CENTER FOR DRUG EVALUATION AND RESEARCH

FY 2022

GDUFA SCIENCE AND RESEARCH REPORT

U.S. FOOD & DRUG ADMINISTRATION

TABLE OF CONTENTS

INTRODUCTION

The U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) continually advances scientific research to ensure that safe, effective, and high-quality drugs are available for people in the United States. This research ensures that regulatory standards, recommendations, and decisions are evidence-based and supported by the most current scientific insights. A major area of FDA research is focused on facilitating the availability of high-quality generic drugs, and much of this is driven by a science and research program established under the Generic Drug User Fee Amendments (GDUFA). Generic drugs are essential to public health in the United States not only because having multiple manufacturers for a drug product stabilizes the supply and reduces the risk of drug shortages, but also because the efficiency with which many generic products can be developed makes them widely available and generally more affordable, allowing hundreds of millions of patients to easily access the medicines they need.

The GDUFA science and research program is particularly important for certain pharmaceutical products, known as complex products, which are harder to develop as generics. Complex products often have few generics, or none at all. In the absence of market competition among generic alternatives, these medicines can be so expensive that patients who need them may not be able to afford them. The GDUFA science and research program supports the development of innovative methodologies and more efficient tools to help establish drug equivalence standards that facilitate the development of safe, effective, and high-quality generic products. FDA publishes annual reports describing the GDUFA science and research activities for each fiscal year (FY).

The FY 2022 GDUFA science and research report describes active research projects and outcomes organized in 13 scientific areas. In each area, we summarize the relevant research initiatives and highlight a research project that illustrates the types of scientific insights being developed. We also provide comprehensive lists of new, ongoing, and completed grants and contracts for research impacting each area, and of the research outcomes in that area generated during FY 2022. These outcomes include general guidances for industry and product-specific guidances (PSGs) published in FY 2022 that were supported by research in each area, as well as lists of scientific journal articles, posters, and presentations. The 13 scientific areas are generally organized based upon the type of product (e.g., inhalation and nasal products) or the scientific methodologies (e.g., locally acting physiologically based pharmacokinetic (PBPK) modeling). However, when research projects impact multiple areas, information about those projects is included or cross-referenced in each area impacted (e.g., research on PBPK modeling of inhalation products is included in both chapters on inhalation products and locally acting PBPK modeling).

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

JOINT DIRECTORS' MESSAGE

Dr. Susan Rosencrance
Acting Director, Office of
Generic Drugs

Dr. Michael Kopcha,
Director, Office of
Pharmaceutical Quality

The Generic Drug User Fee Amendments (GDUFA) science and research program facilitates patient access to high-quality generic drugs by advancing research in areas where generic product development has been limited or prevented due to knowledge gaps about the kind of evidence needed to demonstrate that a generic product is the same as its brand name reference listed drug product. Each fiscal year (FY), leaders and experts across the generic industry collaborate to establish research priorities for the most pressing scientific challenges they face with generic product development. Scientists and clinicians from industry, academia, and the U.S. Food and Drug Administration (FDA) then strategically design studies so that the research outcomes enable FDA to build scientific bridges across the knowledge gaps, thereby establishing efficient new pathways for pharmaceutical manufacturers to develop generic drugs that were previously challenging or unfeasible to develop and make them available for patients.

Aligned with the FY 2022 Science and Research Priority Initiatives, during FY 2022, FDA awarded eight new research contracts and seven new grants (not including supplements to existing projects) for innovative extramural research projects relevant to generic drugs. FDA also utilized its laboratories and computer systems to conduct more than 70 intramural GDUFA science and research projects that leveraged FDA resources and expertise to facilitate both generic product development and FDA's preparedness to assess information submitted in abbreviated new drug applications (ANDAs).

The outcomes from GDUFA-funded research expand our understanding of drug products, including complex products, and often contribute to the development of advanced methods to characterize product quality and performance. These methods may play a critical role in determining how FDA evaluates the quality and bioequivalence (BE) of complex generic products and can establish the scientific basis for novel and more efficient pathways by which to develop generic products. FDA's recommendations related to BE issues and product quality are communicated to the generic industry through the continual publication of new and revised product-specific guidances (PSGs), as well as general guidances for industry.

In FY 2022, FDA issued 177 new and revised PSGs (59 of which were for complex products) that provided recommendations for developing generic drugs and generating the evidence to support ANDA approval. This included 117 PSGs for products (including 41 PSGs for complex products)

with no approved ANDAs at the time of PSG publication. Also, 18 PSGs were revised in FY 2022 to add an efficient in vitro BE option. Among these was a PSG for medroxyprogesterone acetate injection, which was notable as the first PSG for a long-acting injectable suspension to recommend an efficient in vitro BE approach. This PSG was the outcome of years of GDUFA-funded research that elucidated the role of key formulation characteristics on the performance of such products. All these PSGs help prospective generic applicants understand FDA expectations, focus their product development, prepare for ANDA submission, and mitigate certain risks associated with generic product development. The development of these PSGs also facilitates FDA's assessment of ANDAs for those products, once submitted.

The recommendations in many of these PSGs would not have been possible without the GDUFA science and research program. For example, peptide and oligonucleotide-based drugs are emerging therapies that present unique challenges for generic product development. In FY 2022, FDA published a PSG for a nusinersen sodium intrathecal solution to treat patients with spinal muscular atrophy. This was the first PSG for this class of oligonucleotide drugs, and it provided recommendations on assessing pharmaceutical equivalence and BE for this complex product. GDUFA research was essential to the development of this PSG. Similarly, during FY 2022, FDA also published a PSG for a vasopressin solution that was developed based upon GDUFA research relating to the immunogenicity risks of peptide products that was critical to facilitating the generic development of this life-saving medication for vasodilatory shock and as a supportive therapy for treating COVID-19.

Several PSGs published during FY 2022 that were made possible by GDUFA science and research addressed major public health challenges. For example, in FY 2022, FDA published two PSGs for an exenatide subcutaneous suspension which recommend, for the first time, two in vivo pharmacokinetic (PK) BE study options for this diabetes medication. These results of GDUFA-funded research provided information to address challenging product development issues related to the detection limit of a bioanalytical method, data variability, study duration, or sample size.

In addition to informing FDA guidances, GDUFA research also allows FDA to evaluate whether proposed BE approaches presented to FDA in pre-ANDA product development meetings are likely to be suitable. Specifically, GDUFA research outcomes enable FDA to provide prospective ANDA applicants with scientific and technical advice that helps them prepare their submissions in a manner compatible with the most current scientific insights and regulatory expectations. In FY 2022, FDA facilitated 72 such product development and pre-submission pre-ANDA meetings. This GDUFA research also prepared FDA to assess and approve many complex generics, which ultimately improved patient access to complex generics which were practically unfeasible to develop as recently as a few years ago.

For example, on February 2, 2022, FDA approved the first generic cyclosporine ophthalmic emulsion, 0.05% (referencing Restasis®), which helps millions of patients in the United States who suffer from dry eyes. This is an immunomodulatory and anti-inflammatory complex product for which it was exceptionally challenging to demonstrate BE and to assess product quality, for multiple reasons. At the start of the GDUFA science and research program, collaborative discussion between generic industry representatives and FDA established a research priority to develop more efficient BE approaches for locally acting ophthalmic products. The resulting research across multiple years systematically advanced scientific insights and developed new tools that could support an efficient demonstration of BE for complex generic ophthalmic products like this one. This included a series of research projects specifically related to cyclosporine ophthalmic emulsion that successfully addressed challenging product characterization issues, developed analytical measurement and statistical analysis tools, and supported updates to generic product development recommendations

in PSGs prior to the assessment and approval of this first generic product. The scientific advances from this research also positioned FDA to rapidly publish a PSG in FY 2022 with recommendations for the development of a generic product for a different cyclosporine ophthalmic emulsion, 0.1% (referencing Verkazia®) that was just approved as a new drug in FY 2021.

As another example, on March 15, 2022, FDA approved the first generic budesonide and formoterol fumarate dihydrate inhalation aerosol (referencing Symbicort®). This is one of the most commonly prescribed complex drug-device combination products to treat asthma and chronic obstructive pulmonary disease in millions of Americans, many of whom are children. Drug-device combination products, and in particular, inhalation products, pose several unique challenges that make them difficult to develop as generic products. Thus, addressing the scientific issues impacting the demonstration and assessment of BE for this class of complex products was another priority research area for the GDUFA science and research program. The resulting research outcomes led directly to the development of a PSG for this product in FY 2015 and prepared FDA to assess and approve this first generic product during FY 2022.

