharmacokinetics & Bioequivalence of Doxepin Topical Products*. Poster Presentation at the Barrier Function of Mammalian Skin Gordon Research Conference (GRC). Waterville Valley, NH, Aug. 11, 2025.

Maciel Tabosa A, Dancik Y, Thakur K, Zhang Y, Rangappa S, Murthy N, Tsakalozou E, Ghosh P, Polak S, and Clarke J. *Mechanistic Physiologically-Based Pharmacokinetic Modelling of Skin Permeation of Propylene Glycol from Clobetasol Propionate Cream Formulations with variable Propylene Glycol Content*. Poster Presentation at the Barrier Function of Mammalian Skin Gordon Research Conference (GRC). Waterville Valley, NH, Aug. 10, 2025.

Rath S, Abdulhafid K, Niu M, Ghosh P, and Michniak-Kohn B. *Impact of Quantitative Differences in Carbomer on Drug Release from Diclofenac Sodium Topical Gels*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA, Jul. 14, 2025.

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Rath S, Abdulhafid K, and Michniak-Kohn B. *Optimization of Manufacturing Method for Development of Crystal-Free Diclofenac Topical Gels*. Poster Presentation at the Excipient World Conference & Expo. National Harbor, MD, May 12, 2025.

Ramezanli T, Rangappa S, Phan K, Jiang Y, Raney S, Mohammed Y, Murthy Narasimha S, Luke M, and Ghosh P. *Impact of Formulation Differences on Performance of Topical Gels*. Poster Presentation at the Society for Investigative Dermatology (SID) Annual meeting. San Diego, CA, May 8, 2025.

Jiang Y, Ghosh P, and Luke M. *Systematic Evaluation of Topical Dosage Form Types and Approved Indications for Dermatologic Use*. Poster Presentation at the Society for Investigative Dermatology (SID) Annual meeting. San Diego, CA, May 8, 2025.

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*Permeation Post-Application of Binary Mixture Formulations*. Poster Presentation at the 2024 Skin@Bath Conference. Bath, UK, Dec. 05, 2024.

Kamal N, Ali M, Sultana T, Srinivasan P, Russo J, Jiang Y, Ghosh P, Ashraf M, and Zidan A. *Assessment of In Vitro Skin Permeation of Ruxolitinib of OPZELURA (Ruxolitinib Phosphate) Topical Cream, EQ 1.5% Base to Support a Demonstration of Bioequivalence*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Liyanage I, Kelchen M, Ramezanli T, Ghosh P, Ashraf M, and Zidan A. *Mechanistic Evaluation of Microstructure and Performance Attributes of Medicated Topical Shampoos*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Rangappa S, Phan K, AL-Smadi K, Zhu J, Jiang Y, Ghosh P, Ramezanli T, Raney S, Roberts M, Mohammed Y, and Narasimha Murthy S. *Comparing the Performance of Metronidazole Topical Gels with Variant Concentrations of Polyethylene Glycol (PEG) 400 in the Formulation*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

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Kamal N, Sultana T, Ali M, Russo J, Jiang Y, Ghosh P, Zidan A, and Ashraf M. *Development of In Vitro Skin Permeation Testing Method to Assess Bioequivalence of Topical Roflumilast Cream Formulations*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

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Tsakalozou E, Ramezanli T, Raney S, Zhao L, Luke M, and Ghosh P. *Enhanced Understanding of Structure Performance Relationship Using Modeling and Simulation- A Case Study with Dapsone Topical Gel*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

Ashraf-Uz-Zaman M, Ako-Adounvo A, Kelchen M, Ghosh P, Ashraf M, and Zidan A. *Evaluation of Critical Microstructural and Performance Attributes of Azelaic Acid Topical Gels*. Poster Presentation at the 2024 American

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Roy, K and Yang, Y. *Method Development and Validation for the Evaluation of In Vitro Skin Permeation (IVPT) of Tapinarof from VTAMA Topical Cream, 1% (W/W)*. Presentation at the 2025 American Chemical Society (ACS) Fall Meeting. Washington, D.C., Aug. 21, 2025.

Clarke J. *Formulations in Flux: Simulating the Effect of Dynamic Formulation Composition Changes Following Application of Complex Topical Drug Products*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Community. Virtual Meeting, Jul. 25, 2025.

Xu Z. *Impact of Cream Composition on Critical Quality Attributes of Miconazole Nitrate Vaginal Creams*. Presentation at the Controlled Release Society Annual Metting. Philadelphia, PA, July 14, 2025

Tiffner K. *A Clinical Dermal Open Flow Microperfusion (dOFM) Study to Assess Bioequivalence of Different Topically Applied Diclofenac Products*. Presentation at the Skin Forum Annual Conference. Berlin, Germany, Jun. 24, 2025.

Luke M. *FDA's Role in Regulating Products for Dermatology, Including Drugs, Biologics, Devices, and Cosmetics – With a Special Focus on Generic Drugs*. Presentation at the Uniformed Services University. Virtual Meeting, Jun. 18, 2025.

Rath S. *Design, Optimization, and Characterization of Crystal-Free Topical Gels*. Presentation at Topical Products Conference 2025, Atlanta, GA, Jun. 9, 2025.

Ghosh P. *Establishing Equivalence of TDS and OIDPs*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, Jun. 3, 2025.

Walenga R. *Advancing In Silico Methods and Future Opportunities for Understanding Impact of Compositional Differences on Performance*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, Jun. 3, 2025.

Ghosh P. *Beyond the API: Role of Formulation in Topical Product Development*. Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. San Diego, CA, May 10, 2025.

Luke M. *FDA's Role in Regulating Products for Dermatology, Including Drugs, Biologics, Devices, and Cosmetics – With a Special Focus on Generic Drugs*. Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. San Diego, CA, May 10, 2025.

Ramezanli T. *Science-Based Advancements in Assessing Performance of Topical Generic Products*. Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. San Diego, CA May 10, 2025.

Ghosh P. *Current Status and Outstanding Challenges IVPT Studies*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Hybrid Meeting. Rockville, MD, Apr. 29, 2025.

Luke M. *In Vitro Permeation Testing (IVPT)*. Presentation at FDA and the Center for Research on Complex Generics (CRCG) Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Hybrid Meeting. Rockville, MD, Apr. 29, 2025.

Ramezanli T. *FDA-CRCG Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Hybrid Meeting. Rockville, MD, Apr. 29, 2025.

Raney S. *Development of FDA's Guidance for Industry on IVPT Studies for Topical Drug Products Submitted in ANDAs*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Hybrid Meeting. Rockville, MD, Apr. 29, 2025.

Zidan A. *Designing IVPT Methods: Practical Insights for Integrating the IVPT Guidance recommendations*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration. Hybrid Meeting.

Rockville, MD, Apr. 29, 2025.

Jiang, Y. *Navigating Formulation Assessment: Considerations for Products that are Not Required to be Q1Q2*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Navigating Controlled Correspondences to Support Generic Drug Development. Virtual Meeting, Feb. 27, 2025.

Tu D. *Label-Free Imaging of Topical Drugs based on Multivariate Analysis and Sparse Spectral Sampling-Stimulated Raman Scattering Microscopy (S4RS)*. Presentation at the 2025 Society of Photo-Optical Instrumentation Engineers. San Francisco, CA, Jan. 20, 2025.

Raney S. *Topical Drug Delivery - Scientific and Regulatory Considerations for Generic Drug Products*. Presentation at the University of Michigan. Virtual Meeting, Dec. 05, 2024.

Roy K. *A Modeling Approach to Predict Pharmacokinetic Endpoints of Sunscreen Products*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Wang Y. *Role of GDUFA Research on Resolving Technical and Regulatory Challenges for Complex Generic Drug Development and Approval*. Presentation at the 2024 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 22, 2024.

Raney S. *Takeaways from Translational Science Sharpshooters - Simple Strategies for Accuracy, Efficiency, and Impact*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

Feng K. *ANDA Challenges Related to Vasoconstrictor Studies*. Presentation at the FDA Workshop on Guidance Development and Regulatory Assessment of Generic Topical and Dermal Drug Products. Virtual Meeting, Oct. 3, 2024.

Kelchen M. *Development and Status of Product-Specific Guidances for Topical Products*. Presentation at the FDA Workshop on Guidance Development and Regulatory Assessment of Generic Topical and Dermal Drug Products. Virtual Meeting, Oct. 03, 2024.

5

# Drug-Device Combination Products

A major GDUFA III[1] science and research priority is to enhance the efficiency of equivalence approaches for complex drug-device combination products (DDCPs). The advancement of generic drug DDCP research focuses on evaluating the impact of identified differences in the user interface for device hardware and software between a prospective generic test product and the reference listed drug (RLD) product on bioequivalence (BE), therapeutic equivalence, or post-marketing safety. Research during fiscal year (FY) 2025 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 five years from FY 2023 through FY 2027 (GDUFA III).

## Summary of FY 2025 Activities

**In FY 2025, GDUFA research on complex DDCPs focused on evaluating the impact of design differences in user interfaces, hardware, and software between generic DDCPs and their RLD products, with particular attention to how such differences may affect medication errors, BE, therapeutic equivalence, and post-market safety profiles. Research in this area has been a priority because the development and assessment of numerous important generic products have been limited by an inadequate understanding of how differences in device constituent parts between a prospective generic product and its RLD could impact the drug product performance or cause medication errors.**

One research priority in FY 2025 was to improve the design and analysis of comparative use human factors (CUHF) studies. Task Order 1 (75F40123F19001) under the contract with Core Human Factors, Inc. (75F40123D00028) was completed, using a non-inferiority framework to evaluate "other" design differences between a manual pen injector and a semi-automated RLD pen platform. The study successfully demonstrated the feasibility of using a non-inferiority margin to assess use error rates and success rates and provided insights into study design elements such as sample size, recruitment strategies, surrogate endpoints, and statistical analyses. Task Order 2 (75F40124F19002), currently ongoing, is extending these findings to a different drug delivery platform. Collectively, these efforts are expected to provide human factors evidence to guide regulatory decision-making and facilitate generic DDCP development. This contract research will provide the generic drug industry with validated methodological frameworks for conducting CUHF studies and allow them to use the data to support future generic DDCP development.

Another external project developed a method for evaluating the impact of differences in user interface designs between generic DDCPs and their RLDs. A taxonomy-focused grant (U01FD007360) finalized a visual taxonomy of DDCP user interface elements, identified attributes most likely to contribute to use errors on critical tasks, and developed a comparative framework to assess user interface-related risks. The findings of this research were disseminated through an FDA workshop, a peer-reviewed publication, and a presentation at the International Symposium on Human Factors and Ergonomics in Health Care 2025. This standardized taxonomy and comparative framework help enable generic companies to systematically evaluate and mitigate user interface-related risks early in development.

For inhalation products, research examined patient perception of airflow resistance in dry powder inhalers (DPIs). A completed contract project (HHSF223201710072C) validated a questionnaire capturing perceived effort, confidence, and comfort with DPI use, building on a pilot study that was finalized in FY 2024. The results demonstrated the tool's utility for integrating patient-reported perception into DPI performance and usability assessments, providing a foundation for both product development and regulatory review. This validated patient-reported outcome tool provides generic companies with an alternative method to assess DPI usability, reducing development uncertainty and facilitating the development of generic DPIs.

Our research portfolio also advanced the use of in vitro methods to support transdermal and topical delivery systems (TDS) product development. A subaward (Grant U18FD007054-04S1) under the existing Center for Research on Complex Generics (CRCG) grant (U18FD007054) continued work to develop in vitro test methods for assessing adhesion performance of TDS. In FY 2025, with guidance from the CRCG Expert Committee on Adhesion Testing for TDS, a theoretical framework of factors influencing TDS adhesion was outlined, and initial evaluations of skin-mimetic substrates were completed, including analysis of how topographical characteristics affect adhesion outcomes. Parallel research efforts conducted a retrospective review of generic TDS drug applications approved over the past decade, focusing on irritation and sensitization potential. The findings indicated that irritation and sensitization study failures did not correlate with specific inactive ingredients for the products evaluated in the study. Therefore, moving forward it may be helpful to consider the formulation and the indication of a prospective generic product, along with available information within

databases such as the inactive ingredient database, to determine the need for sensitization studies for a TDS. These advances will streamline the development of generic TDS products.

The use of real-world evidence to support post-market evaluation of complex DDCPs was advanced through a research grant (U01FD008316) focused on the safety of switching between complex branded and generic drugs. This project is developing an algorithmic framework to actively monitor the safety and effectiveness of complex DDCPs using large healthcare databases. The framework integrates patient utilization characterization, comparative effectiveness analyses using advanced statistical and machine learning methods, systematic screening for unexpected safety signals, and a refined investigation of identified safety concerns through targeted protocols. The tools developed are intended to enhance FDA's ability to conduct active post-market surveillance of complex generic DDCPs by facilitating rapid signal detection and definitive regulatory action. This real-world evidence framework is intended to provide FDA with enhanced post-market surveillance capabilities, enabling informed regulatory decisions on complex generic DDCPs by ensuring robust safety monitoring after market entry.

In addition, under a new contract (75F40124F19001), FDA initiated research on three-dimensional correlative imaging, quantitative image analysis of critical quality attributes, and image-based in silico modeling of complex drug products. The products under investigation include solid implants, microspheres, in situ forming implants, and inhalers. This work provides structural characterization of complex generic products and develops models that correlate structural characteristics with formulation performance, enhancing understanding of how formulation and manufacturing parameters impact product performance. These advanced imaging and modeling capabilities will enable generic companies to better understand structure-performance relationships in complex products, reducing development risks and providing FDA with more sophisticated tools for assessing product performance and therapeutic equivalence.

## Research Highlight

### Comparative Use Human Factors Study: Evaluating "Other" Design Differences Between Semi-Automated and Manual Injection Pen Platforms

The FDA identified the need to understand which types of user interface differences between RLD pen-injector products and proposed generic alternatives are more or less likely to be associated with increased use error rates. Specifically, the Office of Generic Drugs has repeatedly identified three "other design differences" between semi-automated pen injectors and manual injection pen platforms that may impact critical design attributes involving drug product administration. These differences include: (1) extended dose selector vs. no dose selector extension, (2) visibility of other doses and markings on the extended dose selector, and (3) dynamic push (manual injection driven by pushing down on the dose button on an extended dose selector) vs. static push (semi-automated injection triggered by a static push on a fixed dose button) (**Figure 1**).

A CUHF study was conducted to evaluate the impact of these design differences on use success rates using a noninferiority design. The study compared representative RLD products that use a semi-automated injector platform to a hypothetical generic "Test Product" that utilizes an "off-the-shelf" manual pen injector platform. From Jan to Mar 2025, 100 subjects participated in simulated-use scenarios, including 16 current RLD users and 84 surrogate users (users of the same semi-automated pen platform as the RLD). Each subject performed two use scenarios with each product: 1) selecting a 0.6 mg dose and 2) selecting and injecting a 3 mg dose (**Figure 2**).