Both of these first generic products approved during FY 2022 exemplify what can be achieved with effective coordination between FDA and the generic drug industry. The GDUFA science and research program fosters early engagement between FDA and industry to identify specific priority areas for GDUFA research, facilitates continued engagement through pre-ANDA meetings during product development to discuss how insights from GDUFA research can be leveraged, and provides opportunities for engagement following ANDA submission to discuss scientific matters. As part of FDA's commitment to expanding its collaboration and communication with industry, we continued to work closely with the Center for Research on Complex Generics (CRCG) during FY 2022.

The CRCG solicited detailed feedback from generic industry representatives, helping to ensure that GDUFA research initiatives are focused on the most pressing scientific challenges, and helping generic product developers effectively utilize GDUFA research outcomes including technical methods, study designs, data analyses, and other scientific insights to successfully develop complex generics. To help generic industry stakeholders implement scientific insights from GDUFA research outcomes in a manner consistent with FDA's regulatory expectations, the CRCG hosted four scientific workshops during FY 2022. The CRCG also played a central role in coordinating and enhancing generic industry engagement in the FY 2022 GDUFA Public Workshop, which helped to inform the ongoing priority areas for the GDUFA science and research program.

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

On behalf of all our FDA collaborators,

Dr. Susan Rosencrance, Acting Director, Office of Generic Drugs and
Dr. Michael Kopcha, Director, Office of Pharmaceutical Quality

OPHTHALMIC PRODUCTS

Summary of FY 2022 Activities

In FY 2022, FDA approved the first generic cyclosporine ophthalmic emulsion product, which was a result of multiple years of GDUFA research to set the scientific foundation for bioequivalence (BE) assessments of ophthalmic products. The FDA's research efforts during FY 2022 continued to address challenges for the development and evaluation of generic ophthalmic products in two major areas: 1) the identification and characterization of critical physicochemical properties of complex ophthalmic products in vitro, ex vivo, and in animals; and 2) the advancement of in silico modeling to investigate the impact of formulation properties on ocular pharmacokinetics (PK) and/or pharmacodynamics (PD).

In collaboration with Absorption Systems, Inc. (75F40119D10024-75F40119F19001), cyclosporine ophthalmic emulsion formulations with varying globule size distributions (GSD) and viscosities were evaluated by measuring ocular central tear film thicknesses and tear menisci areas of rabbit eyes post drug product instillation. Additional details are provided in the **Research Highlight** below. In addition, another ongoing research project with Absorption Systems, Inc. (75F40119D10024-75F40120F19002) is generating critical insights into the impact of ophthalmic suspension product attributes, such as particle size distribution and viscosity, on the PK/PD of these complex topically administered ophthalmic drug products following single- and multi-dose regimens in rabbits. These results will be used to validate previously developed in silico models to further support the advancement of a physiologically based pharmacokinetic (PBPK) model to predict the ocular bioavailability and BE of topical ophthalmic emulsion and suspension products.

An integrated, multiscale, multiphysics computational modeling framework for a PBPK assessment of the BE of generic ophthalmic drug products was supported by a contract with CFD Research Corporation (HHSF223201810151C). This framework was implemented and validated based on in vivo/in vitro data, which is useful in mechanistically understanding the impact of physicochemical

properties of ophthalmic formulations on in vivo ocular PK performance. Furthermore, this framework supports the use of in vitro BE approaches for ophthalmic products. In silico modeling research continuing to FY 2023 includes the application of computational biology tools for PBPK/PD model extrapolation from preclinical species to humans to support BE assessments of ophthalmic drug products (1U01FD006929; 1U01FD006927).

Additional GDUFA research conducted during FY 2022 and continuing into FY 2023 includes: 1) investigation of the effect of repeat unit ordering on the properties of polymeric melt-extruded long-acting implants to support BE recommendations for polymeric ophthalmic implants (75F40120C00198); 2) development of a suitable in vitro release testing method for complex ophthalmic formulations (HHSF223201810114C); and 3) evaluation of a dexamethasone intracanalicular insert to support a determination of BE (internal research project).

RESEARCH HIGHLIGHT

Understanding how the physicochemical properties of ophthalmic emulsion formulations affect the ocular tear film properties and local in vivo absorption is beneficial to setting more clinically relevant product quality and BE acceptance limits for these properties. Anterior Segment Optical Coherence Tomography (AS-OCT) was used to measure the tear film thickness (TFT) and menisci [i.e., upper tear film meniscus cross-sectional area (UMA) and lower tear film meniscus cross-sectional area (LMA)] of Dutch Belted (DB) rabbit eyes after instillation of cyclosporine ophthalmic emulsions that were similarly formulated but had differences in GSD and viscosity. The aim of this study was to support a PBPK model combining physics-based and compartmental approaches to predict the bioavailability of cyclosporine to the cornea and the conjunctiva.

Five compositionally identical cyclosporine emulsion formulations (F1-F5, varying in GSD and viscosity) and three placebos (P1-P3, varying in viscosity) were prepared and comparatively characterized with respect to the reference listed drug product Restasis® (**Table 1**). Tear variable measurements were conducted up to 40 minutes post ocular instillation. For comparison, an over-the-counter artificial tear product (Refresh Liquigel®) and sterile water were also tested.

Instillation of any of the test articles on rabbits resulted in initial increases in TFT, UMA, and LMA measurements, followed by sharp decreases within 10 minutes, and gradual decreases afterwards. Restasis® and F1-F4, with similar GSD but differing in apparent viscosity, exhibited comparable UMA and LMA levels at all time points. It was observed that the formulation with the largest GSD (i.e., F5) gave rise to the largest change in the tear variables post instillation. Formulation F1, which had the highest apparent viscosity among the cyclosporine emulsion formulations, also prompted a significant change to TFT in this study, although the impact of GSD and viscosity on tear variables were confounded. Among all tear variables, changes in TFT (**Figure 1**) appeared to be the most sensitive measure for capturing confounded differences in GSD and viscosity of ophthalmic emulsions, and may be an indicator of in vivo performance equivalence.

Data from this study are being used to validate a PBPK model previously developed to predict bioavailability at the ocular site of action. This approach will enable a deeper understanding about how physicochemical properties of ophthalmic emulsions may impact the tear film characteristics, fostering FDA's knowledge in determining significant equivalence parameters for generic ophthalmic drug products.

Table 1. *Z*-average globule size and apparent viscosity of cyclosporine ophthalmic emulsions (F1-F5, Restasis®) and placebo formulations (P1-P3). Values represented as mean ± standard deviation (n=3).

Formulation	*Z*-average (d.nm)	Apparent Viscosity (mPa.s)
F1	112.3 ± 1.2	643.8 ± 20.0
F2	92.2 ± 1.4	238.6 ± 3.7
F3	117.3 ± 2.3	246.6 ± 2.0
F4	120.1 ± 1.4	140.6 ± 7.5
F5	204.4 ± 6.1	249.6 ± 3.5
P1	-	667.0 ± 24.0
P2	-	508.0 ± 70.0
P3	-	1548.0 ± 29.0
Restasis®	117.9 ± 2.0	170.9 ± 13.6

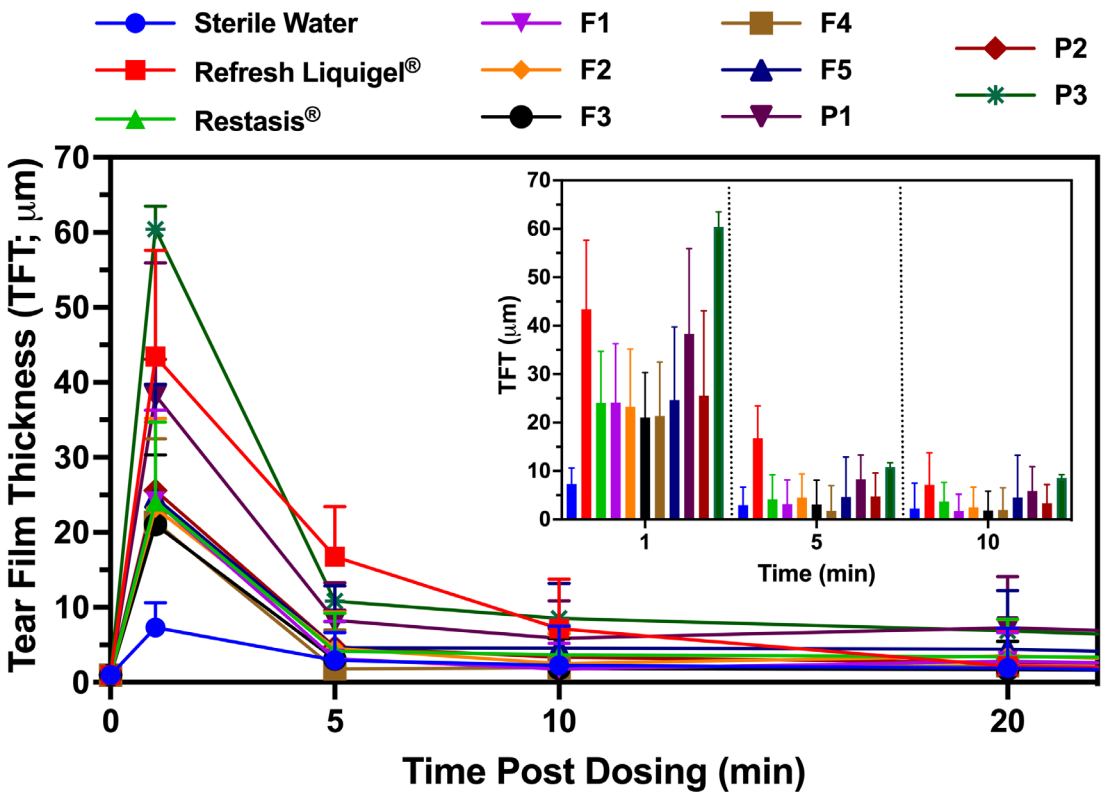


Figure 1. Dynamic measurements of ocular tear film thickness in rabbits post instillation of cyclosporine ophthalmic emulsions with varying GSDs and viscosities. Data points represented as mean ± standard deviation (n=4). Z-average globule size rank order: F5>F4>F3=Restasis®>F1>F2. Apparent viscosity rank order: P3>P1=F1>P2>F3=F5>F2>Restasis®>F4.

RESEARCH PROJECTS AND COLLABORATIONS

Continuing Grants and Contracts

- Grant (1U01FD006929) *Computational Biology (Cobi) Tools as a Framework for Physiologically-Based Pharmacokinetic/ Pharmacodynamic Model Extrapolation from Rabbit to Human for Ophthalmic Drug Products* with Carrie German at CFD Research Corporation.
- Grant (1U01FD006927) *Development and Validation of a PBPK/PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human* with Jessica Spires at Simulations Plus, Inc.
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* with Nathaniel Lynd at the University of Texas at Austin.
- Contract (HHSF223201810114C) *In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence* with Xiuling Lu at the University of Connecticut.

Completed Grants and Contracts

- Contract (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation.
- Contract (75F40119D10024-75F40120F19002) *PK/PD of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Absorption Systems.

Active FDA Research

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

OUTCOMES

General Guidance

- *New Draft Guidance for Industry: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (Apr. 2022) Link to Posting

Product-Specific Guidances

- There were four new PSGs published in FY 2022 related to *Ophthalmic* products. PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Atropine Sulfate Ophthalmic Solution.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Brilliant Blue G Ophthalmic Solution.* (Dec. 2021) Link to Posting
- *New Draft Guidance for Cyclosporine Ophthalmic Emulsion.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Loteprednol Etabonate Suspension/Drops*. (Aug. 2022) Link to Posting

Articles

- Bellantone R, Shah K, Patel P, Kaplan M, Xu X, Li V, Newman B, and Kaisar M. *Cyclosporine Release and Distribution in Ophthalmic Emulsions Determined by Pulsatile Microdialysis.* International Journal of Pharmaceutics. (2022) 615: 121521. https://doi.org/10.1016/j.ijpharm.2022.121521. PMID: 35093461.
- Le Merdy M, AlQaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, Lukacova V, *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2022) Online ahead of Print. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444.
- Naageshwaran V, Ranta V, Toropainen E, Tuomainen M, Gum G, Xie E, Bhoopathy S, Urtti A, and Del Amo E. *Topical Pharmacokinetics of Dexamethasone Suspensions in the Rabbit Eye: Bioavailability Comparison.* International Journal of Pharmaceutics. (2022) 615: 121515. https://doi.org/10.1016/j.ijpharm.2022.121515. PMID: 35091006.
- Wang D, Park J, Zheng J, Cai B, Keire D, and Chen K. *Multiphase Drug Distribution and Exchange in Oil-in-Water Nanoemulsion Revealed by High-Resolution 19F qNMR.* Molecular Pharmaceutics. (2022) 19(7): 2142-2150. https://doi.org/10.1021/acs.molpharmaceut.2c00025. PMID: 35657300.

Posters

- Shakleya D. *A Preclinical Study of Sustained-Release Dexamethasone Intravitreal Implants in New Zealand White Rabbits.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 11, 2022.
- Le Merdy M, Lukacova V, Tan M-L, Babiskin A, and Zhao L. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Moxifloxacin Solution Case Study.* Poster Presentation at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Denver, Colorado, May 01, 2022.
- Le Merdy M, Zheng Y, Lukacova V, Tan M-L, Babiskin A, and Zhao L. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Levofloxacin Solution Case Study.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Smith W, Bae J, Zhang Y, Wang Y, Qin B, Kozak D, Ashraf M, and Xu X. *Impact of Particle Flocculation on Dissolution and Implications on Bioavailability of Injectable Suspensions.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: A Novel In Vitro Drug Release Testing Method for Complex Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Wang J. *Evaluation and Application of New/Novel Data Imputation Approaches to Support BE Assessment.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Gong Y. *Alternative Model-Based Data Analysis Approach to Demonstrate BE.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Hartka K. *Comparing Device User Interfaces and Seeking Advice in the Pre-ANDA Period.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Xu X. *Thinking Outside the Box: A Regulatory Perspective on Innovation through Flow Processes.* Presentation at the 22nd International Symposium on Field- and Flow-based Separations. Riverside, CA, Sep. 12, 2022.

- Jones A, Chung HS, Kozak D. *Decoding the Guidance: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.* Presentation at Small Business & Industry Assistance (SBIA) Webinar. Virtual Meeting, Aug. 10, 2022.

- Shakleya D. *Case Study: Non-Standard Matrices Considerations - Ocular Implant.* Presentation at the 23rd Annual Land O' Lakes Bioanalytical Conference. Virtual Meeting, Jul. 13, 2022.

- Abuznait A. *Expectations and Common Deficiencies with IVRT Studies Submitted in ANDAs for Ophthalmic Emulsion Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Kozak D. *A Scientific and Regulatory Overview of IVRT: Current Considerations and Challenges.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Park E. *Bioequivalence Considerations for IVRT Methods for Ophthalmic Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Qin B. *Regulatory Uses of IVRT Studies on Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Smith W. *Developing Discriminatory IVRT Methods for Injectable Suspensions: Start with Why.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Xu X. *Thinking Outside the Box: Adaptive Perfusion Method to Study Drug Release from Emulsions.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Xu X. *Identifying Complex Product Research Needs to Accelerate Product-Specific Guidance (PSG) Development.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 9, 2022.

- Kozak D, and Xu X. *Approaches Using Proactive Research in Support of Product-Specific Guidance (PSG) Development.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Generic Drugs Forum: The Current State of Generic Drugs. Virtual Meeting, Apr. 27, 2022.

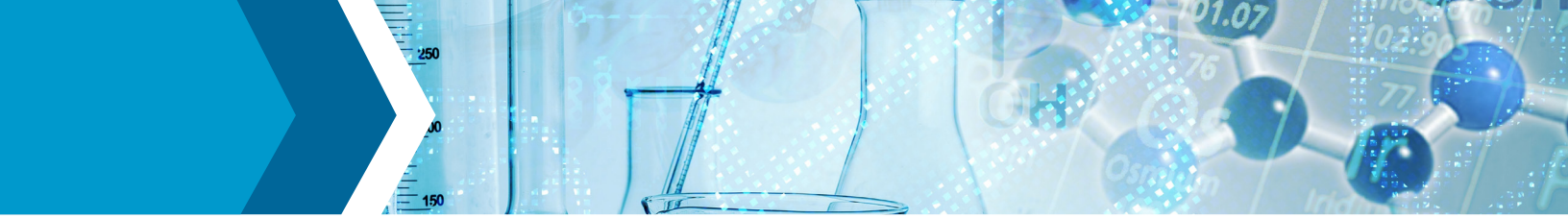
- Xu X. *In Vitro Drug Release Test for Complex Formulations.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) Student Chapter – University of Connecticut (UConn)'s Seminar. Virtual Meeting, Mar. 11, 2022.
- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Forum on Process Analytical Chemistry (IFPAC) 2022. Virtual Meeting, Feb. 27, 2022.
- Xu X. *In Vitro Release Test for Complex Drug Products: Start with Why.* Presentation at the 2021 National Institute for Pharmaceutical Technology and Education (NIPTE) Annual Research Conference: Accelerating the Drug Development Process. Virtual Meeting, Dec. 2, 2021.
- Kozak D. *Formulation Considerations for In Vitro Characterization Based Approaches of Locally Acting Complex Generic Drug Products.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 08, 2021.
- Chen K. *High Resolution ^{19}F qNMR Reveals Mass-balanced Drug Phase Distribution in Oil-in-Water Nano-Emulsion Formulations.* Presentation at the 6th International qNMR Summit 2021. Virtual Meeting, Oct. 06, 2021.