The study had co-primary endpoints measuring use success rates for tasks impacted by the "other" design differences. Statistical analyses demonstrated noninferiority of the Test Product to the RLD. For Use Scenario 1 (selecting 0.6 mg dose), both products achieved 95 percent use success rates with an upper 95 percent confidence limit of 5.7 percent, which was below the pre-specified noninferiority margin of 10 percent. For Use Scenario 2 (selecting and injecting 3 mg dose), the RLD achieved a 100 percent use success rate while the Test Product achieved a 95 percent use success rate, with an upper 95 percent confidence limit of 9.92 percent, also below the 10 percent margin (**Figure 3**). Root cause analyses revealed that none of the use errors were attributed

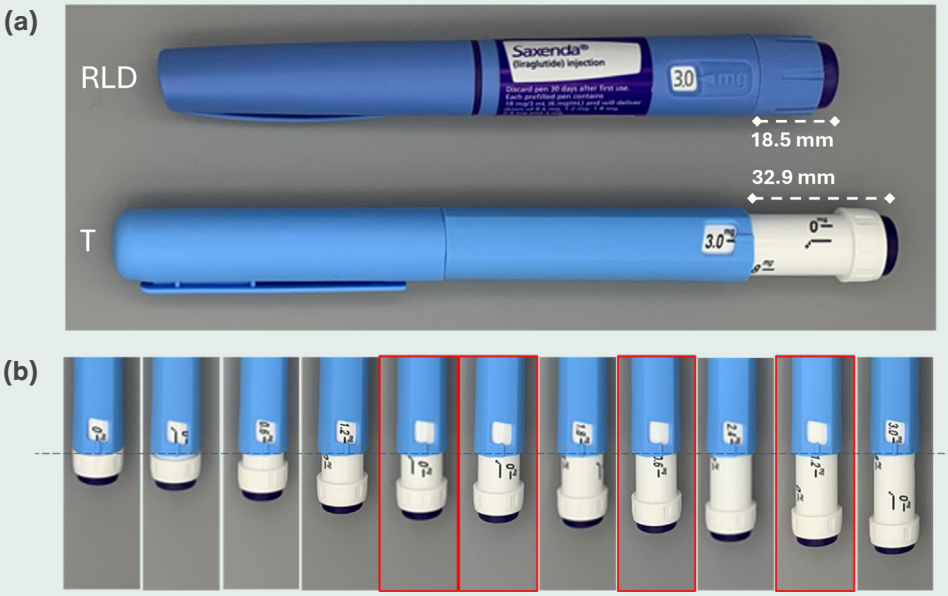


**Figure 1.** Design differences between RLD and Test Product pen-injectors. (a) Dose selector extension comparison at 3.0 mg dose; (b) Dose marking visibility on Test Product's extended dose selector across different dose settings.

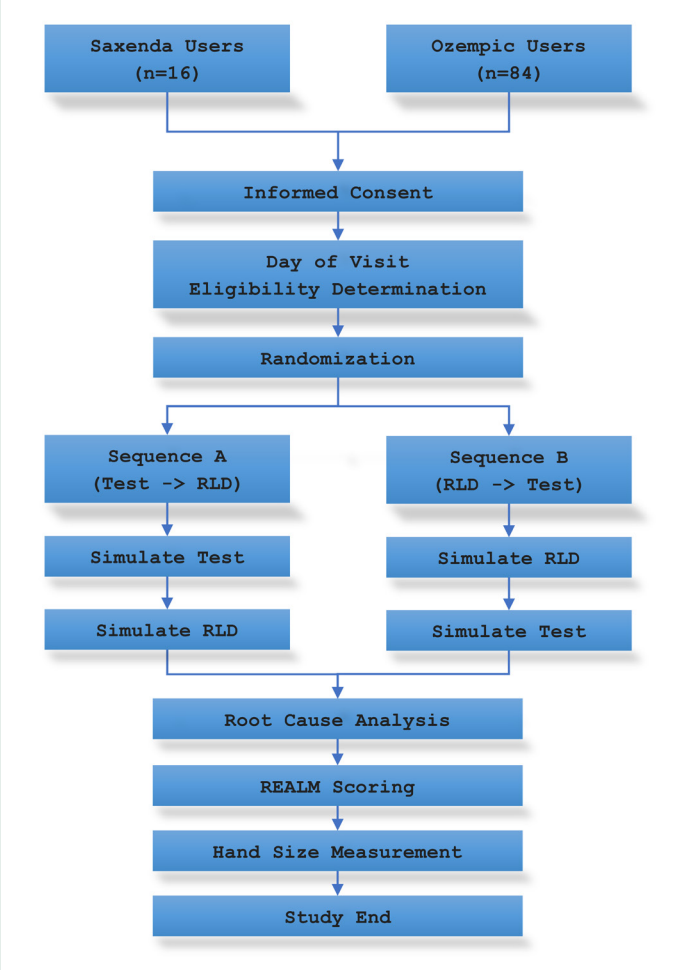


**Figure 2.** CUHF study design

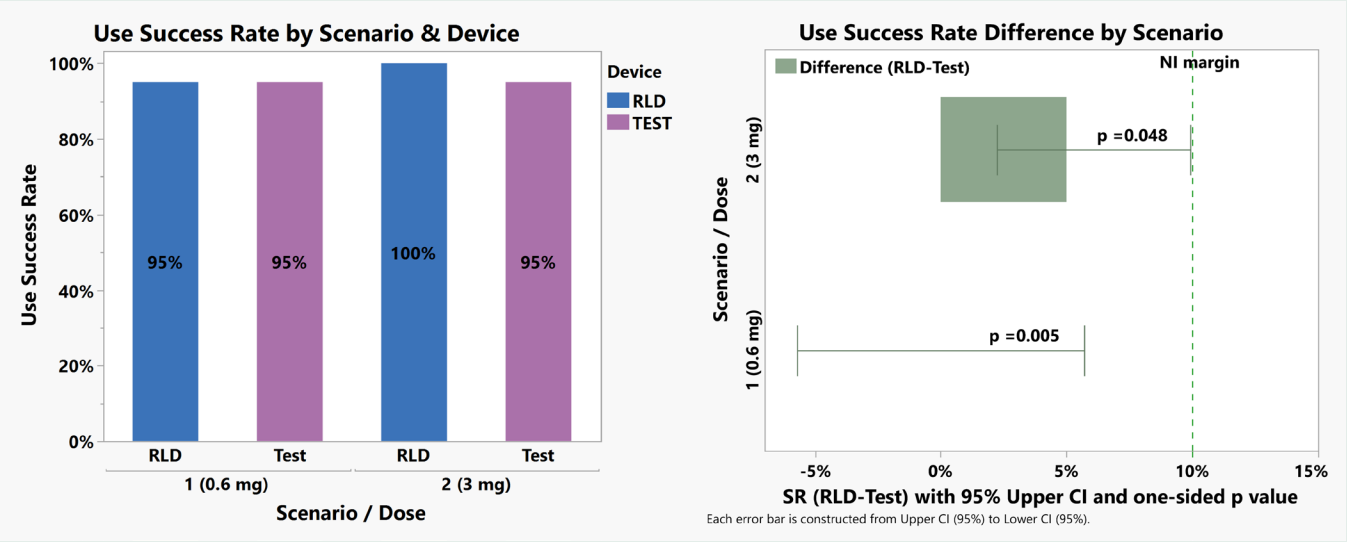


**Figure 3.** Use Success Rates (SR) by Scenario

to the extended dose selector or extraneous dose markings visible on the extended dose selector, while two injection-related use errors were linked to the manual push mechanism of the Test Product. Overall, the results suggest that the Test Product can be substituted for the RLD without healthcare professional intervention or additional training, providing valuable evidence for regulatory decision-making regarding certain "other design differences" in generic DDCPs.

# Research Projects and Collaborations

### Continuing Grants and Contracts

- Grant (U01FD008316) *The 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, Inc.
- 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

### Completed Grants and Contracts

- Grant (U18FD007054) *Center for Research on Complex Generics* with James Polli, Anna A Shenderova Schwendeman at University of Maryland, Baltimore
- 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 New BE Methods for Transdermal Irritation and Sensitization*
- *Navigating the Device Patent Ecosystem of GLP-1 Peptide Drug Products: Case Study of Generic Liraglutide Development*
- *Pen Injectors and Auto-Injectors Used in the Drug Marketplace: Landscape Assessment and Supply Chain.*
- *Research to Facilitate Efficient Product Development and Equivalence Demonstration for Topical and Transdermal Delivery System (TDS) Products*

## Outcomes

### Product-Specific Guidances

There were eight new and five revised PSGs published in FY 2025 related to *Drug-Device Combination Products*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Aripiprazole, Suspension, Extended Release*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Aripiprazole, For Suspension, Extended Release*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Aripiprazole Lauroxil, Suspension, Extended Release*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Enfuvirtide, Injectable*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Eplontersen Sodium, Solution*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Estrogens, Conjugated, Cream*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Levonorgestrel, Intrauterine Device*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Liraglutide, Solution*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Melphalan Hydrochloride, Powder*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Nepafenac, Suspension/Drops* (NDA 021862). (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Nepafenac, Suspension/Drops* (NDA 203491). (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Risperidone, Suspension, Extended Release*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Risperidone, For Suspension, Extended Release*. (May 20, 2025) Link to Posting

### Publications

Conrad MO, Laird ME, Privitera MB, Lemke MR, and Story MF. *Seeking a Common Human Factors Language for the Development and Testing of Injection Devices*. Drug Delivery. (2025) 32(1): 2541660. https://doi.org/10.1080/10717544.2025.2541660. PMID: 40771144.

Conrad MO, Privitera MB, Laird ME, and Lemke MR. *Survey Analysis on Comparative Use Human Factors Processes*. Human Factors in Healthcare. (2025) 7: 100099. https://doi.org/10.1016/j.hfh.2025.100099. PMID: 41477634. PMCID: PMC12750625.

Reed NA, Dar R, Holtgrewe N, Cao LN, Liu X, Conti DS, Newman B, Bielski E, Rodriguez JD, and Guo C. *Evaluating 3D-Printed Pre-separator Inserts in a Fast Screening Impactor for Physicochemical Characterization of Fine Particle Dose Release from Dry Powder Inhalers*. AAPS PharmSciTech. (2025) 26(7): 205. https://doi.org/10.1208/s12249-025-03196-3. PMID: 40739372.

Srivastava I, Lee Y, Feibus KB, Bielski ER, Sterrett L, Harris DM, and Luke MC. *Development of Drug-Device Combination Products and Generic Substitution in the United States: An Overview*. Pharmacy Practice & Practice-Based Research. (2025) 16(2): 6461. https://doi.org/10.24926/iip.v16i2.6461.

### Posters

Chakma MS, Meah S, Biddiscombe M, Han L, Newman B, Murnane D, and Usmani OS. *Dry Powder Inhaler Resistance: Understanding Patient Preference and Confidence Using the In-Check DIAL*. Poster Presentation at the ERS Congress 2025. Amsterdam, Netherlands, Sep. 27-Oct. 1, 2025.

Chakma MS, Meah S, Biddiscombe M, Han L, Newman B, Murnane D, and Usmani OS. *Deconstructing Pavlovian Paradigms in Dry Powder Inhaler Technique*. Poster Presentation at the International Society for Aerosols in Medicine (ISAM) Congress 2025. College Park, MD, Jun. 22, 2025.

Conrad MO, Privitera MB, Lemke MR, and Larid ME. *Development of a New ANDA Comparative Use HF Method for Comparing Products with Consideration of Potential Harm Resulting from Use Errors*. Poster Presentation at the International Symposium on Human Factors and Ergonomics in Health Care 2025. Toronto, Canada, Apr. 1, 2025.

### Presentations

Luke M. *FDA's Role in Regulating Products for Dermatology, Including Drugs, Biologics, Devices, and Cosmetics – With a Special Focus on Generic Drugs*. Presentation at the Uniformed Services University 2025. Virtual Meeting, Jun. 18, 2025.

Conrad MO and Privetera MB. *A Taxonomy for Categorizing User Interface Design in Medical Device Development: Human Factors Application, Development Opportunities, and Potential Integration of AI and Machine Learning*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, Jun. 3, 2025.

Ghosh P. *Establishing Equivalence of TDS and OIDPs*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, Jun. 3, 2025.

Beringhs AO and Delvadia R. *FDA's Perspectives on Current Quality and Bioequivalence Challenges for Complex Products*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Hybrid Meeting. Silver Spring, MD, Jun. 3, 2025.

Conrad MO and Privetera MB. *Translating Input from Biostatisticians for HFE Team Members*. Presentation at the 6th Human Factors Engineering & Usability Studies Congress. Philadelphia, PA, May 16, 2025.

Luke M. *FDA's Role in Regulating Products for Dermatology, Including Drugs, Biologics, Devices, and Cosmetics – With a Special Focus on Generic Drugs*. Presentation at the Society for Investigative Dermatology (SID) Annual meeting 2025. San Diego, CA, May 10, 2025.

Jiang, Y. *Navigating Formulation Assessment: Considerations for Products that are Not Required to be Q1Q2*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Navigating Controlled Correspondences to Support Generic Drug Development. Virtual Meeting, Feb. 27, 2025.

Conrad MO. *Challenges and Best Practices for Implementing the CUHF Process for the Approval of DDCPs*. Presentation at the 5th Human Factors Engineering & Usability Studies Congress, Philadelphia, PA, Oct. 24, 2024.

Clerman A. *Pre-ANDA Opportunities for Generic Drug-Device Combination Product Development*. Presentation at the 2024 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 22, 2024.

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 in order to reduce regulatory burdens while ensuring the quality, safety, and effectiveness of generic drugs. 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 International Council for Harmonisation (ICH) ICH M13A[2] and ICH M13B;[3]

[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 five years from FY 2023 through FY 2027 (GDUFA III).

[2] FDA Guidance for Industry. M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms. (October 2024). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms.

[3] FDA Draft Guidance for Industry. M13B Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver. (May 2025). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13b-bioequivalence-immediate-release-solid-oral-dosage-forms-additional-strengths-biowaiver.

conducting internal research to seek data-driven harmonization of BE criteria for narrow therapeutic index (NTI) drugs to support harmonization under ICH M13C; and acquiring data to support future harmonization for modified-release (MR) oral products.

This included research to assess the feasibility of Biopharmaceutics Classification System (BCS)-based biowaivers for prospective generic immediate-release (IR) oral drug products with formulation differences greater than currently recommended in FDA guidance. It also included research to understand how formulation design features can influence the in vivo pharmacokinetics (PK) of a drug product, as well as research investigating the utility of in vitro methodologies to support a demonstration of BE when MR oral drug products are administered with soft food. Additional research priorities included the development of in vivo BE study designs that maintain subject safety and ensure BE with specific populations (e.g., pediatric or geriatric patients) to establish improved tools and methodologies with which to efficiently assess the equivalence of therapeutic outcomes in diverse populations. Research during fiscal year (FY) 2025 that was aligned with this GDUFA science and research priority area is described below. The research details related to the use of physiologically based pharmacokinetic (PBPK) modeling to support BE assessments for oral IR and MR products are provided in Chapter 7.2: Oral Absorption Models and Bioequivalence.

# Bioequivalence Methods and Analysis, IR and MR Oral Products, and Human Subject Safety

## Summary of FY 2025 Activities

**During FY 2025, FDA continued research in seven key areas 1) BE methods and analyses, 2) IR and MR oral products, 3) impact of food on human subject safety, 4) acid-reducing agents, 5) alcohol on drug release behavior, 6) understanding drug in vivo and in vitro release performances and mechanism, and 7) improving global harmonization for oral drug products. These research efforts were supported by several internal FDA research projects (listed below) and external research collaborations, which included exploring of in vitro mechanistic understanding of amorphous solid dispersion (ASD) drug products (Grant U01FD008388), examining effects of sodium lauryl sulfate on drug absorption (Grant U01FD005978-04S3), understanding factors related to drug and formulation affecting alcohol dose dumping (Grant U01FD008305; see Research Highlight), supporting the BE of additional strengths of MR drug products (Grant U01FD007959), and establishing patient centric quality standards (Contract 75F40120C00200). Additionally, FDA enhanced global harmonization efforts by developing and revising product-specific guidances (PSGs) through comprehensive assessment of both high-risk and non-high-risk IR drug products to align with M13A.**

Grant U01FD008388 focused on developing and validating an in vitro model (controlled transfer dissolution) to predict how food intake and acid-reducing medications affect drug absorption from ASD formulations. While drug products containing ASDs are considered high-risk drug products under the FDA M13A Guidance for Industry[4], additional in vivo BE studies are needed to assess the risk of bioinequivalence under fed conditions and/or in the presence of gastric acid-reducing medications resulting in higher development costs. The goal is to create predictive tools that can support efficient BE approaches for generic ASD formulations and inform regulatory decision-making. The research team conducted a comprehensive review to identify appropriate controls for in vitro experiments, selecting drug products with the same active pharmaceutical ingredient (API) available in both non-ASD and ASD formulations that demonstrate different pH or food effects to evaluate the predictive ability of the in vitro system for ASD formulations. Experimental data will be systematically compared against available human clinical pharmacokinetic data to validate model performance and establish mechanistic understanding of how formulation differences and manufacturing processes impact drug release under varying gastrointestinal conditions.