COMPLEX MIXTURES AND PEPTIDE PRODUCTS

Summary of FY 2022 Activities

Ensuring the quality of complex mixtures and peptide products and determining the equivalence between generic and brand name drugs raises several challenges. In particular, the presence of impurities may affect the quality and safety of drug products, even in trace amounts, posing potential health risks to patients due to their potential carcinogenic or immunogenic effects. Impurity profiling is necessary in the manufacturing process of these complex drug products. Undesired compounds must be detected, identified, and quantified to ensure efficacy and safety. Thus, it is essential to have reliable, accurate, and efficient analytical methods for characterizing drug products and detecting impurities.

In FY 2022, research efforts continued in the characterization of complex drug products with an emphasis on peptide and oligonucleotide products. Technological advances in peptide synthesis and characterization make it possible to demonstrate the active ingredient in a proposed generic peptide drug product is the “same” as the active ingredient in the approved peptide of rDNA origin. The FDA developed a liquid chromatography-high resolution mass spectrometry (LC-HRMS) method to identify and quantitate impurities in liraglutide products. Liraglutide, a recombinant peptide derivative of the GLP-1 receptor agonist (7-37), was approved in 2010 for Type II diabetes (Victoza®) and in 2014 for weight loss (Saxenda®). Impurity profiling of liraglutide drug products is crucial for identifying differences that may arise from manufacturing and purifications processes. FDA also continues to collaborate with EpiVax (Grant 75F40120C00157) to evaluate in silico tools including the “What If Machine” (Whim) to assess the immunogenic potential of peptide impurities that may be generated during peptide synthesis. This effort further optimizes the tools available and provides useful insights and recommendations on the use of non-clinical methods to evaluate the immunogenicity risk of these complex generics.



Several synthetic oligonucleotide drugs including antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) have been approved by FDA. However, oligonucleotides pose even greater challenges than peptides in API characterization and impurity identification. In February 2022, FDA published the first product-specific guidance (PSG) for an oligonucleotide drug, nusinersen. Internal research by FDA resulted in an LC-HRMS method for impurity profiling of synthetic oligonucleotide therapeutics (ONTs) and the **Research Highlight** section below briefly describes this method. FDA also engaged with external collaborators to investigate analytical methods to analyze the diastereomeric compositions of inotersen. A grant (1U01FD007651) has been awarded to a research group at the University of Maryland, Baltimore to investigate the diastereomeric composition of inotersen.

Synthetic ONTs are an evolving and rapidly expanding drug class that have the potential to treat a myriad of indications from common to rare and life-threatening diseases. The efficacy and safety of ONTs are highly impacted by specific sequences and structurally related impurities. However, ONTs are specifically excluded from the International Council for Harmonisation (ICH) guidelines for synthetic small molecules for impurities (Q3A and Q3B) and specifications (Q6A). In February 2022, FDA published a PSG on generic nusinersen sodium, the first PSG for this class of drugs. Comparative impurity characterization is very important in generic nusinersen development. Using custom synthesized oligonucleotides simulating nusinersen and associated impurities, FDA laboratories recently developed an LC-HRMS method to discriminate coeluting isobaric sequence variant impurities and, thereby, facilitate in-depth impurity profiling in comparative studies (**Figure 1**).

Complex Coeluting Isobaric Impurity Analysis Made Simple: HRMS-enabled In-depth Impurity Profiling of Synthetic Oligonucleotide Therapeutics (ONTs)

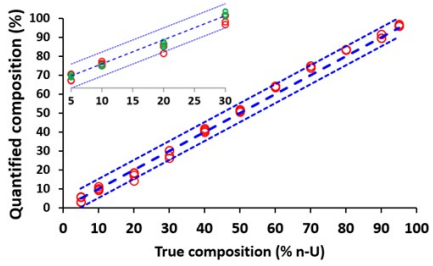
Problem statement:

- The structural modifications introduced to improve the stability, efficacy, and safety of ONTs result in a significant degree of complexity, not only in the final structure of the intended full-length product (FLP) but also in product-related impurities. Some of the impurities are challenging to analyze, such as n-U and n-C that are coeluting isobars, thus not resolved by either dimension of the conventional LC-MS.

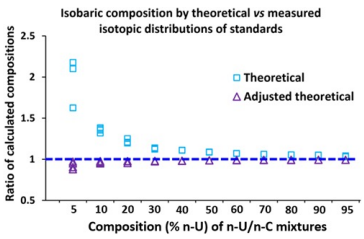
Approach:

- LC-HRMS approach to quantify mixed n-U and n-C sequence variants from multiple deletion sites by isotopic distributions

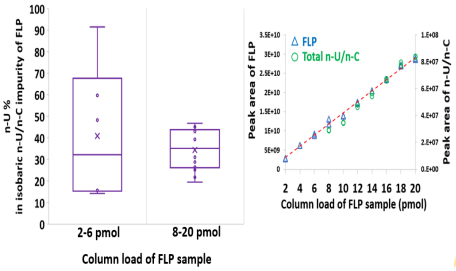
Quantified isobaric compositions of n-U/n-C mixtures



Quantified % n-U of the isobaric when standards are not available



Determined % n-U of the isobaric impurity mixture in the test sample



Summary

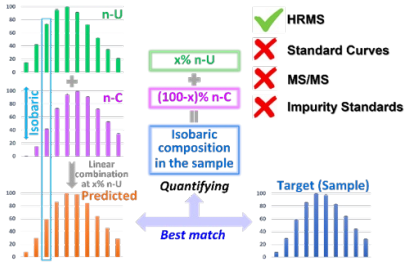


Figure 1. HRMS-enabled in-depth oligonucleotide impurity profiling exemplified by resolution of coeluting isobaric deletion sequence variant impurities.

New Grants and Contracts

- Grant (1U01FD007651-01) *Multidimensional Analytical and Computational Approach to Determine Diastereomer Compositions in Oligonucleotide Drug Products* at the University of Maryland Baltimore.

Completed Grants and Contracts

- Contract (75F40120C00157) *Immunogenicity Risk of Peptide Drug Generics and their Impurities: In Silico and In Vitro Assessment and Validation Methods* with Katie Edwards at CUBRC, Inc.

Active FDA Research

- *Analytical Characterization of Recombinant and Synthetic Peptide Product Impurities*
- *Characterization and Confirmation of the Active Pharmaceutical Ingredients in Conjugated Estrogens Cream*
- *Characterization of Synthetic Oligonucleotides to Support Generic Drug Equivalence*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Process-Related Impurity Profile Characterization in Peptide Drug Products*
- *In Vitro Innate Immune Response Assessment*

Product-Specific Guidances

There were seven new and two revised PSGs published in FY 2022 related to *Complex Mixtures and Peptide* products. The PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Colesevelam Hydrochloride Oral Bar Chewable.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Colesevelam Hydrochloride Oral Tablet.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Colesevelam Hydrochloride Oral for Suspension.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Dasiglucagon Hydrochloride Subcutaneous Solution.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Glucagon Subcutaneous Solution.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Heparin Sodium Injection Injectable.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Nusinersen Sodium Intrathecal Solution.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Secretin Synthetic Human Intravenous for Solution.* (May 2022) Link to Posting
- *New Draft Guidance for Vasopressin Intravenous Solution.* (Feb. 2022) Link to Posting

Articles

- Abdullah A, Sommers C, Hawes J, Rodriguez J, and Yang K. *Tandem Mass Spectrometric Sequence Characterization of Synthetic Thymidine-Rich Oligonucleotides.* Journal of Mass Spectrometry. (2022) 57(4): e4819. https://doi.org/10.1002/jms.4819. PMID: 35347805.

- Chen K. 2D *NMR Peak Profiling to Compare Chemical Differences between Batches of Pentosan Polysulfate Sodium.* Journal of Pharmaceutical and Biomedical Analysis. (2022) 211: 114589. https://doi.org/10.1016/j.jpba.2022.114589. PMID: 35038672.

- Holley C, Cedrone E, Donohue D, Neun B, Verthelyi D, Pang E, and Dobrovolskaia M. *An In Vitro Assessment of Immunostimulatory Responses to Ten Model Innate Immune Response Modulating Impurities (IIRMIs) and Peptide Drug Product, Teriparatide.* Molecules. (2021) 26(24): 7461. https://doi.org/10.3390/molecules26247461. PMID: 34946542.

- Thacker S, Her C, Kelley Baker L, Ireland D, Manangeeswaran M, Pang E, and Verthelyi D. *Detection of Innate Immune Response Modulating Impurities (IIRMI) in Therapeutic Peptides and Proteins: Impact of Excipients.* Frontiers in Immunology. (2022) 13: 970499. https://doi.org/10.3389/fimmu.2022.970499. PMID: 36148237.

Presentations

- Sun W. *In Vitro Binding Studies for Bioequivalence Demonstration.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.

- Li Y. *Common Deficiencies Associated with Comparative Peptide Impurity Profile Studies and Qualification of Impurity Levels and Proposed Limits.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Pang E. *Guidance for Peptide Products and Assessing Immunogenicity Risk.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Verthelyi D. *Assessing Impurities to Inform Peptide Immunogenicity Risk: Developing Informative Studies.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Yang K. *In-depth Impurity Assessment of Synthetic Oligonucleotides Enabled by High Resolution Mass Spectrometry.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Zhang D. *Oligonucleotides: Current Thinking and Analytical Challenges Identified in the Nusinersen PSG Development.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Yang K. *In-depth Impurity Profiling of Synthetic Oligonucleotides by High Resolution Mass Spectrometry.* Presentation at the 7th USP Workshop on Therapeutic Peptides and Oligonucleotides. Virtual Meeting, Feb. 28, 2022.
- Zhang D. *Developing Product-Specific Guidances on Oligonucleotides for Generic Drug Development.* Presentation at the 7th USP Workshop on Therapeutic Peptides and Oligonucleotides. Virtual Meeting, Feb. 28, 2022.
- Smith C, and Geerlof-Vidavsky I. *Research Fueling Approvals: A Case Study of Glucagon.* Presentation at the Small Business and Industry Assistance (SBIA) 2021: Pharmaceutical Quality Symposium: Innovations in a Changing World. Virtual Meeting, Oct. 26, 2021.
- Yang K. *Mass Spectrometry-based Characterization of Synthetic Oligonucleotides and Structurally Related Impurities.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Virtual Meeting, Oct. 17, 2021.

LONG-ACTING INJECTABLE, INSERTABLE OR IMPLANTABLE PRODUCTS

Summary of FY 2022 Activities

In FY 2022, research projects on long-acting injectable, insertable, or implantable (collectively LAI) products continued to focus on: 1) developing tools for characterizing complex polymeric excipients; 2) exploring methods and advanced imaging tools to better understand how variations in raw materials affect the physicochemical and drug release characteristics of a formulation; 3) creating in vitro drug release testing (IVRT) methods that have better clinical relevance and/or formulation discriminatory ability; and 4) using modeling to support, or serve as, a bioequivalence (BE) approach.

Significant progress was made exploring new methods and tools for characterizing complex polymeric excipients and related formulations including: 1) 3D-focused ion beam scanning electron microscopy (FIB-SEM) and artificial intelligence (AI)-based image analysis, 2) X-ray and micro-computed tomography (micro-CT), and 3) 3D laser scanning microscopy. A variety of products were investigated, such as poly[lactide-co-glycolide] (PLGA)-based microspheres and in situ forming implants, as well as polydimethylsiloxane levonorgestrel intrauterine systems (LNG-IUSs). The X-ray and micro-CT tools provide non-invasive methods for characterizing in situ depot formation. Laser scanning microscopy is a new tool that may be helpful to investigate the impact of manufacturing on the product surface morphology. FIB-SEM and AI-based image analysis is generating promising results, indicating potential utility for determining the underlying microstructure of LNG-IUSs and PLGA microspheres and for assessing critical formulation characteristics (see **Research Highlight** below).

In the area of in vitro release testing (IVRT), the discriminatory ability and reproducibility of different United States Pharmacopeia (USP) Apparatuses (i.e., USP Apparatus II and IV) and of different experimental conditions were evaluated for assessing drug release from LAI and implant suspension products with differences in manufacturing processes. The results indicated that it is feasible to develop reproducible and discriminatory IVRT methods to support an equivalence assessment. For LNG-IUSs, the IVRT studies seem to indicate that the drug release mechanism in an aqueous environment is solely mediated by the partitioning of the drug from reservoir to membrane then to the release media.

In the area of developing model-integrated evidence BE strategies, FDA continued to collaborate with Uppsala University (75F40119C10018) to develop and disseminate the model-integrated BE evaluation framework. Leveraging these research outcomes, a public workshop engaging multiple stake holders was held in collaboration with the Center for Research on Complex Generics on November 30, 2021. This virtual workshop helped to build consensus on the use of model-integrated evidence to demonstrate BE for complex generics, using LAI products as an example, and helped to initiate a discussion on the development of best practices for model-integrated evidence approaches to establish BE.

The potential for FIB-SEM imaging combined with AI analytics to determine the underlying microstructure of PLGA microspheres containing minocycline hydrochloride (**Table 1**) and to assess their critical quality attributes (CQAs) was demonstrated (**Figure 1**). FIB-SEM imaging combined with AI analytics was used to quantify the microstructural CQAs of the prepared PLGA microspheres. Through in-depth investigation of microsphere formulations prepared with intentional formulation and/or manufacturing differences, microstructural CQAs were identified. These CQAs included the abundance, domain size, and distribution of the active pharmaceutical ingredient (API), the PLGA polymer, and the microporosity. 3D models, digitally transformed from the FIB-SEM images, were reconstructed to understand drug release behavior and to predict drug release. The image-based release modelling predictions were validated with IVRT experiments. Sensitivity analysis revealed that the release can be affected by the distribution and size of the API particles and by the porosity within the polymeric microspheres, as captured through FIB-SEM imaging. The results of this research improved our understanding of the impact of processing parameters on product quality and performance. The study also provided a proof of concept for using AI-based imaging analysis to quantitatively and predictively correlate the microstructure of a polymeric matrix with formulation and manufacturing parameters.

Table 1. PLGA microsphere samples and preparation conditions

Sample ID	PLGA source	Facility	Stir method	Stir speed (RPM)	Span 85	Silicone oil η (cSt)	Drug loading (%, w/w) *	Particle Size (D_{50}, µm)	
								Volume distribution	Number distribution
D1153	Lactel	A	Stir bar	550	-	350	28.86 ± 0.35	121.99 ± 1.24	7.85 ± 0.16
D1228	Resomer® RG503H	B	Overhead	350	0.1%	350	27.63 ± 0.88	81.11 ± 1.46	59.83 ± 1.82
D1270	Resomer® RG503H	B	Overhead	350	-	350	27.53 ± 0.17	84.89 ± 3.97	55.68 ± 1.44
D1271	Resomer® RG503H	B	Overhead	350	0.005%	350	27.59 ± 0.26	69.69 ± 0.53	50.83 ± 0.31
D1370	Resomer® RG503H	C	Overhead	350	-	350	26.18 ± 0.31	74.01 ± 1.81	55.95 ± 0.34
D1397	Resomer® RG503H	C	Overhead	350	-	1000	26.17 ± 0.14	62.34 ± 0.39	48.03 ± 0.18
D1406	Resomer® RG503H	C	Overhead	600	-	350	26.37 ± 0.27	72.47 ± 0.81	54.12 ± 0.16
D1407	Resomer® RG503H	C	Overhead	600	-	1000	26.41 ± 0.47	57.56 ± 0.40	41.43 ± 0.36
D830 (RLD)	On the market product from Bausch Health Companies						27.91 ± 0.56	60.08 ± 2.50	43.58 ± 3.43

* The experiments were performed in triplicate and the results are expressed as mean ± SD.