Grant U01FD005978-04S3 is a clinical study designed to investigate how excipients in the formulation may influence the absorption of drug substances that are transporter substrates. Certain excipients can affect intestinal transporters that impact drug absorption. One of these transporters is OATP2B1. Sodium lauryl sulfate (SLS), a common excipient used in many drugs, was shown to inhibit OATP2B1[5]. However, it is unclear to what extent

[4] FDA Guidance for Industry. M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms. (October 2024). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms.

[5] Zou L, Ni Z, Tsakalozou E, and Giacomini KM. *Impact of Pharmaceutical Excipients on Oral Drug Absorption: A Focus on Intestinal*

SLS inhibits OATP2B1 in humans. In this study, twelve healthy subjects aged 18 to 65 years received fexofenadine, a known OATP2B1 substrate, in combination with low and high concentrations of SLS. Blood and stool samples were analyzed to measure fexofenadine and SLS levels. All participants have completed study visits and data analysis is underway to evaluate the impact of SLS on fexofenadine absorption. Findings are expected to improve drug formulation development strategy.

Grant U01FD007959 focuses on identifying critical quality attributes and design features of MR products, while determining appropriate scaling factors for developing additional strengths of MR tablet formulations with consistent bioavailability across strengths. During FY 2025, the research team identified formulation variables that affect drug release mechanisms and established formulation design spaces for hydroxypropyl methyl cellulose (HPMC) matrix-based extended-release (ER) tablets across multiple strengths. The team selected marketed quetiapine fumarate (QF) ER tablets as the model product for this investigation. Using a quality-by-design approach, researchers developed in-house QF ER tablets to systematically explore key formulation variables and interactions between different grades of HPMC (i.e., HPMC K100 LV and HPMC K4M). The study examined critical parameters including: HPMC amount and their concentration levels, ratios of different HPMC grades, and variable HPMC grade interactions affecting in vitro QF release characteristics. The team successfully identified safe formulation design spaces across different strengths that ensure dissolution similarity factor (f2) values comparable to RLDs. These findings will support the development of PBPK models. These models will link in vitro dissolution behavior to in vivo performance, enabling identification of appropriate scaling factors for additional formulation strengths. The study results establish acceptable formulation design spaces that can improve product design strategy and guide future development of matrix-based ER tablets across multiple strengths.
For Contract 75F40120C00200 in FY 2025, this project studied two glipizide ER tablet products with different release mechanisms. The research measured in vivo drug release behaviors of glipizide ER tablet products across various gastrointestinal tract regions and analyzed drug concentrations in plasma. The collected data will be used to establish modeling to elucidate how in vitro differences may be associated with variable absorption in vivo. These findings can elucidate the relationship between in vitro performance and in vivo behavior for products with different release mechanisms but comparable pharmacokinetic performance.

## Research Highlight

Alcohol-induced dose dumping effects in MR oral dosage forms have received increased attention in recent years. Dose dumping, which is the unintended rapid release of drug in a MR dosage form in a short period of time can have severe adverse events. When alcohol and an oral MR product that has a dose-dumping-susceptible formulation are co-ingested, a major fraction of the drug is immediately dissolved in the stomach. After a sufficient gastric retention time, the entire amount of the dissolved drug is uncontrollably emptied into the small intestine which may result in very high plasma concentrations. Not many research studies have been reported in the literature on alcohol-induced dose dumping. It is important to understand the effect of formulation, excipients, and manufacturing method on the vulnerability of MR formulations to dose dumping by alcohol. From a regulatory perspective, these findings have significant implications for generic drug development, as manufacturers should demonstrate that their formulations exhibit alcohol-induced dose dumping behavior no worse than the reference listed drug through appropriate in vitro testing. The FDA has issued PSGs for certain ER formulations that recommends alcohol dose dumping studies using specified ethanol concentrations (typically 5%, 20%, and 40% v/v) to ensure BE and patient safety, particularly for NTI drugs where dose dumping could result in serious adverse events. The objectives of Grant U01FD008305 are to mechanistically and systemically understand the effect of formulation composition, formulation design, and rate-controlling polymer on alcohol-induced dose dumping of carbamazepine and venlafaxine ER formulations. Our results indicated that alcohol-induced dose dumping will be affected by physicochemical properties of the drug, rate-controlling agent, and product design, etc., and interplay of these variables. For example, osmotic system-based ER formulations of carbamazepine were found to resist dose dumping due to the slow dissolution

*Drug Transporters*. Clinical Pharmacology & Therapeutics. (2019) 105(2), 323–325. https://doi.org/10.1002/cpt.1292. PMID: 30663035.

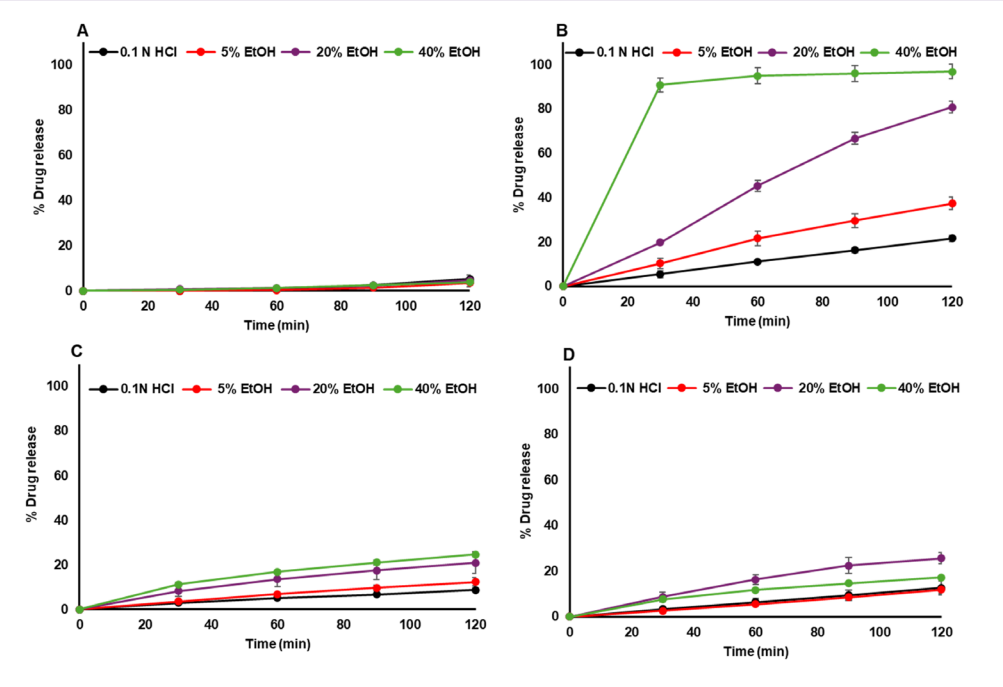


**Figure 1.** Dissolution of carbamazepine ER formulations in 0.1 N HCl and 0.1 N HCl with 5, 20 and 40% ethanol from (A) osmotic system, (B) matrix system based on Eudragit® polymer, (C) matrix system based on HPMC polymer and (D) matrix system based on Polyox™ polymer.

characteristics of the polymer membrane in alcoholic media, which maintains the integrity of the osmotic delivery system even in the presence of ethanol (**Figure 1A**). On the other hand, alcohol dose dumping of matrix system depends on drug and polymer solubility in the alcohol. Matrix ER formulations based on Eudragit® polymers were found to dump the drug due to their solubility in the alcohol compared to Polyox™ or HPMC, which are insoluble in the alcohol (**Figures 1B-1D).** By elucidating the mechanistic relationships between formulation variables and alcohol-induced dose dumping susceptibility, this research directly supports the regulatory framework by providing scientific rationale for appropriate in vitro testing, enabling FDA to revise PSG recommendations for ER formulations, and equipping generic drug manufacturers with the knowledge needed to design formulations that demonstrate comparable alcohol dose dumping behavior to reference listed drugs.

# Research Projects and Collaborations

### 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
- 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 Maxime Le Merdy at Simulations Plus, Inc.

- 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
- Contract (75F40124P00142) *Construction of a Database Containing Drug Biopharmaceutics Classification System (BCS) Class Information* with Hualou Liang at Drexel University
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive In Vitro Dissolution-Models* with Duxin Sun, Amit Pai Manjunath at University of Michigan, College of Pharmacy

### Completed Grants and Contracts

- Contract (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

### 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*
- *Bioequivalence of High-Risk Oral Products*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Development of a Decision-Making Procedure in Relation to Female Reproductive Toxicity for Selection of Bioequivalence Study Population*
- *Establish the Framework for Partial AUC Recommendations*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *Evaluation of Oral Peptide Impurity Profiles on Immunogenicity Risk and Excipient Effect on Permeation*
- *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 Products*
- *Identification of Critical Factors for Oral Solution Bioequivalence*
- *Risk Assessment and Resolving Regulatory Discrepancies for the Product-Specific Guidances Under ICH 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*
- *Optimization of Concomitant Drugs in Pharmacokinetic Bioequivalence Studies*
- *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 Approval Standards*
- *Utilization of Pharmacogenomic Information for Subject Recruitment in Bioequivalence Studies for Generic Drug Development*

## Outcomes

### Product-Specific Guidances

There were seven new and one revised PSGs published in FY 2025 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 Carbinoxamine Maleate, Orally Disintegrating Tablet*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Clonidine Hydrochloride, Suspension, Extended Release*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Etrasimod Arginine, Tablet*. (May 20, 2025) Link to Posting

- *New Draft Guidance for Gepirone Hydrochloride, Tablet, Extended Release*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Macitentan; Tadalafil, Tablets*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Metformin Hydrochloride, Tablet, Chewable*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Phytonadione, Tablets*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Repotrectinib, Capsule*. (May 20, 2025) Link to Posting

In addition to the above mentioned PSGs, in FY 2025 FDA revised PSGs for a subset of IR oral drug products in response to the implementation of the *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms*. A total of 814 draft revised PSGs were published on Oct 31, 2024. For a full list of the revised draft PSGs, please refer to the Federal Register Notice: https://www.federalregister.gov/documents/2024/10/31/2024-25391/product-specific-guidances-revised-draft-guidances-for-industry-availability.

### Publications


Amin Anno K, Mina M, Zhang Z, Zhang L, and Jiang W. *Analysis on the Impact of U.S. FDA's Narrow Therapeutic Index Bioequivalence Criteria on Generic Drug Applications*. The AAPS journal. (2025) 27(1): 42. https://doi.org/10.1208/s12248-025-01020-1. PMID: 39939514.

Bae J, Shon J, Kim MJ, and Li K. *Pharmacogenetic Approaches to Optimize Bioequivalence Studies in Generic Drug Development. Journal of Clinical Pharmacology*. (2025) 65(11): 1598-1608. https://doi.org/10.1002/jcph.70058. PMID: 40501016.

Donnelly M, Fang L, Madabushi R, Zhu H, Luke M, Canterbury C, Lerman B, Kaur P, Patel D, Sun W, Schuirmann D, Dinsmore S, Mehta M, Zhao L. *Narrow Therapeutic Index Drugs: FDA Experience, Views, and Operations*. Clinical Pharmacology and Therapeutics. (2025) 117/1:116–129. https://doi.org/10.1002/cpt.3460. PMID: 39529254.

Hopefl R, Gong Y, Bielski E, Pillai V, Newman B, Qin B, Wang Y, Yoon M, Zhang Q, Stier E, Uppoor R, Zhu H, Zhang L, Fang L. *A 2024 Update on US FDA Implementation of Partial Area Under the Curve into Bioavailability and Bioequivalence Assessments*. Clinical Pharmacology and Therapeutics. (2025) 117(5):1185-1193. https://doi.org/10.1002/cpt.3561. PMID: 39825841.

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Rudolph N, Charbe N, Plano D, Shoyaib A, Pal A, Boyce H, Zhao L, Wu F, Polli J, Dressman J, and Cristofoletti R. *A Physiologically Based Biopharmaceutics Modeling (PBBM) Framework for Characterizing Formulation-Dependent Food Effects: Paving the Road towards Fed Virtual BE Studies for Itraconazole Amorphous Solid Dispersions*. European Journal of Pharmaceutical Sciences. (2025) 209:107047. https://doi.org/10.1016/j.ejps.2025.107047. PMID: 39983931.

Schug B, Beuerle G, Bilensoy E, Cook J, Fernandes E, Haertter S, Kuribayashi R, Mehta M, Paixao P, Seidlitz A, Tampal N, Tsang Y, Walstab J, Wedemeyer R, Welink J, and Jiang W. *The Global Bioequivalence Harmonisation Initiative (GBHI): Report of the sixth international EUFEPS/AAPS conference*. European Journal of Pharmaceutical Sciences. (2025) 212:107129. https://doi.org/10.1016/j.ejps.2025.107129. PMID: 40379059.

Taylor L, Trasi N, Purohit H, Sun D, Kinjo M, Ni Z, Mahjabeen S, Feng K, Sun W, Matta M, Decker B, and Galinsky R. *Changes in Drug Crystallinity in a Commercial Tacrolimus Amorphous Formulation Result in Variable Pharmacokinetics*. Journal of Pharmaceutical Sciences. (2025) 114(1): 313 – 322. https://doi.org/10.1016/j.xphs.2024.09.025. PMID: 39414078.

Wang J, Campbell G, Lee J, Hu M, Feng K, Chattopadhyay S, Zhao L, and Peck C. *Bioequivalence of ANDA Data using a Non-Informative Bayesian Procedure (BEST) Compared with the Two One-Sided t-Tests (TOST)*. The AAPS Journal. (2025) 27(2): 47. https://doi.org/10.1208/s12248-024-00981-z. PMID: 39971785.

Zidan A, Siddique AB, Shaklah M, Anand O, O'Connor. T, and Ashraf M. *Development of In Vitro-In Vivo Correlation for Establishing Patient-Centric Quality Standards of Dissolution for Lamotrigine Extended-Release Tablets*. European Journal of Pharmaceutics and Biopharmaceutics. (2025) 216, 114874. https://doi.org/10.1016/j.ejpb.2025.114874. PMID:40997957.

### Posters

So G, Li K, Shon J, Kim M, and Nguyen D. *Current Landscape on the Use of Antiemetics in Pharmacokinetic Bioequivalence Studies for Generic Drug Development*. Poster Presentation at the American College of Clinical Pharmacology (ACCP) Annual Meeting 2025. Phoenix, AZ, Sep. 15, 2025.

Cheng Y, Wu F, Mousa Y, Zhao L, and Fang L. *Assessment of the Impact of Non-Comparable In Vitro Alcohol Dose Dumping Release on Systemic Exposure using PBPK Absorption Modeling for Topiramate Extended-Release Capsules*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 29, 2025.

Jamil R, Babiskin A, Zhang L, Fang L, and Wu F. *PBPK Modeling to Predict the Effect of Gastric pH on Bioequivalence of Palbociclib Tablets*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 28, 2025.

Moore A, Li K, Shon J, Kim MJ, and Nguyen D. *Impact of Risk Evaluation and Mitigation Strategy Programs on Product-Specific Guidance for Generic Drug Development*. Poster Presentation at the 2025 American Society for Clinical Pharmacology and Therapeutics (ASCPT). Washington DC, May 28, 2025.

Pal A, Ren P, Zhang Y, Fang L, Zhao L, and Wu F. *PBPK Modeling to Support the Expansion of Biowaiver to Non-Q1/Q2 BCS Class III Drug Products*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 28, 2025.

Badge S, Hossain M, Boyce H, Kim M, and Al-Ghabeish M. *Ethanol Solubility of Rate Controlling Polymer in Modified Release Formulation Can Impact Alcohol Dose Dumping: An Assessment Through Principal Component Analysis*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Zhao G, Wei K, Nguyen D, Lim H, Rege B, Lu D, and Zhang Q. *FDA Perspective on Dissolution Testing for Development of High-Risk Oral Drug Products Containing Amorphous Solid Dispersions*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Chang Y, Zhao G, Nguyen D, Zhang Q, and Lim H. *A Literature Review on the Performance of Tiny Tract for In Vitro Modeling (tiny-TIM) to Predict Food-Drug and pH-Dependent Drug-Drug Interaction Risks*. Presentation at the American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting. Phoenix, AZ, Oct. 14, 2024.

## Presentations

Zhang L, Tampal N, and Raines K. *Navigating the Draft ICH M13B Additional Strengths Biowaiver Guideline*. Presentation at the ICH M13B Webinar 2025. Silver Spring, MD, Sep. 11, 2025.

Zhang L. *ICH M13 Guideline Series*. Presentation at the 3rd Bioequivalence Conference 2025. Amsterdam, The Netherlands, Feb. 26, 2025.

Tan, M-L. *PBPK Modeling to Predict Drug-Drug Interactions between Omeprazole and Extended-Release Nifedipine*. Presentation at the Simcyp Scientific Webinar Series. Virtual Meeting, Nov. 26, 2024.

Zhang L, Tampal N, and Kim M. M13A: *Bioequivalence for Immediate-Release Solid Oral Dosage Forms – Implementing the Final Guidance*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms - Implementing the Final Guidance. Virtual Meeting, Nov. 21, 2024.

Wu F. *Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Examples*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence

Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

Zhang Q, Managing Bioequivalence Risks for Nitrosamine Impacted Drug Products Containing BCS IV Drug Substances. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

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# 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, MIE-based strategies are being actively researched to develop more efficient in vivo pharmacokinetic (PK) BE study designs for long-acting injectable, insertable, or implantable (collectively, LAI) products that include reducing the study duration by assessing BE at non-steady-state conditions (also refer to Chapter 3 – subsection on "Long-Acting Injectable, Insert-

[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 five years from FY 2023 through FY 2027 (GDUFA III).

able, 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 the demonstration of BE for these products. Research during fiscal year (FY) 2025 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 2025 Activities

**In FY 2025, external research supported by multiple grants and contracts, significantly advanced the development of mechanistic modeling and simulation approaches for non-orally administered drug products that include, but are not limited to, ophthalmic, orally inhaled, nasal, LAI drug products, and products applied on the skin. In alignment with the FY 2025 research priorities and the regulatory landscape for complex, non-orally administered generics, research focused on developing novel and enhancing existing in silico tools such as physiologically based pharmacokinetic (PBPK) and computational fluid dynamics (CFD) models and other semi-mechanistic models, that integrate drug product quality attributes, device characteristics, and human physiology information. These model capabilities allow for building mechanistic in vitro-in vivo correlations/relationships (IVIVCs/IVIVRs) that when applied can limit the need for human testing via conducting virtual bioequivalence (VBE) assessments. Ultimately, these mechanism-based methodologies and tools can serve as MIE approaches that support drug product program development decision-making and address lifecycle management questions for non-orally administered drug products. Internally, the FDA continued to leverage mechanistic modeling to support the development of product-specific guidances (PSGs) and regulatory decision-making at the pre- and post-market space for non-orally administered drug products.**

For orally inhaled drug products (OIDPs), research focused on advancements in CFD regional deposition and PBPK models. An internal CFD model was constructed to predict and validate spray velocity and plume geometry of a suspension-based meter dose inhaler (MDI) drug product,[2] and development continued for two new CFD regional deposition models for solution-based MDIs in support of Grant U01FD007353. The results of an in vivo single photon emission computed tomography (SPECT)/computed tomography (CT) study conducted in support of Grant U01FD005837 were published,[3] providing a deposition modeling validation data set and illuminating intersubject variability of ventilation for asthmatic patients. Concurrently, work continued for an in vivo nuclear imaging study under Grant U01FD007987. For Contract 75F40122C00182, in vitro lung cell permeability assays were used with two versions of an existing state-of-the-art PBPK model to predict in vivo PK for tobramycin and fluticasone propionate, where results

[2] Sul B, Babiskin A, and Walenga R. *Computational Fluid Dynamics Model Validation of Spray Characteristics from a Suspension-Based Pressurized Metered-Dose Inhaler*. Poster Presentation at the International Society for Aerosols in Medicine (ISAM) Congress 2025. College Park, MD, Jun. 22, 2025.

[3] Zhang X, Rajaraman P, Li F, Choi S, Comellas A, Hoffman E, Fain S, Kaczka D, Smith B, Choi J, Castro M, Wenzel S, Jarjour N, Schiebler M, Israel E, Levy B, Fahy J, Erzurum S, Babiskin A, Kinjo M, Walenga R, and Lin C. *Assessment of Ventilation Heterogeneity and Particle Deposition in Asthmatics using Combined SPECT/CT Imaging and Computational Modeling Approaches*. European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences. (2025) 209: 107093. https://doi.org/10.1016/j.ejps.2025.107093. PMID: 40185289. PMCID: PMC12145795.

showed improved model performance with the enhanced physiology model inputs[4]. Work continued on developing population pharmacokinetics (PK) and PBPK models under Grant U01FD007936 that are intended to elucidate potential connections between systemic PK and regional lung drug delivery.

Research for nasal drug products focused on combining CFD and PBPK to simultaneously predict deposition and PK as well as advances in nose-to-brain PBPK modeling. An internal CFD-PBPK model was used to predict nasal absorption of oxycodone following insufflation of manipulated oxycodone hydrochloride formulations, which emphasized the impact of residence time and dissolution on PK for those products[5]. For nose-to-brain drug delivery, further progress was made on the PBPK model supported by Grant U01FD007657 as well as supporting in vivo PK studies. Also, within the scope of Grant U01FD007657, a review paper was published examining the current state of nose-to-brain PBPK modeling and identified future directions for model development[6].

The research related to ophthalmic drug products focused on developing a combined CFD and PBPK modeling framework, supported by in vitro drug release and characterization data of formulation variants and ex vivo measurements of tissue permeability (Contract 75F40123C00072). Ex vivo cornea and conjunctiva permeability of formulation variants under different dissolution media were studied. The permeability measurements were incorporated into mechanistic models used for VBE assessments for ophthalmic products. Under Contract HHSF223201810151C (completed in FY 2022), a quasi-3D mechanistic model predicting eye drop distribution in the human tear film was developed and published[7]. The model showed improved exposure predictions when coupled with a PBPK model. Another noteworthy case study under Grant U01FD006927 (completed in FY 2024) was a model-based interspecies extrapolation performed for ophthalmic ointments[8]. Clinical predictions of local bioavailability for ophthalmic ointments, based on drug product quality attributes, were extrapolated from validated rabbit PBPK models to inform human predictions while accounting for interspecies differences of anatomy and physiology.

For products intended to be applied on the skin, research under ongoing Grants U01FD007954 and U01FD007957 and completed Grant U01FD007323 focused on designing and performing studies (i.e., in vitro permeation testing (IVPT) and physicochemical and structural (Q3) characterization studies) for marketed topical products and their formulation variants that describe the impact of metamorphosis and of absorbed inactive ingredients on skin permeation for the studied active pharmaceutical ingredients (APIs). Informed by these studies, novel model enhancements provided improved model predictions of bioavailability and bioequivalence assessments in the generic space. Research completed under Grant U01FD007323 demonstrated that PBPK models sensitive to Q3 attributes can be used to optimize IVPT study design[9]. This research resulted in a semi-mechanistic framework for assessing the impact

[4] Mullin J, Le Merdy M, Chopski S, Walenga R, Bielski E, Boc S, Clerman A, Newman B, Pineiro-Llanes J, Eltanameli B, and Cristofoletti R. *Enhanced PBPK-Based In Vitro to In Vivo Extrapolation Method to Support the Development of Pulmonary Drug Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

[5] Walenga RL, Babiskin AH, Boyce HJ, Feng X, Zidan A, Kamal NS, Xu X, Kim MJ, and Zhao L. *Nasal Absorption of Oxycodone Predicted Using a Novel Computational Fluid Dynamics-Physiologically Based Pharmacokinetic Model*. Journal of Controlled Release. (2025) 378: 982-996. https://doi.org/10.1016/j.jconrel.2024.12.049. PMID: 39722305.

[6] Rezaee S, Al-Majdoub ZM, Galetin A, Rostami-Hodjegan A, and Ogungbenro K. *Challenges and Opportunities for Incorporating Physiological Information into Pharmacokinetic Models of Intranasal Drug Delivery to the Brain: A Review of the Current Status and Future Trajectories*. Molecular Pharmaceutics. (2025) 22(7): 3563-3577. https://doi.org/10.1021/acs.molpharmaceut.5c00297. PMID: 40524468.

[7] Garimella H T, Norris C, German C, Przekwas A, Walenga R, Babiskin A, Tan M-L. *Quasi-3D Mechanistic Model for Predicting Eye Drop Distribution in the Human Tear Film*. Bioengineering. (2025) 12(8):825. https://doi.org/10.3390/bioengineering12080825. PMID: 40868337. PMCID: PMC12383929.

[8] Le Merdy M, Tan M-L, and Lukacova V, *Clinical Ocular Exposure Extrapolation for an Ophthalmic Ointment Using PBPK Modeling and Simulation*. AAPS Journal. (2025) 27:150. https://doi.org/10.1208/s12248-025-01138-2. PMID: 39065612.

[9] Zhang Y, Murthy N, Rangappa S, Paterson D, Polak S, Dancik Y, Tsakalozou E, Ghosh P, and Clarke J. *Application of PBPK Modelling to Optimize IVPT Study Design and Predict the Impact of Formulation Changes on Skin Permeation*. Poster Presentation at the Skin

of inactive ingredients such as propylene glycol, on skin permeation of APIs from topical dermatological drug products[10]. Noteworthy research funded by FDA's generic drug research program and specifically Grant U01FD006522, involved a mechanistic skin absorption model which allows for accurate predictions of lidocaine/prilocaine skin absorption following the application of the EMLA® cream (lidocaine/prilocaine topical cream, 2.5%/2.5%) and other formulation variants on the skin of virtual subjects while considering the Q3 product attributes and relevant IVPT study data. A description of this research can also be found in **Chapter 4 "Complex Routes of Delivery"**, and, specifically in subsection 4 describing **"Topical Products"**.

Under Contract 75F40119C10139, the development of a system-based multi-scale model for the nanoparticle drug liposomal doxorubicin was completed. This model assessed target site bioavailability by accounting for specific nanoparticle characteristics. Under Contract 75F40121C00133, several PBPK model-informed mechanistic in vitro-in vivo correlations (IVIVCs) were developed for medroxyprogesterone acetate[11], paliperidone palmitate[12], and aripiprazole lauroxil[13] LAI suspension drug products. These validated mechanistic IVIVCs may support efficient alternative BE approaches that minimize dependence on expensive and time-intensive in vivo bioequivalence trials (see Research Highlight below for more information). Ongoing research for Grant U01FD008304 aimed to examine the intricate relationships between physicochemical characteristics of Q1/Q2[14] same LAI formulations and local tissue physiology. The effect of API particle size distribution, the potential for agglomeration in vivo, and the impact of the manufacturing processes such as particle size reduction techniques (i.e., jet milling, wet media milling, and antisolvent recrystallization) on in vitro drug release behavior were studied. Comprehensive characterization of Q1/Q2 variants of Depo Provera 150 revealed that agglomeration behavior and surface area are determinants of drug release, with some larger particle formulations showing unexpectedly faster release due to loosely bound agglomerates. Under Grant U01FD008303, comprehensive in vitro characterization of selected injectable poly(lactic-co-glycolic acid) (PLGA) implants offered new insights on how formulation quality attributes impact local and systemic drug exposure in animal models. These research outcomes enhanced an, under development, PLGA implant in silico model that can now describe in vitro study conditions and in vivo scenarios, such as local tissue metabolism.

## Research Highlight

Research under Contract 75F40121C00133 established a preclinical IVIVR in the rat and an IVIVC in the human by linking in vivo and in vitro dissolution profiles of paliperidone palmitate LAI suspensions[15]. These IVIVRs/Cs

Forum 2025. Berlin, Germany. Jun. 23, 2025.

[10] Maciel Tabosa A, Dancik Y, Thakur K, Zhang Y, Rangappa S, Murthy S, Tsakalozou E, Ghosh P, Polak S, and Clarke J. *Mechanistic Physiologically-Based Pharmacokinetic Modelling of Skin Permeation of Propylene Glycol from Clobetasol Propionate Cream Formulations with Variable Propylene Glycol Content*. Poster Presentation at the Gordon Research Conference on Barrier Function of Mammalian Skin, 2025. Waterville Valley, NH. Aug 10, 2025.

[11] 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.

[12] Silva DA, Lukacova V, Alam K, Tsakalozou E, and Al Abdullah S. *Physiologically Based Pharmacokinetic Modeling and Mechanistic In Vitro-In Vivo Correlation for Long-Acting Injectable Suspension*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting and Exposition. Philadelphia, PA. Jul. 18, 2025.

[13] Silva DA, Malavia N, Burgess DJ, 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). Orlando, FL, Oct. 22, 2023.

[14] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product. Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

[15] Silva DA, Lukacova V, Alam K, Tsakalozou E, and Al Abdullah S. *Physiologically Based Pharmacokinetic Modeling and Mechanistic In Vitro-In Vivo Correlation for Long-Acting Injectable Suspension*. Poster Presentation at the Controlled Release Society (CRS) Annual meeting and Exposition. Philadelphia, PA. Jul. 18, 2025.

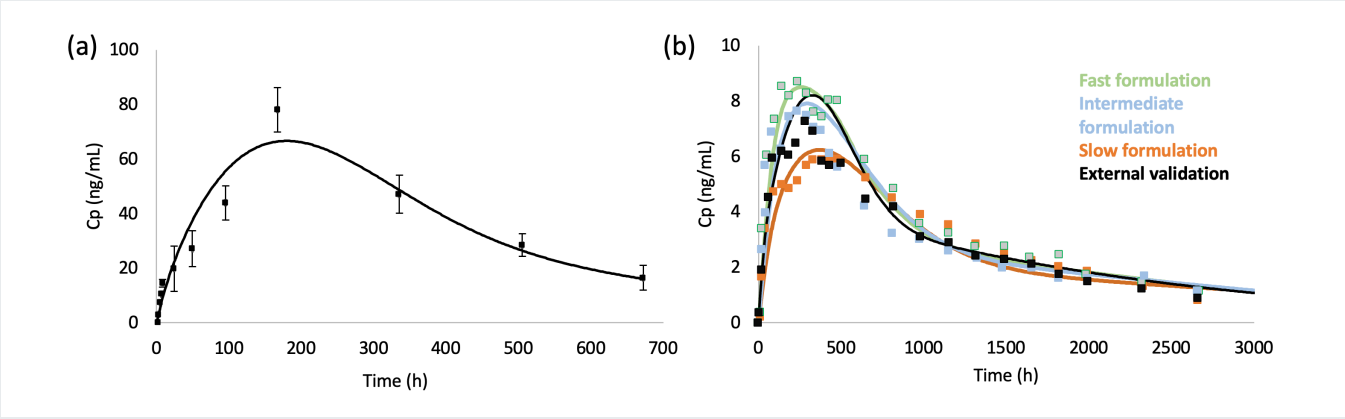


**Figure 1:** Comparison of observed[16] versus predicted plasma concentration (Cp) profiles for paliperidone palmitate once-monthly LAI suspension following intramuscular administration. Panel (A) shows preclinical IVIVR results in rats (n=4), while panel (B) demonstrates IVIVC outcomes in humans using a time scaling approach. In vitro dissolution and clinical PK data from an independent formulation with intermediate particle size were used for external validation. Data points (squares) represent observed mean concentrations; error bars are standard deviations; solid lines indicate model predictions.