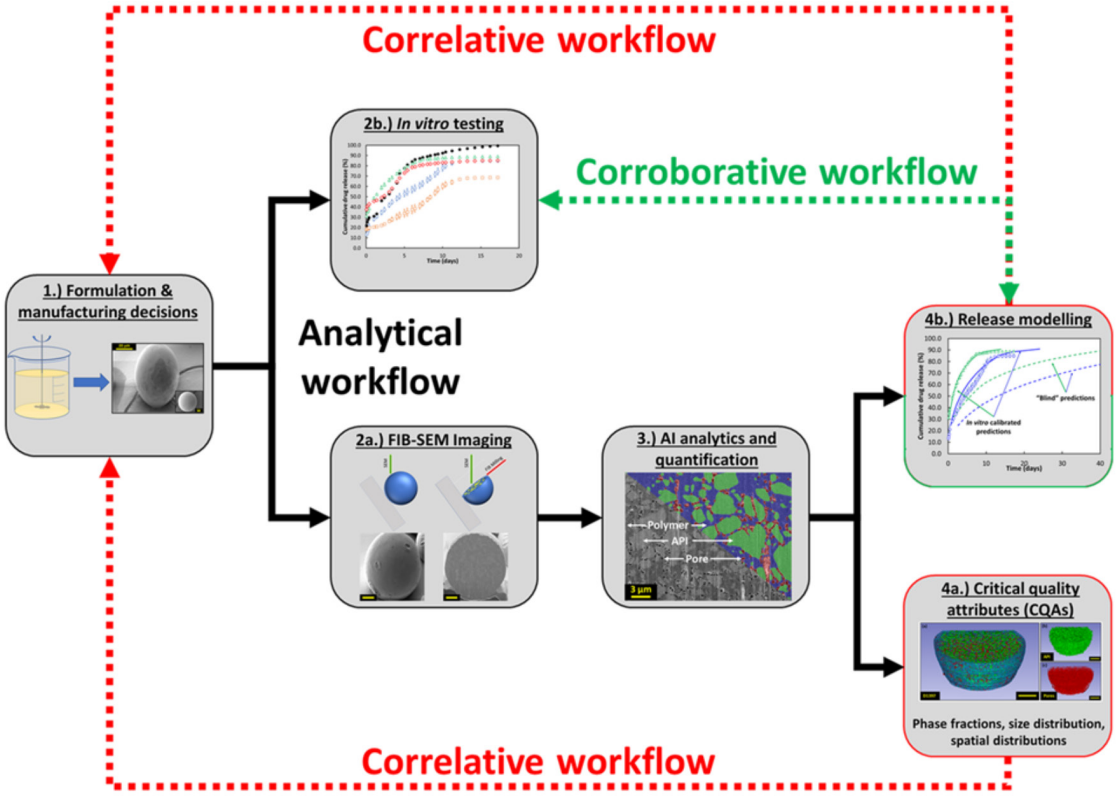


Figure 1. Image-based controlled release microsphere characterization workflow starting with formulation and manufacturing design, followed by limited in vitro release testing simultaneously conducted alongside FIB-SEM imaging and quantification. Solid black arrows indicate the analytical workflow, while the dotted red and green lines indicate correlative and corroborative workflow steps, respectively. The final quantification of the CQAs (Step 4a) can be used to refine the formulation and processing parameters (correlative workflow), while the release modelling (Step 4b) is refined by potentially limited in vitro testing (corroborative workflow) and also is used to refine formulation and processing parameters (correlative workflow).

New Grants and Contracts

- Contract (75F40122C00163) *Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation* at DigiM Solution LLC ; University of Connecticut, Department of Pharm. Sciences.
- Contract (75F40122C00019) *Correlation between Material Properties, Manufacturing Process, Structural Properties, and Quality Attributes of Long-Acting, Biodurable Implants* at the University of Texas at Austin.

Continuing Grants and Contracts

- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane Jane Burgess at the University of Connecticut.
- Contract (75F40120C00136) *Assessing Long-Acting Injectable Formulations Using In Vivo Imaging* with Xiuling Lu at the University of Connecticut.
- Contract (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at Regents of the University of Michigan, College of Pharmacy.
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long-Acting Injectable Drug Products to Accelerate their Generic Development* with Dianne Burgess at the University of Connecticut.
- Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert Beis at State University of New York at Buffalo.
- Contract (75F40120C00127) *Characterization of Exparel, Understanding of Critical Manufacturing Process Parameters and Characterization of Drug Release Mechanisms In Vitro and In Vivo* at Regents of the University of Michigan.
- Contract (75F40120C00021) *Impact of Polymer Attributes on the Performance of in Situ Forming Implants Improve Scientific Approaches to Evaluate Generic Drugs* at the University of Connecticut.
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* at the University of Texas at Austin.

Completed Grants and Contracts

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

Active FDA Research

- *Affordable Generics for Menopausal Women: Mechanistic Evaluation of Formulation Design and Performance of Estradiol Intravaginal Ring Products*
- *Assessing Impact of Excipient Source and Manufacturing Process on Quality and Performance of Bupivacaine Implants*
- *Characterization and Development of Accelerated In Vitro Release Testing Method for Intrauterine Systems.*
- *Evaluation of Dexamethasone Intracanalicular Insert to Support Determination of Bioequivalence*
- *Evaluation of Levonorgestrel Particle Size and Distribution in Intrauterine Systems using Raman Spectroscopy*
- *In Vivo Evaluation of Dexamethasone Intravitreal Unilateral Implants in Rabbits*
- *In Vitro Characterization and Development of In Vitro Release Testing Method for Bupivacaine Multivesicular Liposomes*
- *Manufacturing of Peptide Containing PLGA Microspheres to Support Immunogenicity Assessment*

General Guidance

- *New Draft Guidance for Industry Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (Apr. 2022) Link to Posting

Product-Specific Guidances

There were seven new and two revised PSGs published in FY2022 related to *Long-Acting Injectable, Insertable or Implantable* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Bupivacaine Infiltration Solution Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Chlorhexidine Gluconate Dental Tablet.* (May 2022) Link to Posting
- *New Draft Guidance for Etonogestrel Implant Implantation.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Exenatide Synthetic Subcutaneous for Suspension, Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate Subcutaneous Powder, 45mg.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate Subcutaneous Powder, 30mg.* (Feb. 2022) Link to Posting
- *Revised Draft Guidance for Medroxyprogesterone Acetate Injectable, Injection, 150mg/ml.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Methylprednisolone Acetate Injectable, Injection.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Progesterone Vaginal System.* (Feb. 2022) Link to Posting

Articles

- Bao Q, Wang X, Zou Y, Wang Y, and Burgess D. *In Vitro Release Testing Method Development for Long-Acting Injectable Suspensions.* International Journal of Pharmaceutics. (2022) 622: 121840. https://doi.org/10.1016/j.ijpharm.2022.121840. PMID: 35595043.

- Beig A, Ackermann R, Wang Y, Schutzman R, and Schwendeman S. *Minimizing the Initial Burst of Octreotide Acetate from Glucose Star PLGA Microspheres Prepared by the Solvent Evaporation Method.* International Journal of Pharmaceutics. (2022) 624: 121842. https://doi.org/10.1016/j.ijpharm.2022.121842. PMID: 35609832.

- Clark A, Wang R, Qin Y, Wang Y, Zhu A, Lomeo J, Bao Q, Burgess D, Chen J, Qin B, Zou Y, and Zhang S. *Assessing Microstructural Critical Quality Attributes in PLGA Microspheres by FIB-SEM Analytics.* Journal of Controlled Release. (2022) (349): 580-591. https://doi.org/10.1016/j.jconrel.2022.06.066. PMID: 35803326.

- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Effect of Crosslinking on the Physicochemical Properties of Polydimethylsiloxane-Based Levonorgestrel Intrauterine Systems.* International Journal of Pharmaceutics. (2021) 609: 121192. https://doi.org/10.1016/j.ijpharm.2021.121192. PMID: 34666142.

- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Impact of Polymer Crosslinking on Release Mechanisms from Long-Acting Levonorgestrel Intrauterine Systems.* International Journal of Pharmaceutics. (2022) 612: 121383. https://doi.org/10.1016/j.ijpharm.2021.121383. PMID: 34919997.

- Garner J, Skidmore S, Hadar J, Park H, Park K, Otte A, Jhon Y, Xu X, Qin B, and Wang Y. *Scanning Analysis of Sequential Semisolvent Vapor Impact to Study Naltrexone Release from Poly(lactide-co-glycolide) Microparticles.* Molecular Pharmaceutics. (2022) 19(11): 4286-4298. https://doi.org/10.1021/acs.molpharmaceut.2c00595. PMID: 36166409.