The workflow developed during this research demonstrates the utility of PBPK model-based mechanistic IVIVCs for understanding LAI suspension behavior by predicting formulation-specific performance. This approach addresses the challenging nature of developing complex generic LAIs and provides a foundation for regulatory science applications for LAI drug products. This methodology, developed by the FDA's generic drug research program, paves the way for an MIE-based BE approach for LAI suspensions and dramatically improves the feasibility of developing these complex generic products.

were based on validated mechanistic LAI PBPK models that leveraged mechanistic deconvolution methods to predict in vivo dissolution profiles in both rat and human models. The human IVIVC was developed using in vitro and corresponding clinical PK profiles obtained for a fast, intermediate, and slow releasing paliperidone palmitate LAI suspension. A time scaling approach successfully predicted the plasma concentrations for both species based on in vitro dissolution profiles (**Figure 1**), with prediction errors for Cmax and AUC ranging from 0.6% to 14.6% in the rat model and from 3.46% to 12.8% in the human IVIVC. The preclinical IVIVR in the rat was successfully used to inform the mechanistic IVIVC in humans, demonstrating the translational value of the approach.

# Research Projects and Collaborations

### Continuing Grants and Contracts

- 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

[16] NDA 022264. *Clinical Pharmacology and Biopharmaceutics Review(s)*. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf.

Commonwealth University

- Grant (U01FD008303) *Developing PBPK-Model based Mechanistic IVIVC for PLGA Implants* With Feng Zhang at University of Texas at Austin

- 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 (U01FD008304) *Development of PBPK Model-Based Mechanistic IVIVCs for Long-Acting Injectable Suspensions* with Diane Burgess at University of Connecticut

- 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 Bernd Bulitta at University of Florida

- 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 (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

- 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 (75F40123C00072) *A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs* with Carrie German at CFD Research Corporation

### Completed 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 (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 (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

### Active FDA Research

- *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways*

- *CFD Analysis of Spreadability of Topical Formulations*

- *CFD and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*

- *CFD Models of Soft Mist Inhalers*

- *Development of PBPK/PD Modeling Approaches for Ophthalmic Drug Products*

- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*
- *Development of PBPK Modeling and Simulation Approaches for LAI Suspension Drug Products*
- *Informing Design and Developing Best Practices for Virtual Bioequivalence Trials Conducted Using Physiologically Based Pharmacokinetic Modeling Approaches*
- *Nasal PBPK Modeling of Suspension-based Nasal Sprays*

## Outcomes

### Product-Specific Guidances

There were three new and nine revised PSGs published in FY 2025 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.

- *New Draft Guidance for Albuterol Sulfate; Budesonide*. (May 20, 2025) Link to Posting
- *New Draft Guidance for Budesonide; Formoterol Fumarate*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Budesonide; Formoterol Fumarate Dihydrate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Epinephrine Aerosol, Metered*. (May 20, 2025) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Fluticasone Propionate; Salmeterol Xinafoate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Formoterol Fumarate; Mometasone Furoate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Formoterol Fumarate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Mometasone Furoate Aerosol, Metered*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Salmeterol Xinafoate Powder*. (Nov. 19, 2024) Link to Posting
- *Revised Draft Guidance for Tiotropium Bromide Powder*. (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Treprostinil Powder*. (Nov. 19, 2024) Link to Posting

### Publications


Chopski S, Walenga RL, Tan M-L, Alam K, Babiskin A, Fang L, and Tsakalozou E. *Impact of Mechanistic Modeling and Simulation Methodologies on Product Specific Guidance Development for Non-Orally Administered Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2025) 14(9):1421-1430. https://doi.org/10.1002/psp4.70078. PMID: 40704493.

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### Posters

Fallon J, Cholon D, Boyles s, Tiley J, Smith P, Rao G, Gentzsch M, Tan M-L, Zhao L, and Esther C Jr. *Effect of Inflammation on Drug Transporter Concentrations in Human Airway Epithelia Measured by Quantitative Targeted Absolute Proteomics*. Poster Presentation at the 14th International ISSX Meeting. Chicago, IL, Sept. 21, 2025.

Sharkawy A, Jamaledin R, Williams AC, Bunge AL, Guy RH, Pettarin M, Spires J, Ghosh P, Tsakalozou E, and Delgado-Charro MB. *Impact of Topical Product Metamorphosis on Absorption of Metronidazole*. Poster Presentation at the Gordon Research Conference on Barrier Function of Mammalian Skin, 2025. Waterville Valley, NH, Aug 11, 2025.

Maciel Tabosa A, Dancik Y, Thakur K, Zhang Y, Rangappa S, Murthy S, Tsakalozou E, Ghosh P, Polak S, and Clarke J. *Mechanistic Physiologically-Based Pharmacokinetic Modelling of Skin Permeation of Propylene*

*Glycol from Clobetasol Propionate Cream Formulations with variable Propylene Glycol Content*. Poster Presentation at the Gordon Research Conference on Barrier Function of Mammalian Skin, 2025. Waterville Valley, NH, Aug 10, 2025.

Silva DA, Lukacova V, Alam K, Tsakalozou E, and Al Abdullah S. *Physiologically Based Pharmacokinetic Modeling and Mechanistic In Vitro-In Vivo Correlation for Long-Acting Injectable Suspension*. Poster presentation at the Controlled Release Society (CRS) Annual meeting and Exposition. Philadelphia, PA, Jul. 18, 2025.

Zhang Y, Murthy N, Rangappa S, Paterson D, Polak S, Dancik Y, Tsakalozou E, Ghosh P, and Clarke J. *Application of PBPK Modelling to Optimize IVPT Study Design and Predict the Impact of Formulation Changes on Skin Permeation*. Poster Presentation at the Skin Forum 2025. Berlin, Germany, Jun. 24, 2025.

Chopski S, Babiskin A, Newman B, Dhapare S, Boc S, Kakhi M, and Walenga R. *Quantitative Studies to Inform PSG Development for Tiotropium Bromide Inhalation Spray, Metered*. Poster Presentation at the International Society for Aerosols in Medicine (ISAM) Congress 2025. College Park, MD, Jun. 22, 2025.

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Craig J, Morris NM, McNally K, Corpstein C, Telaprolu KC, Bogdanovich P, Turner DB, Rostami-Hodjegan A, Jamei M, and Bois FY. *Pirana–Simcyp Virtual Bioequivalence (VBE) Workflow: Software Demonstration and Case Study on Paliperidone Palmitate Long-Acting Injectables*. Poster Presentation at the Population Approach Group in Europe (PAGE) at 33rd meeting. Thessaloniki, Greece, Jun. 6, 2025.

Le Merdy M, Mullin J, Tan M-L, and Lukacova V. *Predicting Brinzolamide Ocular Response in Humans Using an Ocular PBPK-PD Modeling and Simulation*. Poster Presentation at the AAPS 2025 annual meeting. Washington, DC, May 28, 2025.

Novakovic J, van Osdol WW, Spires J, Le Merdy M, Tsakalozou E, Ghosh P, and Lukacova V. *Dermal Drug Distribution in Normal and Psoriatic Skin Assessed in Silico via PBPK Modeling and Simulations*. Poster Presentation at the 2025 Canadian Society for Pharmaceutical Sciences, Annual Symposium. Montreal, Canada, May 28, 2025.

Sharkawy A, Williams A, Bunge A, Guy R, Ghosh P, Van Osdol W, Novakovic J, Pettarin M, Spires J, Le Merdy M, Tsakalozou E, and Delgado-Charro M. *Topical Product Metamorphosis: Impact on Metronidazole In Vitro Skin Permeation Post-Application of Binary Mixture Formulations*. Poster Presentation at the 2024 Skin@Bath Conference. Bath, UK, Dec. 05, 2024.

Mullin J, Le Merdy M, Chopski S, Walenga R, Bielski E, Boc S, Clerman A, Newman B, Pineiro-Llanes J, Eltanameli B, and Cristofoletti R. *Enhanced PBPK-Based In Vitro to In Vivo Extrapolation Method to Support the Development of Pulmonary Drug Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

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Schroeter J, Garcia G, Rose M, Kimbell J, and Walenga R. *A Hybrid CFD-PBPK Approach to Simulate Deposition, Absorption, and Bioavailability of Corticosteroid Nasal Sprays*. Poster Presentation at the Fourth Aerosol

Dosimetry Conference – Inhaled Aerosol Dosimetry: Advances, Applications, and Impacts on Risk Assessments and Therapeutics. Irvine, CA, Oct. 16, 2024.

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Clarke JF. *Formulations in Flux: Simulating the Effect of Dynamic Formulation Composition Changes Following Application of Complex Topical Drug Products*. Presentation at Seminar Series - American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Community. Virtual, Jul. 25, 2025.

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Fang L. *Introduction and Overview of the Model Master File*. Presentation at the Small Business & Industry Assistance (SBIA) Webinar on Model Master Files: Advancing Modeling and Simulation in Generic Drug Development and Regulatory Submissions. Virtual Meeting, Mar. 13, 2025.

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Fang L. *The Development and Framework of MMF as a Regulatory Initiative*. Presentation at Physiologically Based Biopharmaceutics Modelling (PBBM) Conference on Best Scientific Practices to Define Drug Product Performance: Latest Regulatory and Industry Perspectives. London, England, Nov. 8, 2024.

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Bois FY. *Virtual Bioequivalence Frameworks and Workflows*. Presentation at the American Association of Pharmaceutical Scientists (AAPS). Salt Lake City, Utah, Oct. 23, 2024.

Roy K. *A Modeling Approach to Predict Pharmacokinetic Endpoints of Sunscreen Products*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Wang Y. *Role of GDUFA Research on Resolving Technical and Regulatory Challenges for Complex Generic Drug Development and Approval*. Presentation at the 2024 Association for Affordable Medicines (AAM): GRx + Biosims Conference. Rockville, MD, Oct. 22, 2024.

Garcia, Wu J, Bennett W, Kimbell J, and Schroeter J. *Validation of Computational Fluid Dynamics Simulations of Nasal Sprays with Regional Doses Measured by Gamma Scintigraphy*. Presentation at the Aerosol Dosimetry Conference. Irvine, CA, Oct. 16, 2024.

Walenga R. *In Silico Modeling to Support Development and Approval of Generic Orally Inhaled Drug Products in the United States*. Presentation at the Fourth Aerosol Dosimetry Conference – Inhaled Aerosol Dosimetry: Advances, Applications, and Impacts on Risk Assessments and Therapeutics. Irvine, CA, Oct. 16, 2024.

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# Oral Absorption Models and Bioequivalence

## Summary of FY 2025 Activities

**In FY 2025, the internal (FDA) and external (grant and contract) research projects related to oral absorption models for bioequivalence (BE) assessment encompassed three scientific areas. The first area evaluated the utility of in vitro biopredictive testing and physiologically based pharmacokinetic (PBPK) modeling to support an assessment of BE under fed conditions, or under conditions with elevated gastric pH, for immediate-release (IR) oral products including amorphous solid dispersion (ASD) products. The second area focused on exploring the utility of in vitro biopredictive testing and PBPK modeling for modified-release (MR) oral, buccal, and sublingual drug products. The third research area focused on enhancing the capabilities of PBPK oral absorption modeling and on establishing best practices for virtual BE study designs.**

In the area of the utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions, one research initiative studies how PBPK models could help assess the impact of food on BE evaluations for 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. 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 Biopharmaceutics Classification System (BCS) Class II drugs. In FY 2025, this grant published a research paper[17], summarizing the method and framework for generating in vitro biopharmaceutics data to be incorporated into PBPK models to predict food impact on the BE of ASD products including Sempera® and Tolsura® (see **Research Highlight** for more details). The grant also supported a project that investigated the use of an in vitro lipolysis model to predict positive food effects of poorly water-soluble drugs including rivaroxaban, itraconazole, and ritonavir - using Fe-lipolysis (fed state) and Fa-lipolysis (fasted state) media to simulate intestinal conditions during lipid digestion. The underlying hypothesis is that partially hydrolyzed lipids from food enhance drug solubilization through mixed micelles, leading to increased dissolution and absorption. Research results showed a strong concordance between in vitro predictions and in vivo human outcomes for rivaroxaban and itraconazole formulations: the lipolysis in vitro testing model correctly predicted rivaroxaban's dose-dependent food effect and itraconazole's formulation-dependent effects (positive for Sporanox-like formulations, none for Tolsura). However, the model failed to predict the negative food effect of ritonavir products (Norvir tablet and powder), instead showing false positive predictions. The lipolysis model demonstrated promise as a screening tool for anticipating positive food effects during drug development, further refinement is needed for complex formulations like amorphous solid dispersions that exhibit negative food effects[18].

[17] Rudolph N, Charbe N, Plano D, Shoyaib AA, Pal A, Boyce H, Zhao L, Wu F, Polli J, Dressman J, and Cristofoletti R. *A Physiologically Based Biopharmaceutics Modeling (PBBM) Framework for Characterizing Formulation-Dependent Food Effects: Paving the Road towards Fed State Virtual BE Studies for Itraconazole Amorphous Solid Dispersions*. European Journal of Pharmaceutical Sciences. (2025) 209:107047. https://doi.org/10.1016/j.ejps.2025.107047. PMID: 39983931.

[18] 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.

An internal research project was conducted to address concerns about reduced palbociclib efficacy when taken with acid-reducing agents (ARAs), which increase gastric pH and reduce drug solubility for this BCS Class II weak base compound. The project developed and validated PBPK models for three conditions: fasting, fasting with ARA co-administration, and fed states. The validated models support the FDA's product-specific guidance recommendation for additional BE studies with ARAs for generic palbociclib tablets, and provide a tool to assess whether generic formulations maintain BE under various gastric pH conditions that patients may experience in clinical settings.

In the area of exploration of in vitro biopredictive testing and using PBPK modeling for MR products, Grant U01FD007959 aimed to identify critical quality attributes (CQAs) and design features of MR products, and to determine the appropriate factors for developing additional strengths (scaling factors) for MR tablet formulations. In FY 2025, the work identified formulation variables affecting drug release mechanisms and formulation design spaces for hydroxypropyl methylcellulose (HPMC) matrix-based extended release (ER) tablets across multiple strengths. The marketed quetiapine fumarate (QF) ER tablet was chosen as the model product. In-house QF ER tablets were designed using Quality-by-Design approach to explore the key formulation variables (e.g., HPMC amount and ratio of different grades of HPMC) and their interactions on in vitro QF release characteristics. The result provided insights into the impact of key formulation variables on the in vitro QF release characteristics. Safe formulation design spaces were identified across strengths to ensure dissolution similarity factor (f2) values compared to the respective reference listed drug products. This result will be further used to develop physiologically based biopharmaceutics modeling (PBBM)-PBPK models to link the in vitro dissolution behavior to in vivo performance, which identifies appropriate factors to scale the formulation for additional strengths. The result of this study can determine acceptable formulation design spaces for future matrix-based ER tablets development across strengths. Details can also be referred to **Chapter 6**.

For Contract 75F40120C00200, this project measured in vivo drug release behaviors of two glipizide ER tablet products with different release mechanism across various gastrointestinal tract regions using an incubation tube and analyzed drug concentration in plasma. The collected data will be used to establish modeling to elucidate how in vitro differences may be associated with variable absorption in vivo. These findings can elucidate the relationship between in vitro performance and in vivo behavior for products with different release mechanisms but comparable pharmacokinetic performance.

Under Contract 75F40120C00150, a mechanistic PBPK modeling approach was used for in vitro-in vivo extrapolation (IVIVE) of oral cavity permeability for buccal and sublingual drug products. These models integrated in vitro permeability data, dissolution and absorption data generated from the innovative Dynamic In Vitro Dissolution and Absorption Model under physiological conditions, along with clinical pharmacokinetic data from selected oral cavity products.

Another research initiative is related to studying how oral absorption modeling could be enhanced. In FY 2025, research under Grant U01FD007906 involved the development of PBBM on several oral dosage forms such as IR and ER metformin tablets. The developed case studies were leveraged towards the development of "best practices" on model building and validation when these models will be applied for virtual BE (VBE) assessments. Grant U01FD007904 has developed mechanistic PBPK models for selected oral drug products as well as some injectables. The team has developed a VBE workflow addressing key questions for model-based BE approaches, including methodologies for power analysis-based sample size calculations, safe space estimation for formulation CQA(s), and type-1 error calculations.

xphs.2024.04.007 PMID: 38614321.

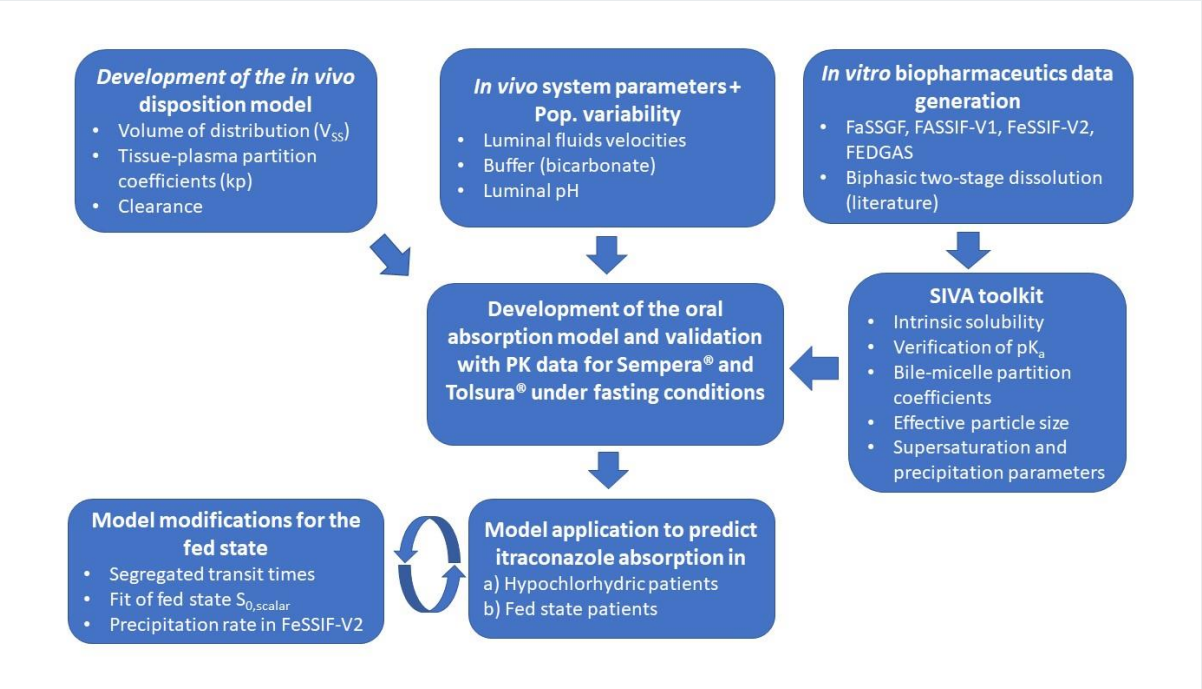


**Figure 1.** Schematic workflow applied for the model development of itraconazole, as well as its validation and application. Abbreviations: FaSSGF, Fasted State Simulated Gastric Fluid; FASSIF, Fasted State Simulated Intestinal Fluid; FeSSIF, Fed State Simulated Intestinal Fluid; FEDGAS, Fed Gastric Fluid Dissolution Media.

## Research Highlight

The study supported by Grant U01FD007352 presents a comprehensive PBBM framework to predict formulation-dependent food effects for two itraconazole ASD products: Sempera® and Tolsura®, which show distinct food effect[19]. The research conducted extensive in vitro biopharmaceutical testing under fasted and fed conditions, revealing significant differences in dissolution behaviors between the two formulations. Using a stepwise mechanistic deconvolution-reconvolution PBBM approach in Simcyp, the research successfully predicted that Sempera® (a hypromellose-based ASD) exhibits a positive food effect while Tolsura® (containing microencapsulated amorphous nanoparticles in a hypromellose phthalate matrix) shows a negative food effect. The PBBM captured between-subject variability and predicted the impact of acid-reducing agents and hypochlorhydria on drug absorption. The research demonstrates the potential of PBBM to predict formulation-dependent food impact on PK, streamline BE assessment of generic formulations under varying physiological conditions, potentially reducing the need for clinical fed BE studies and supporting more informed regulatory decision-making for generic drug development.

[19] Rudolph N, Charbe N, Plano D, Shoyaib AA, Pal A, Boyce H, Zhao L, Wu F, Polli J, Dressman J, and Cristofoletti R. *A Physiologically Based Biopharmaceutics Modeling (PBBM) Framework for Characterizing Formulation-Dependent Food Effects: Paving the Road towards Fed State Virtual BE Studies for Itraconazole Amorphous Solid Dispersions*. European Journal of Pharmaceutical Sciences. (2025) 209:107047. https://doi.org/10.1016/j.ejps.2025.107047. PMID: 39983931.

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

- 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 (U01FD008388) *From Bench to Bioequivalence: In Vitro Mechanistic Understanding of ASD Drug Products in Simulated Gastrointestinal Conditions* with Maxime Le Merdy at Simulations Plus, Inc.

### 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

- 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

### 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 BCS Class-III Generic Drug Products*

- *Informing Design and Developing Best Practices for Virtual Bioequivalence Trials Conducted Using Physiologically-Based Pharmacokinetic Modeling Approaches*

# Outcomes

### Product-Specific Guidances

There was one revised PSG published in FY 2025 related to *Oral Absorption Models and Bioequivalence*. The PSG listed below was directly impacted by GDUFA - funded research in this area.

- *Revised Draft Guidance for Olaparib, Tablet* (Nov. 19, 2024) Link to Posting

### Publications


Cheng Y, Thomas S, Tsang Y, Almeida S, Ashraf M, Fotaki N, Heimbach T, Patel N, Shah H, Jiang X, Kim M, Moody R, Rostami-Hodjegan A, Singh R, Zhao L, Babiskin A, and Wu F. *Advances in Physiologically Based Pharmacokinetic (PBPK) Modeling and its Regulatory Utility to Support Oral Drug Product Development and Harmonization*. Pharmaceutical Research. (2025) 42:819-833. https://doi.org/10.1007/s11095-025-03849-9. PMID: 40155500. PMCID: 12158835.

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Li T, Felton J, Lewis J, Cheng Q, Meredith R, Lu HT, Benken A, Dutta PP, Liao J, Zhao XD, Matvekas A, Baker J, Hasler WL, Babiskin A, Walenga R, Fang L, Lionberger R, Pal MP, Sun D, and Gianchandani YB. *An Ingestible Device for Automated Sampling and Location Tracing in Gastrointestinal Tract*. PLoS One. (2025) 20(7):e0327667. https://doi.org/10.1371/journal.pone.0327667. PMID: 40644523.

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Tannergren C, Arora S, Babiskin A, Borges L, Chatterjee P, Cheng Y, Dallmann A, Govada A, Heimbach T, Hingle M, Kollipara S, Kotsagiorgis E, Lindhal A, Mackie C, Malamatari M, Mitra A, Moody R, Pepin X, Polli J, Raines K, Rullo G, Sanghavi M, Savkur R, Singh R, Sjogren E, Suarez-Sharp S, Thomas S, Veerasingham S, Wei K, Wu F, Xu Y, Yoon M, and Rege B. *Current State and New Horizons in Applications of Physiologically Based Biopharmaceutics Modeling (PBBM): A Workshop Report*. Molecular Pharmaceutics. (2025) 22(1):5-27. https://doi.org/10.1021/acs.molpharmaceut.4c01148. PMID: 39680866. PMCID: 11707736.

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03846-y. PMID: 40140126. PMCID: 12158840.

### Posters

Martins F, Vora T, Fraczkiewircz G, Lukacova V, Varanasi K, Ribot O, Gomez L, Kanagasabapathy Y, Alam K, Tsakalozou E, Wu F, and Le Merdy M. *Physiologically Based Biopharmaceutics Modeling for Virtual Bioequivalence Assessment of Metformin Immediate and Extended-Release Formulations*. Poster Presentation at Population Approach Group Europe (PAGE) Annual Meeting. Thessaloniki, Greece, Jun. 6, 2025.

Cheng Y, Wu F, Mousa Y, Zhao L, and Fang L. *Assessment of the Impact of Non-comparable in vitro Alcohol Dose Dumping Release on Systemic Exposure Using PBPK Absorption Modeling for Topiramate Extended-release Capsules*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 29, 2025.

Jamil R, Babiskin A, Zhang L, Fang L, and Wu F. *PBPK Modeling to Predict the Effect of Gastric pH on Bioequivalence of Palbociclib Tablets*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 28, 2025.

Pal A, Ren P, Zhang Y, Fang L, Zhao L, and Wu F. *PBPK Modeling to Support the Expansion of Biowaiver to Non-Q1/Q2 BCS Class III Drug Products*. Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2025 Annual Meeting. Washington, DC, May 28, 2025.

Kalra P, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Pauletti G, and Zhou H. *Mechanistic Model of In Vitro Intraoral Absorption of Buprenorphine for the Buccal and Gingival Mucosa*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

Kalra P, Lukacova V, Dwivedi P, Khondoker A, Tsakalozou E, Pauletti G, and Zhou H. *Mechanistic In Vitro Oral Absorption Model to Predict Mucosal Permeability of Oral Cavity Drug Products*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

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Dwivedi P, Alam K, Tsakalozou E, Al Ghabeish M, and Pauletti G. *Formulation Effects of Marketed Oral Cavity Products on In Vitro Buccal Permeability*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

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### Presentations

Tan, M-L. *PBPK Modeling to Predict Drug-Drug Interactions between Omeprazole and Extended-Release Nifedipine*. Presentation at the Simcyp Scientific Webinar Series. Virtual Meeting, Nov. 26, 2024.

Wu F. *Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Examples*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products. Hybrid Meeting. Rockville, MD, Nov. 07, 2024.

Bois F. *Virtual Bioequivalence Frameworks and Workflows*. Presentation at American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

## Quantitative Clinical Pharmacology

# Summary of FY 2025 Activities

**During FY 2025, FDA continued to research and use quantitative clinical pharmacology approaches, along with model-integrated evidence (MIE), to develop innovative study designs and methods to support demonstrations of bioequivalence (BE). For example, FDA's research in this area directly supported a more efficient BE approach in two product-specific guidances (PSGs) for levonorgestrel intrauterine systems[20,21], recommending a shortened one-year in vivo/ex vivo BE study based on internal modeling and simulation work. Through modeling and simulation, FDA identified that this one-year study measuring residual levonorgestrel amounts with a tighter BE acceptance limit can serve as a surrogate for conventional three-year or five-year studies, substantially reducing the study duration and dramatically improving the feasibility of generic product development, while maintaining high standards of evidence to assure the BE of generic levonorgestrel intrauterine systems.**

Through internal research, FDA developed an alternative BE approach that enables bridging to the reference listed drug (RLD) with a different comparator when the RLD is discontinued and no reference standard (RS) is available. Again, FDA's research in this area directly supported updated information in a revised PSG for trazodone extended-release tablets[22], providing step-by-step statistical analysis recommendations using this methodology (see **Research Highlight** for details).

FDA is also developing innovative study designs for pharmacokinetics (PK) BE studies conducted in patients. Internal research is ongoing to evaluate reduced or sparse sampling schemes for BE studies for oncology products and alternative study designs to conventional steady-state BE studies that can shorten study durations. Additionally, internal research continues studying best practices for using MIE approaches in BE assessment, aiming to develop well-structured processes and support efficient implementation of such methodology.

In addition, FDA's external research collaborations continued advancing population PK modeling methods to develop alternative BE study designs and approaches. FDA continued collaborating with Uppsala University (Contract 75F40122C00139), which demonstrated the utility of population PK-based MIE for BE evaluation of drugs with high variability and/or long half-lives in incomplete washout designs. Additionally, Grant U01FD007936 with the University of Florida continued studying regional lung exposure from systemic PK data of generic orally inhaled drug products using population PK modeling methods. Preliminary results showed that partial area under the curve (pAUC) assessment

[20] *New Draft Guidance for Levonorgestrel Intrauterine Device* (Recommended May 2025); https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208224.pdf.

[21] *Revised Draft Guidance for Levonorgestrel Intrauterine System* (Recommended Apr 2014; Withdrawn Oct 2014; Revised Nov 2024); https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_203159.pdf.

[22] *Revised Draft Guidance for Trazodone Hydrochloride Tablet, Extended Release* (Recommended Jun 2011; Revised Sep 2012, Oct 2025); https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022411.pdf.

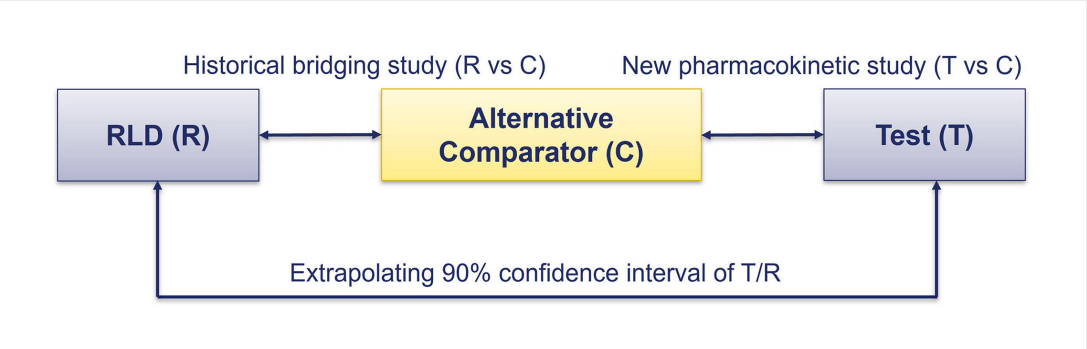


**Figure 1.** Schematic representation of extrapolation of pharmacokinetics bioequivalence to an alternative comparator

may capture differences in in vivo drug deposition for certain drugs and could potentially eliminate the need for charcoal block PK BE studies. This research outcome represents a major advance that can facilitate the development of numerous orally inhaled generic drug products that are otherwise very challenging to develop.

## Research Highlight

Through internal research, FDA has investigated a potential BE approach that allows bridging BE to RLD with an alternative comparator, such as a product with a different dosage form for the same route of administration. This methodology could provide a potential alternative BE approach for generic applicants developing products when the original RLD has been discontinued and there is no RS available on the market, ultimately supporting improved patient access to generic medications.

This potential alternative BE approach focuses on identifying relative PK differences between the RLD or test product compared to the alternative comparator. For this methodology, a study comparing the RLD and the alternative comparator is used to establish the relative PK difference between these products, such as through historical bridging studies conducted by the innovator from publicly available reviews or literature. With this foundational information, a generic applicant could perform a relative bioavailability study of their test product against the same alternative comparator using a similar design. Research efforts focused on cases where the RLD is not bioequivalent to the alternative comparator, as in such cases BE transitivity cannot be directly applied. As illustrated in **Figure 1**, by combining historical and new study data, the 90% confidence intervals for both the test product and RLD can be extrapolated based on their relative PK ratios compared to the alternative comparator. Bioequivalence is concluded when the extrapolated 90% confidence interval for the test-to-reference (T/R) ratio falls within the standard acceptance criteria of 80.00%-125.00%.

The research outcomes supported the PSG revision for trazodone extended-release tablets[23], with the revised guidance including step-by-step recommendations for statistical analysis using this alternative approach. This innovative research is enabling patient access to generic products that would otherwise have been unfeasible to develop.

## 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*

[23] The revised *Draft Guidance on Trazodone Hydrochloride* was published on October 1, 2025.

*Approaches* with Jürgen Bernd Bulitta at University of Florida

### Completed Grants and Contracts

- Contract (75F40122C00139) *Model-Integrated Strategies for Bioequivalence Evaluation of Drugs with High Variability and/or Long Half-Life* with Mats 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*
- *Informing Design and Developing Best Practices for Virtual Bioequivalence Trials Conducted Using Physiologically-Based Pharmacokinetic Modeling Approaches*
- *Model-based Assessment on Bioequivalence Limits for Anticoagulants*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-based Approach*

## Outcomes

### Product-Specific Guidances

There were two new and one revised PSGs published in FY 2025[24] 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 Epinephrine Nasal Spray* (May 20, 2025) Link to the Posting
- *New Draft Guidance for Levonorgestrel Intrauterine System* (NDA 208224) (May 20, 2025) Link to the Posting
- *Revised Draft Guidance for Levonorgestrel Intrauterine System* (NDA 203159) (Nov. 19, 2024) Link to the Posting

### Publications


Fang L, Tsakalozou E, Wu F, Ritterbeck D, Zhao L, Zhang L, and Lionberger R. *Adopting the Model Master File Framework to Enhance Modeling and Simulations Approaches for Regulatory Use*. Pharmaceutical Research. (2025) 42(5):731-735. https://doi.org/10.1007/s11095-025-03861-z. PMID: 40461748.