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

- Kuehster L, Jhon Y, Wang Y, Smith W, Xu X, Qin B, Zhang F, and Lynd N. *Stochastic and Deterministic Analysis of Reactivity Ratios in the Partially Reversible Copolymerization of Lactide and Glycolide.* Macromolecules. (2022) 55(16): 7171-7180. https://doi.org/10.1021/acs.macromol.2c00757.

- Sharan S, Choi S, Zou Y, Wang Y, Kim M, Fang L, Choi S, Makhlouf F, Grosser S, Zhang X, and Zhao L. *Application of Modeling and Simulation to Identify a Shortened Study Duration and Novel Bioequivalence Metric for a Long-Acting Intrauterine System.* The AAPS Journal. (2022) 24(3): 63. https://doi.org/10.1208/s12248-022-00715-z. PMID: 35501412.
- Wan B, Bao Q, Zou Y, Wang Y, and Burgess D. *Effect of Polymer Source Variation on the Properties and Performance of Risperidone Microspheres.* International Journal of Pharmaceutics. (2021) 610: 121265. https://doi.org/10.1016/j.ijpharm.2021.121265. PMID: 34748813.

Posters

- Costello M, Zhang F, Liu J, Wang Y, and Qin B. *Manufacture and Process Control of Dexamethasone Intravitreal Implants Produced by Hot Melt Extrusion.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 13, 2022.
- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Qin B, Jhon Y, and Wang Y. *Morphological Analysis of Naltrexone-Poly(lactide-co-glycolide) (NTX-PLGA) Microparticles: Dynamic Role of Naltrexone on PLGA Degradation.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 13, 2022.
- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Qin B, Jhon Y, and Wang Y. *Scanning Analysis of Semi-Solvent Impact Using Sequential Solvent Vapor (SASSI-SSV): Assay of Poly(lactide-co-glycolide)-Naltrexone (PLGA-NTX) Microparticles.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 13, 2022.
- Clark A, Wang R, Burgess D, and Zhang S. *Assessing the Impact of Formulation on Microstructure Critical Quality Attributes in PLGA Microspheres.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 11, 2022.
- Fanse S, Bao Q, Zou Y, Wang Y, and Burges D. *Effect of Polymer Crosslinking on Release Mechanisms from Long-acting Intrauterine Systems.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 11, 2022.
- Clark A, Wang R, Wang Y, Qin B, Zhu A, Bao Q, Lomeo J, Burgess D, and Zhang S. *PLGA Microsphere Formulation Development Guided by Microstructure Equivalence Assessment Using FIB-SEM Imaging and AI Image Analytics.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.

- 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.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Impact of Polymer Crosslinking on the Properties and Performance of Levonorgestrel Intrauterine Systems.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Lin X, Beringhs A, Hargrove D, Jay M, Wang Y, Qin B, and Lu X. *Assessing Long-Acting Injectable Formulations Using In Vivo Imaging.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Wan B, Andhariya J, Bao Q, Wang Y, Zou Y, and Burgess D. *Impact of Polymer Source Variation on Risperidone Microsphere Performance.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Wang R, Bao Q, Wang Y, Qin B, Lomeo J, Zhang S, and Burgess D. *Effect of Coacervation Processing Parameters on Drug Release from Minocycline Hydrochloride Microspheres.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Zaman R, Smith W, Park J, Liang J, Feng X, Fan Z, Wang Y, Zheng J, and Xu X. *Understanding the Drug Release Mechanism of Long-term Intrauterine Systems.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Zhang F. *Melt-Extruded Dexamethasone Ophthalmic Implants: Process, Structure and In Vitro Drug Release.* Presentation at the 12th American Drug Delivery Formulation Summit. San Diego, California, Sep. 26, 2022.

- Feng K. *Application of Quantitative Modeling and Simulations to Bioequivalence Determination for Long-Acting Injectables – Sharing Research Progress and Regulatory Experience.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Qin B. *Current Thinking and Research On In Vitro Only Approaches for Injectable Drug Substance Suspensions-A Scientific Discussion.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Smith W. *Challenges and Considerations in Developing In Vitro Release Testing Methods for Parenteral Suspensions.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.

- Costello M, Zhang F, Liu J, Wang Y, and Qin B. *Manufacture and Process Control of Dexamethasone Intravitreal Implants Produced by Hot Melt Extrusion.* Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 13, 2022.

- Shakleya D. *Case Study: Non-Standard Matrices Considerations - Ocular Implant.* Presentation at the 23rd Annual Land O' Lakes Bioanalytical Conference. Virtual Meeting, Jul. 13, 2022.

- Kozak D. *A Scientific and Regulatory Overview of IVRT: Current Considerations and Challenges.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Qin B. *Regulatory Uses of IVRT Studies on Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Burgess D. *IVRT Method Development for API Suspension Products and Validation with In Vivo Model.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Zhang F. *Melt-extruded Dexamethasone Ophthalmic Implants-Process, Structure, and In Vitro Drug Release.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting. Jun. 29, 2022.

- Zhang S. *Advanced Imaging Technologies and AI Based Image Analysis for Mechanistic Characterization and Prediction of Complex Drug Release.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Smith W. *Developing Discriminatory IVRT Methods for Injectable Suspensions: Start with Why.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Forum on Process Analytical Chemistry (IFPAC) 2022. Virtual Meeting, Jun. 14, 2022.

- Hooker, A. *Research Related to Model Master Files to Establish the Concept and Details for Practical Implementation of Model- Integrated BE Packages in Regulatory Submissions.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 9, 2022.

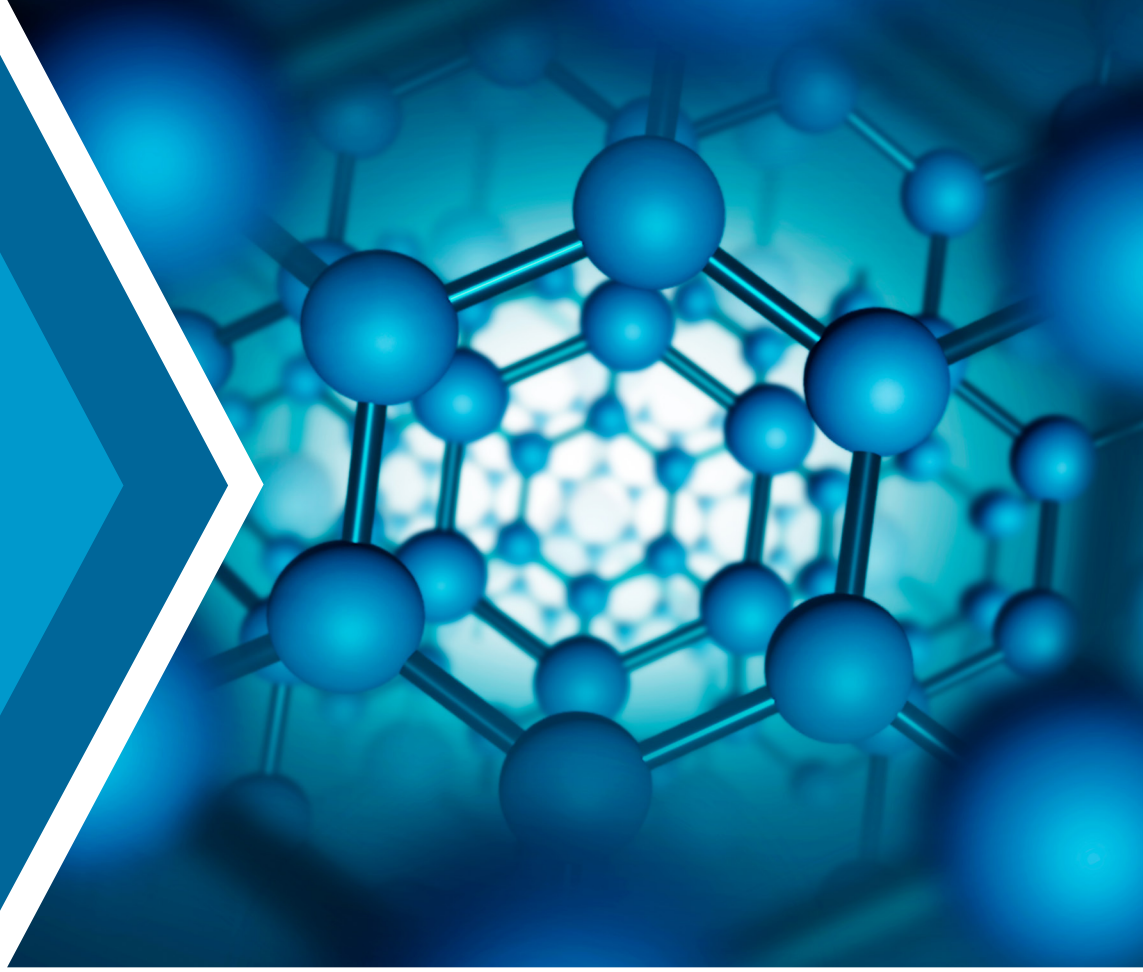
- O'Connor T. *Characterization of Excipients in Complex Dosage Forms – FDA Research Highlights.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 9, 2022.