Gong Y, Hopefl R, Li T, Hooker A, Silva D, Alam K, Ducharme M, Moody R, Saha P, and Babiskin A. *Leveraging Model Master Files for Long-Acting Injectables*. Pharmaceutical Research. (2025) 42(5):747-752. https://doi.org/10.1007/s11095-025-03824-4. PMID: 39875758. PMCID: 12159082.

Hopefl R, Gong Y, Bielski E, Pillai V, Newman B, Qin B, Wang Y, Yoon M, Zhang Q, Stier E, Uppoor R, Zhu H, Zhang L, and Fang L. *A 2024 Update on US FDA Implementation of Partial Area Under the Curve into Bioavailability and Bioequivalence Assessments*. Clinical Pharmacology and Therapeutics. (2025) 117(5):1185-1193. https://doi.org/10.1002/cpt.3561. PMID: 39825841.

Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Exploration of the Potential Impact of Batch-to-Batch Variability on the Establishment of Pharmacokinetic Bioequivalence for Inhalation Powder Drug Products*. CPT: Pharmacometrics & Systems Pharmacology. (2024) 14(2):331-339. https://doi.org/10.1002/psp4.13276. PMID: 39575671. PMCID: 11812940.

Loingeville F, Rakez M, Thuy Nguyen T, Donnelly M, Fang L, Feng K, Zhao L, Grosser S, Sun G, Sun W, Mentré F, and Bertrand J. *Model-Based Approach for Two-Stage Group Sequential or Adaptive*


[24] The revised *Draft Guidance on Trazodone Hydrochloride* was published on October 1, 2025, which is the first day of FY 2026, and is therefore not included among the list of PSGs published in FY 2025 that were impacted by GDUFA-funded research.

*Designs in Bioequivalence Studies using Parallel and Crossover Designs*. Statistical Methods in Medical Research. (2025) 34(10):1968-1981. https://doi.org/10.1177/09622802251354925. PMID: 40653846.

Tsakalozou E, Fang L, Skoda E, Nicholas T, Kollipara S, Ren K, Grosser S, Rege B, Roy P, Zhu H, and Zhao L. *Considering Opportunities and Challenges When Implementing the Model Master File Framework – a Meeting Report*. Pharmaceutical Research. (2025) 42(5):737-746. https://doi.org/10.1007/s11095-025-03839-x. PMID: 40055245. PMCID: 12158848.

### Posters

Martins F, Vora T, Fraczkiewircz G, Lukacova V, Varanasi K, Ribot O, Gomez L, Kanagasabapathy Y, Alam K, Tsakalozou E, Wu F, and Le Merdy M. *Physiologically Based Biopharmaceutics Modeling for Virtual Bioequivalence Assessment of Metformin Immediate and Extended-Release Formulations*. Poster Presentation at Population Approach Group Europe (PAGE) Annual Meeting. Thessaloniki, Greece, Jun. 6, 2025.

### Presentations

Gong Y. *Considerations of Bioequivalence Studies for Long-Acting Injectables and the Application of Model-Integrated Evidence Approaches*. Presentation at the Scientists Advancing Affordable Medicines (SAAMnow) 2025 Spring Workshop. Virtual, Jun. 10, 2025.

Gong Y. *Enabling the Conduct of Patient Pharmacokinetics Bioequivalence Studies Using Model-Integrated Evidence*. Presentation at the Fiscal Year (FY) 2025 Generic Drug Science and Research Initiatives Public Workshop. Silver Spring, MD, Jun. 3, 2025.

Fang L. *Adopting the Model Master File Framework to Enhance Modeling and Simulations Approaches for Regulatory Use*. Presentation at American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting. Washington, DC, May 31, 2025.

Fang L. *Introduction and Overview of the Model Master File*. Presentation at the Small Business & Industry Assistance (SBIA) Webinar on Model Master Files: Advancing Modeling and Simulation in Generic Drug Development and Regulatory Submissions. Virtual Meeting, Mar. 13, 2025.

Tsakalozou E. *Model Master File: How to Develop and Submit One?* Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Model Master Files: Advancing Modeling and Simulation in Generic Drug Development and Regulatory Submissions. Virtual Meeting, Mar. 13, 2025.

Donnelly M. *Controlled Correspondence on Clinical Pharmacology Topics in Generic Drug Development*. Presentation at the Small Business and Industry Assistance (SBIA) Webinar on Navigating Controlled Correspondences to Support Generic Drug Development. Virtual Meeting, Feb. 27, 2025.

Fang L. *The Development and Framework of MMF as a Regulatory Initiative*. Presentation at Physiologically Based Biopharmaceutics Modelling (PBBM) Conference on Best Scientific Practices to Define Drug Product Performance: Latest Regulatory and Industry Perspectives. London, England, Nov. 8, 2024.

Bies R. *User Friendly Tools for Population PK and PBPK modeling*. Presentation at the 2024 American Conference on Pharmacometrics (ACoP 2024). Phoenix, AZ, Nov. 12, 2024.

Hooker A. *Development of a User-Friendly Platform for Model-Integrated Bioequivalence Analysis*. Presentation at the American Conference on Pharmacometrics (ACoP) Annual Conference. Phoenix, AZ, Nov. 12, 2024.

Fang L. *Regulatory Considerations in Development of Generic Long-Acting Injectable (LAI) Formulations for HIV Treatment and Prevention*. Presentation at the Advancing Access Planning for Long-Acting HIV Treatment in LMICs. Washington, DC, Oct. 24, 2024.

Bois F. *Virtual Bioequivalence Frameworks and Workflows*. Presentation at American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 23, 2024.

Feng K. *ANDA Challenges Related to Vasoconstrictor Studies*. Presentation at FDA Workshop on Guidance Development and Regulatory Assessment of Generic Topical and Dermal Drug Products. Virtual Meeting, Oct. 3, 2024.

8

# Data Analytics and 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 to improve the efficiency and consistency of FDA's 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) 2025 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 five years from FY 2023 through FY 2027 (GDUFA III).

## Summary of FY 2025 Activities

**During FY 2025 FDA engaged in research and development enabling AI to support the Agency's mission by strengthening data infrastructure and streamlining business workflows. This included using generative AI (GenAI) based on large language models (LLMs) to develop agentic AI automation tools to streamline complex workflows, such as determining the maximum daily dose (MDD) from drug labeling, and facilitating the construction of databases, such as pharmacokinetic (PK) data warehouses, to facilitate PK-focused analysis and meta-analysis. Research in this area is described below.**

Given the remarkable advancements in the performance and capabilities of GenAI, FDA dedicated resources to determine how to safely and effectively leverage these technologies to enhance the FDA's review process. This included developing AI agents for streamlining workflows such as MDD extraction from drug labeling. In a proof-of-concept study, AI agents were developed to conduct specific tasks, following a workflow to determine MDD (such as data ingestion, information categorization, situation analysis, and final summary). This study served as an important milestone in exploring best practices for developing AI automation tools based on GenAI to streamline regulatory workflows (additional details can be found in the **Research Highlights** section of this chapter).

More agentic AI tools are under development to support pre-ANDA meeting assessment, PSG development, controlled correspondence assessment, formulation assessment, and other regulatory functions. An ongoing initiative in building supportive data infrastructure is the development of a PK data warehouse. This warehouse aims to provide executable PK datasets to support flexible data analysis requirements, including meta-analysis. The PK data warehouse features a flexible query engine based on LLMs for efficient data retrieval, enabling comprehensive PK analyses to support regulatory decision-making.

Furthermore, an ongoing grant (U01FD005978-08: Large Language Models to Support BE Evaluation) 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, the contract (75F40124P00142: Construction of a Biopharmaceutics Classification System (BCS) Database based on Large Language Models) continues to explore the use of LLMs to extract BCS classification-related information including solubility and permeability data, from various publicly available data sources. This work supports BCS classifications and aims to construct a comprehensive database containing provisional BCS classifications of a large number of drug substances. Building on the LLM pipeline developed under this contract, an ongoing internal project involves collecting additional in-house data (e.g., solubility and permeability data) to enhance BCS classification capabilities.

In addition, the FDA continues to enhance its internal analytical capabilities through the development of AI-assisted image analysis methodologies for characterizing critical microstructure attributes in complex pharmaceutical formulations. As part of ongoing efforts to support ANDA assessments, AI-enhanced analytical approaches were developed to address knowledge gaps identified in conventional microstructure characterization methods for gel formulations. The AI-assisted methodology demonstrated the ability to accurately assess API particle distribution and oil droplet characterization in emulsion-based systems. This work represents the Agency's initiative to apply image-based AI analysis across semisolid product evaluations, establishing enhanced analytical standards that support evidence-based regulatory decision-making. The implementation of this AI-assisted image analysis approach helps to address existing analytical limitations and can establish a framework for the characterization and quality assessment of complex formulations.

## Research Highlight

The MDD plays a vital role in excipient evaluation, establishing FDA-approved maximum daily exposure limits of excipients to determine whether excipient levels in the products are safe, and setting acceptable limits for impurities. Determining the MDD is also a critical component in the PSG development. However, the current process of manually extracting and updating MDD information from drug labeling is labor-intensive and subject to reviewer-dependent variability. In this study, researchers developed an agentic AI system locally hosted at FDA to automate MDD determination from drug labeling. The system uses an open source LLM Instruct model enhanced with retrieval-augmented generation (RAG) and an innovative agentic workflow that mirrors the FDA's internal guidelines. The agentic approach employs four specialized agents working sequentially: a retrieval agent for collecting relevant labeling content, an extraction and curation agent for identifying and filtering dosing scenarios, a calculation agent for determining MDD values based on FDA guidelines, and a summary agent for final MDD determination (**Figure 1**). Importantly, the system generates responses in structured JSON format with detailed documentation including source quotes, calculation steps, and reasoning processes, enabling thorough verification by reviewers. These findings demonstrate the significant potential of GenAI to streamline regulatory workflows while maintaining the rigor required for drug safety assessments. The established pipeline can be extended to pediatric populations, addressing an existing gap in the MDD data, and offers the promise of reducing reviewer burden while minimizing potential variability in MDD determinations. This work represents an important step toward integrating AI tools into FDA regulatory processes, potentially improving both efficiency and consistency in generic drug evaluation.

## Research Projects and Collaborations

### Continuing Grants and Contracts

- 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
- Grant (U01FD005978-08) *Large Language Models to Support BE Evaluation* with Kathleen M Giacomini at University of California-San Francisco

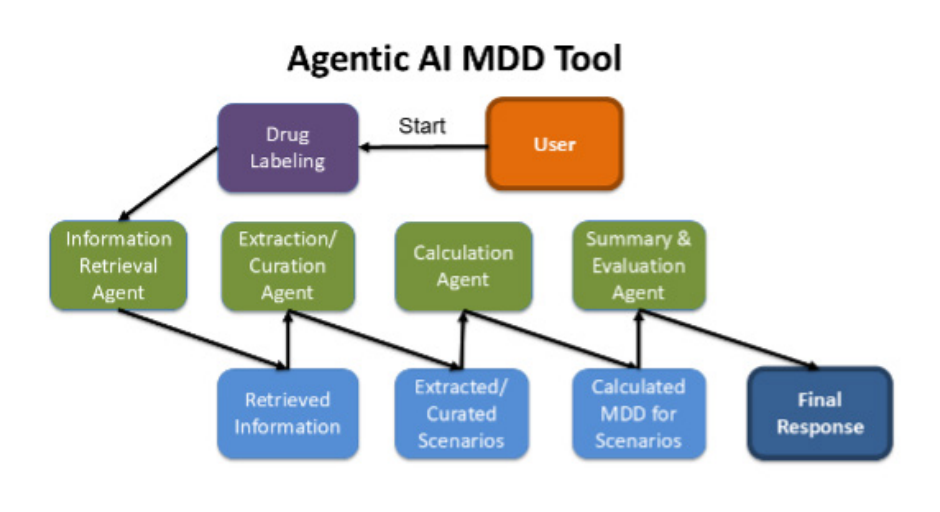


**Figure 1.** A schematic diagram of the workflow realized by the agentic AI for the extraction of the maximum daily dose (MDD) from a drug labeling.

### Completed Grants and Contracts

- Grant (U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Contract (75F40124P00142) *Construction of a Database Containing Drug Biopharmaceutics Classification System (BCS) Class Information* with Hualou Liang at Drexel University
- Contract (75F40122C00121) *Machine-Learning based Heterogeneous Treatment Effect Models for Informing Product-Specific Guidance Development* with Hualou Liang at Drexel University

### Active FDA Research

- *Development and Analysis of a Complex Product Database*
- *Development of PK Data Warehouse for BE Analysis*
- *Establishing Internal Capability to Build up Large Language Models for Enhancing Regulatory Efficiency*
- *Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products using Non-Invasive Techniques*
- Laboratory-Based Experimental Methodologies to Support in Vitro-Based BE Approaches (Details)
- Machine Learning for Generic Drug Analysis

## Outcomes

### Publications

Kanakia A, Sale M, Zhao L, and Zhou Z. *AI In Action: Redefining Drug Discovery and Development*. Clinical and Translational Science. (2025) 18(2):e70149. https://doi.org/10.1111/cts.70149. PMID: 39912678; PMCID: PMC11800368.

### Presentations

Lee J. *Generative AI-Powered Regulatory Efficiency and Excellence*. Presentation at Scientists Advancing Affordable Medicines, Inc. (SAAMnow) Spring Workshop. Virtual Meeting, Jun. 11, 2025.

Bies R. *User Friendly Tools for Population PK and PBPK modeling*. Presentation at the 2024 American Conference on Pharmacometrics (ACoP 2024). Phoenix, AZ, Nov. 12, 2024.

Wang J. *Leveraging Large Language Models (LLMs) to Support Regulatory Assessments*. Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 21, 2024.

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# 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. The research activities in this section highlight FDA's focus on enhancing patient access to generic orphan drug products (ODPs) and alternative bioequivalence approaches for generic drugs for which FDA permits a difference from the RLD under an approved suitability petition (petitioned drugs).

# Orphan Products and Alternative Bioequivalence Approaches for Petitioned Drugs

## Summary of FY 2025 Activities

**In FY 2025, FDA addressed generic drug development challenges related to ODPs, and related to certain petitioned drugs where there is a lack of readily available reference standards. The research for orphan products identified key factors influencing generic orphan drug applications using a machine learning analysis. The project for petitioned drug initiatives advanced scientific methodologies and led to the publication of product-specific guidances (PSGs) for petitioned drugs with clear recommendations on an option-based framework to enhance patient access to essential medications.**

The FDA's internal research during FY 2025 focused on identifying factors influencing the first submission of abbreviated new drug applications (ANDAs) for generic orphan drugs. The results generated from the research showed that the likelihood of ANDA submissions can be predicted to a promising level of accuracy for both new chemical entity (NCE) and non-NCE ODPs as well as identify the most predictive factors for these submissions. For NCE ODPs, economic factors (sales data) were most predictive of ANDA submissions, while for non-NCEs, regulatory factors (particularly PSG availability) were most important. This research outcome provides a way for FDA to help increase patient access to generic orphan drugs by identifying how FDA's actions, such as developing a PSG for an orphan drug product, can positively influence the submission of an ANDA for that product (see **Research Highlight** for further information).

The FDA's research during FY 2025 also focused on bioequivalence approaches for drug products contemplated through suitability petition pathways. This research focused on two key areas: 1) developing strategies to establish scientific bridges, and 2) accelerating the development and publication of regulatory recommendations. Indeed, during FY 2025, FDA published six PSGs for petitioned products through a proactive approach that provides immediate regulatory clarity before first ANDA approvals. These guidances introduced an option-based framework with respective reference standards covering new dosage forms approved through suitability petitions based on Section 505(j)(2)(C), including orally disintegrating tablets, chewable tablets, and oral suspensions. The guidances directly addressed industry requests from numerous controlled correspondences, demonstrating FDA's responsiveness to real-world development challenges. The combined research and regulatory strategy demonstrate FDA's commitment under GDUFA III to provide clear guidance before ANDA submission, facilitating generic drug development and reducing regulatory uncertainty while ensuring scientific rigor. FDA will continue to evaluate additional drug products that are the subject of approved suitability petitions and develop corresponding PSGs with clear recommendations on BE approaches to support generic drug development. This ongoing effort represents a systematic approach to addressing GDUFA research priorities and facilitating timely access to medically necessary medications.

## Research Highlight

Orphan drug products (ODPs) treat rare diseases affecting fewer than 200,000 Americans, but their high development costs result in significantly higher treatment expenses compared to non-orphan drugs. While the Orphan Drug Act of 1983 successfully incentivized brand-name ODP development through market exclusivity and tax benefits, generic alternatives remain limited, restricting patient access to affordable treatments. Understanding factors that influence when pharmaceutical companies submit ANDAs for generic orphan

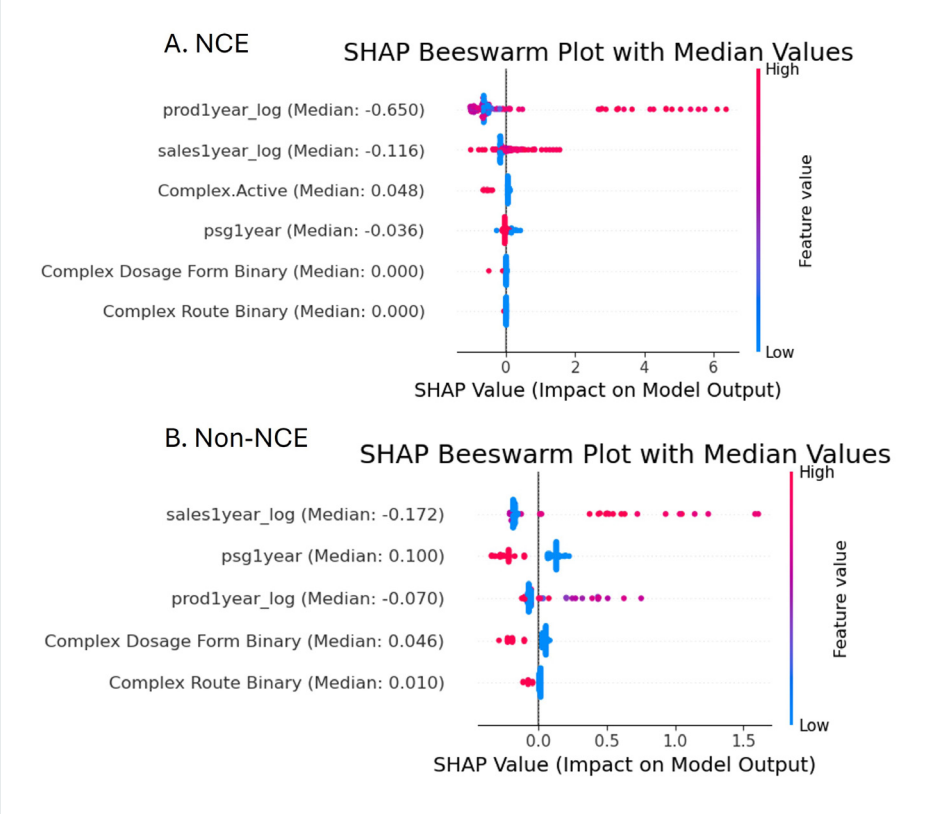


**Figure 1. (A) SHAP (SHapley Additive exPlanations) Analysis Beeswarm Plots for NCE ODPs, (B) SHAP Analysis Beeswarm Plots for Non-NCE ODPs.** The x axis represents the SHAP values for each variable in the model. Each instance of the variable (i.e., row in the dataset) is represented by one point. Higher raw values for each instance are shown in red and lower raw values are shown in blue. Median of the SHAP values were calculated to demonstrate overall impact on the model due to the skewed distribution. ELASD = earliest lawful ANDA submission date.

drugs is crucial for improving market competition and reducing treatment costs.

A study was conducted that involved the application of a machine learning methodology to predict ANDA submission timing for orphan drugs. Data were collected from multiple sources, including the FDA Orphan Drug Designations and Approvals database, Orange Book, internal drug product complexity designations, and the IQVIA sales database. These sources provided comprehensive information on drug product characteristics, regulatory factors including PSG availability, and pharmacoeconomic factors.

A Random Survival Forest (RSF) method, a nonparametric machine learning algorithm for analyzing time-to-event data, was employed to examine 140 NCEs and 97 non-NCE orphan drugs approved between 2008 and 2023. The modeling analysis was validated through both internal and external validation methods.

The RSF models demonstrated a robust predictive capability with repeated cross-validation C-indices of 0.675±0.0261 for NCEs and 0.754±0.0441 for non-NCEs. Variable importance analysis revealed distinct drivers for each product category.

For NCE ODPs, economic factors dominated the prediction model. Sales revenue and units sold one year before the earliest lawful ANDA submission date were most predictive of shorter submission times (**Figure 1A**). This reflects generic manufacturers' focus on high-revenue products to maximize return on investment.

For non-NCE ODPs, regulatory factors proved more influential, with PSG availability within one year post-NDA approval and early sales data serving as key predictors (**Figure 1B**). PSGs provide critical guidance for developing therapeutically equivalent generic products, and these results suggest that FDA's timely publication of PSGs for ODPs can accelerate generic ODP development and ANDA submissions.

These machine learning-derived insights offer actionable intelligence for FDA regulatory planning, including PSG prioritization and resource allocation for ANDA reviews. As more data become available in the future, the RSF methodology will likely be able to predict ANDA submissions of ODPs even more effectively. This methodology enables proactive strategies to promote generic ODP development, ultimately expanding patient access to cost-effective treatments for rare diseases while maintaining safety and efficacy standards.

## Research Projects and Collaborations

### Active FDA Research

- *Bridging Guidance on Generic Oral Drug Products under Unavailable Reference Listed Drug or Reference Standard*

## Outcomes

### Product-Specific Guidances

There were five new and one revised PSG published in FY 2025 related to *Orphan Products and Alternative Bioequivalence Approaches for Petitioned Drugs*. Among those, PSGs listed below were directly impacted by GDUFA - funded research in this area.

- *New Draft Guidance for Allopurinol, Oral, Suspension* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Carbinoxamine Maleate, Oral, Orally Disintegrating Tablets* (May 20, 2025) Link to Posting
- *New Draft Guidance for Clonazepam, Oral, Suspension* (Nov.19, 2024) Link to Posting
- *Revised Draft Guidance for Enzalutamide, Oral, Tablets* (Nov. 19, 2024) Link to Posting
- *New Draft Guidance for Memantine Hydrochloride, Oral, Orally Disintegrating Tablets* (Nov. 19, 2024), Link to Posting
- *New Draft Guidance for Metformin Hydrochloride, Oral, Chewable Tablets* (May 20, 2025) Link to Posting

# Other Activities

## Summary of FY 2025 Activities

**In FY 2025, 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

### Continuing Grants and Contracts

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

### Completed Grants and Contracts

- Grant (U01FD005486) *Educating Groups Influencing Generic Drug Use* with Jingjing Qian at Auburn University
- Grant (U01FD005485) *Identifying Messages to PROmote Value Education (IMPROVE) of Generic Prescribing* with Vineet Arora at University of Chicago
- Grant (U01FD005875) *Generic Drug Substitution in Special Populations* with Ilene Harris, Jingjing Qian at Auburn University
- Grant (U01FD005271) *Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes Adherence and Immune Responses* with Suphamai Bunnapradist at University of California Los Angeles
- Contract (75F40121C00178) *In-Vitro Tools to Simulate Chewing of Pharmaceutical Opioid Drug Products* with Peter Xu, Feng Zhang at University of Auckland
- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Artan Markollari at Biopharma Services USA Inc.

### Active FDA Research

- *Global Manufacturing Sites for Complex Drug Products*

### Publications


Alexeenko A, Korang-Yeboah M, and Tchessalov S. *Critical Needs and Opportunities for Advanced Manufacturing of Lyophilized Injectables*. Pharmaceutical Research. (2025) 42(6):1059-1064. https://doi.org/10.1007/s11095-025-03869-5. PMID: 40579685; PMCID: PMC12222488.

Gao Z, and Smith A. *Response to the Commentary from A Dissolution Working Group on "The Effect of Sampling Cannula on In Vitro Dissolution Testing with USP Paddle Method": Clarifications and Opportunities for Engagement*. The AAPS Journal (2025). 27(5), 120. https://doi.org/10.1208/s12248-025-01107-9. PMID: 40670776.

Li T, Felton J, Lewis J, Cheng Q, Meredith R, Lu HT, Benken A, Dutta PP, Liao J, Zhao XD, Matvekas A, Baker J, Hasler WL, Babiskin A, Walenga R, Fang L, Lionberger R, Pal MP, Sun D, Gianchandani YB. *An Ingestible Device for Automated Sampling and Location Tracing in Gastrointestinal Tract*. PLoS One. 2025;20(7):e0327667. https://doi.org/10.1371/journal.pone.0327667. PMID: 40644523.

Pozy EJ, and Tian L. *Impact of Mechanical Calibration Variations on USP Prednisone PVT with Standard and Apex Vessels*. Analytical Methods: Advancing Methods and Applications. (2025) 17(12):2559-2566. https://doi.org/10.1039/d4ay02008a. PMID: 40062384.

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Shih M, Faustino PJ, O'Connor TF, Zhang J. *Influence of Mass Spectrometry Source Settings on Native Protein Ion Mobility Mass Spectrometry Measurements*. International Journal of Mass Spectrometry. (2025) 509,117411. https://doi.org/10.1016/j.ijms.2025.117411.

Sierra-Vega NO, Ashraf M, O'Connor T, Kopcha M, Di Prima M, Coburn J, Zidan A. *Emerging 3D Printing Technologies for Solid Oral Dosage Forms: Processes, Materials and Analytical Tools for Real-Time Assessment*. International Journal of Pharmaceutics. (2025). 673, 125415. https://doi.org/10.1016/j.ijpharm.2025.125415. PMID: 40023346.

Zaker Y, Yilmaz H, Lex T, Guo C, Rodriguez JD, and Willett D. *Advancing Pharmaceutical Tablet Analysis with Laser Direct Infrared (LDIR) Imaging*. Journal of Pharmaceutical and Biomedical Analysis. (2025) 262: 116897. https://doi.org/10.1016/j.jpba.2025.116897. PMID: 40239561.

Zhang J, and Faustino PJ. *Mass Spectrometry for Clinical Bioanalysis without Chromatographic Separation: Bioequivalence for Bupropion and its Metabolites*. Bioanalysis. (2025) 17(18):1133-1143. https://doi.org/10.1080/17576180.2025.2557187. PMID: 40910749; PMCID: PMC12536770 (available on 2026-09-05).

### Presentations

Xu X. *Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices. Hybrid Meeting. Rockville, MD, Sep. 23, 2025.

Al-Ghabeish M. *Regulatory Science in Action: Supporting Innovative Opioid Formulations Development & Advancing Overdose Treatments*. Presentation at the American College of Clinical Pharmacology (ACCP) Annual Meeting 2025. Phoenix, AZ, Sep. 15, 2025.

Kozak D. *ANDA Common Major Deficiencies*. Presentation at the Small Business and Industry Assistance (SBIA) Generic Drugs Forum (GDF) 2025. Silver Spring, MD, Apr. 10, 2025.

Kotsybar J. *Product Specific Guidance (PSG) Program Overview*. Presentation at the Small Business and Industry Assistance (SBIA) Generic Drugs Forum (GDF) 2025. Silver Spring, MD, Apr. 09, 2025.

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Krull S, Ding T, and Xu X. *Evaluation of Near Infrared (NIR) for the Quantification of Low Dose Drugs*. Poster Presentation at the 2024 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting PharmSci 360. Salt Lake City, UT, Oct. 22, 2024.

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# Appendix: GDUFA Science and Research Outcomes for Fiscal Year 2025

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)

### 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

The following are research outcomes from fiscal years 2018[1], 2019, 2020, 2021, 2022, 2023, 2024, 2025.

**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 FY2025 |
|---|---|---|---|---|---|---|---|---|
| Number of pre-ANDA meetings impacted by research | 62 | 93 | 92 | 113 | 92 | 89 | 116 | 83 |
| Number of Controlled Correspondences impacted by research | 113 | 178 | 291 | 97[2] | 137 | 309 | 400 | 459 |
| Number of PSGs impacted by research | 86 | 82 | 86 | 40 | 73 | 19 | 18 | 18 |
| Number of Post-CRL Scientific Meetings | na | na | na | na | na | 2 | 0 | 1 |
| Number of PSG Teleconferences | na[3] | na | na | na | na | na | 1 | 1 |
| Number of publications, presentations, and posters that are relevant to this category | 244 | 162 | 156 | 233 | 169 | 301 | 268 | 213 |
| Number of workshops that communicate scientific advances and regulatory advice to the generic drug industry | 8 | 5 | 5 | 14 | 17 | 19 | 15 | 18 |
| Other Items that fall in this category (i.e., general guidance) | 2 | 2 | 3 | 5 | 1 | 10 | 5 | 4 |

**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 FY2025 |
|---|---|---|---|---|---|---|---|---|
| Number of pre-ANDA meetings impacted by research | 16 | 39 | 59 | 33 | 22 | 46 | 57 | 59 |
| Number of ANDA submissions impacted by research | 138 | 167 | 166 | 81 | 65 | 183 | 175 | 211 |
| Number of ANDA reviews impacted by research | 44 | 36 | 62 | 50 | 65 | 80 | 96 | 46 |
| Number of ANDA approvals impacted by research | 63 | 102 | 152 | 161 | 126 | 167 | 161 | 153 |
| Number of PSGs impacted by research | 29 | 35 | 48 | 11 | 65 | 33 | 32 | 24 + 814 (M13A)* |
| Number of Post-CRL Scientific Meetings | na | na | na | na | na | 1 | 6 | 3 |
| Number of publications, presentations, and posters that are relevant to this category | 82 | 92 | 100 | 102 | 68 | 212 | 268 | 203 |

**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 FY2025 |
|---|---|---|---|---|---|---|---|---|
| Number of pre-ANDA meetings impacted by research | 32 | 52 | 24 | 28 | 50 | 33 | 32 | 33 |
| Number of ANDA submissions impacted by research[4] | na | na | na | na | na | na | 288 | 255 |
| Number of ANDA approvals impacted by research[5] | na | na | na | na | na | na | 67 | 75 |
| Number of Controlled Correspondences discussing alternative BE approaches[6] | na | na | na | na | na | 32 | 32 | 38 |
| Number of PSGs that provided new approaches to equivalence | 36 | 27 | 30 | 21 | 78 | 67 | 31 | 41 + 814 (M13A)* |
| Number of Post-CRL Scientific Meetings | na | na | na | na | na | 2 | 2 | 1 |
| Number of publications,presentations, and posters that are relevant to this category | 37 | 36 | 21 | 58 | 140 | 118 | 154 | 125 |

[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 FY2024

[6] This additional metric was added in this category in FY2023

* In FY2024 FDA revised PSGs for a subset of immediate release oral drug products in response to the implementation of the M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms. A total of 814 draft revised PSGs were published on Oct 31, 2024, the first day of FY2025. For a full list of the revised draft PSGs, please refer to the Federal Register Notice: https://www.federalregister.gov/documents/2024/10/31/2024-25391/product-specific-guidances-revised-draft-guidances-for-industry-availability.