- Hooker A. *Model-Integrated Methods and Innovative Study Designs for Generic LAI Product Development and Regulatory Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products. Virtual Meeting, Nov. 30, 2021.

- Yoon M. *Model-Integrated Evidence for Bioequivalence Assessment of Long-Acting Injectables from a Generic Drug Perspective.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products. Virtual Meeting, Nov. 30, 2021.

- Yoon M. *Model-Integrated Bioequivalence Establishment: Long-Acting Injectable Drug Products.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 10, 2021.

COMPLEX INJECTABLES, FORMULATIONS AND NANOMATERIALS

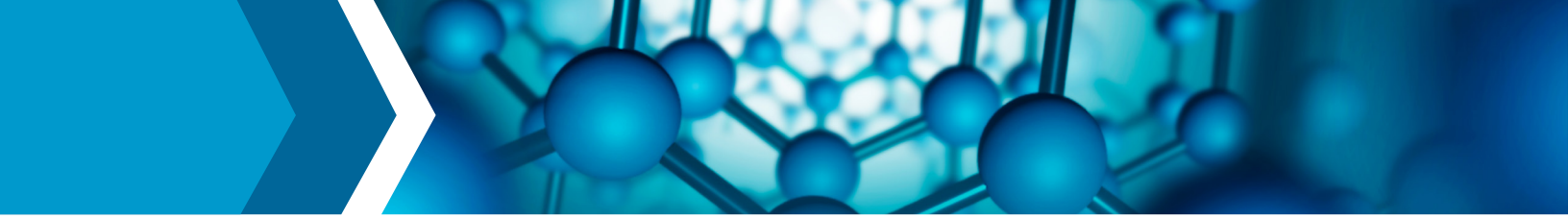


Summary of FY 2022 Activities

In FY 2022, Generic Drug User Fee Amendments (GDUFA) funded research efforts for complex injectables, formulations, and nanomaterials focused on developing new analytical characterization and in vitro drug release test (IVRT) methods.

Colloidal iron-carbohydrate products are core shell-structured nanoparticles generally indicated for treating iron deficiency. Differences in the manufacturing process and the carbohydrate used can give rise to differences in the physicochemical properties (e.g., interaction between the carbohydrate and iron core) as well as absorption, distribution, metabolism, and excretion properties. To elucidate the factors influencing such differences, FDA collaborated with academic institutions to develop new analytical methods to better characterize these complex drug products. A contract awarded to Purdue University (contract #75F40121C00189) focuses on (1) developing an understanding of the structure of ferric carboxymaltose drug substance using a suite of analytical techniques, including Mössbauer spectroscopy, powder and synchrotron X-ray diffraction, nuclear magnetic resonance (NMR) spectroscopy, particle size, and charge determination; (2) identifying the critical quality attributes (CQAs) that impact product performance; and (3) determining how variation in a manufacturing process impacts the product performance.

A grant awarded to the University of Maryland, Baltimore (grant #1U01FD007363) focuses on understanding the composition of a recently approved new colloidal iron carbohydrate drug product, ferric derisomaltose. The project aims to develop and validate analytical methods to analyze the iron core structure, the carbohydrate ligand, and the interaction between the iron core and the ligand. The project also aims to characterize drug substance composition, drug product physicochemical properties, as well as inter-batch and intra-batch variability of the brand name product. Collectively, the insights gained from the two research projects should greatly facilitate generic drug development for this class of products.



Additional external research conducted in FY 2022 included: 1) developing an in silico systems-based multiscale model to capture the various biological and physicochemical events that affect the transport and residence of nanoparticles and their active pharmaceutical ingredient cargo among different extracellular and intracellular compartments (contract #75F40119C10139); 2) developing hyperspectral interferometric scattering microscope method to characterize nanoparticle-based therapeutics (grant #U01FD005946); and 3) identifying formulation CQAs, establishing a mechanistic (i.e., physiologically based pharmacokinetics (PBPK) model-based) in vitro-in vivo correlation (IVIVC) model, and elucidating potential reasons for the observed discrepancy between IVIVCs with animal models and human subjects for long-acting injectable suspension products (contract #75F40121C00133).

FDA's internal studies in FY 2022 continued to focus on developing new IVRT methods and characterization methods. There have been challenges to characterize the in vitro release of paclitaxel from albumin-bound paclitaxel nanoparticle drugs due to the hydrophobic nature of paclitaxel and difficulty in separating the free drug from particulate drug. FDA researchers developed a drug release method using a USP type 2 dissolution apparatus and a bi-phasic release media containing aqueous and organic phase (1-octanol). This bi-phasic release media helps the released paclitaxel to partition rapidly from the aqueous phase into the organic phase, providing a 'sink'. This approach made it possible to measure the amount of paclitaxel released from albumin-bound paclitaxel nanoparticles with fast enough sampling to characterize the burst release, while avoiding the interference of albumin or plasma proteins. In addition, the FDA lab conducted comparative physicochemical characterizations on brand and approved generic doxorubicin HCl liposomal injection products. The methods developed as an outcome of this research supported the development of international consensus standards by the ASTM Committee E56 on Nanotechnology. Moreover, FDA evaluated the antitumor efficacy of these products using a preclinical ovarian xenograft animal model. The study demonstrated that the antitumor efficacy observed with the brand name and approved generic doxorubicin HCl liposomal injection products was similar, contrary to a previous report in the literature suggesting inferior performance of generic liposomal doxorubicin compared to brand name Doxil in preclinical tumor models[1].

[1] Smith JA, Mathew L, Burney M, Nyshadham P, and Coleman RL. *Equivalency Challenge: Evaluation of Lipodox® as the Generic Equivalent for Doxil® in a Human Ovarian Cancer Orthotropic Mouse Model.* Gynecologic Oncology. (2016). 141(2): 357-363. https://doi.org/10.1016/j.ygyno.2016.02.033 PMID: 26946092.

Phytonadione injection contains an oil-like immiscible drug substance, which is mixed with surfactant, then further dispersed in an aqueous phase. The Orange Book, product labeling, and USP monograph designated the dosage form of phytonadione injection using terminologies which represent subtly different dispersion states (injection, aqueous colloidal solution, and emulsion, respectively). Consequently, a lack of clarity about the dosage form(s) presented significant regulatory challenges, including the determination of appropriate characterizations and criteria for assessing product equivalence. To address these challenges, FDA conducted a study to compare how different sources of surfactant and manufacturing processes impact the formulation dispersion state, the particle size distribution (PSD), and the determination of the product's dosage form.

To help address these questions, critical formulation characteristics such as critical micelle concentration (CMC), micelle PSD, and processing behavior during the formulation procedure of three surfactants were evaluated. Three polyoxyethylated fatty acid derivative surfactants made with different ratios of ethylene oxide (n = 30, 35, 40) exhibited comparable characteristics (CMC, micelle size) and similar behavior during preparation, indicating that it might be possible to use them interchangeably. Both the manufacturing process (e.g., mixing, temperature) and formulation composition (i.e., surfactant to oil ratio) affected the initial dispersion state of the formulation, producing macro-, nano-, or micro-emulsions (**Figure 1**. top panel). Notably, both appearance (turbidity) and, more quantitatively, PSD were found to be useful surrogates for distinguishing nanoemulsions (with a broad PSD and turbid appearance) from microemulsions (with a monodisperse PSD and translucent appearance). For the phytonadione injection composition the nanoemulsion dispersion state represented a transient state for the system, which was limited by kinetic constraints like surfactant lability. With enough time and energy (thermal or mechanical) the phytonadione injection formulations could revert to the most energetically favored microemulsion dispersion state (**Figure 1**. Bottom panel).

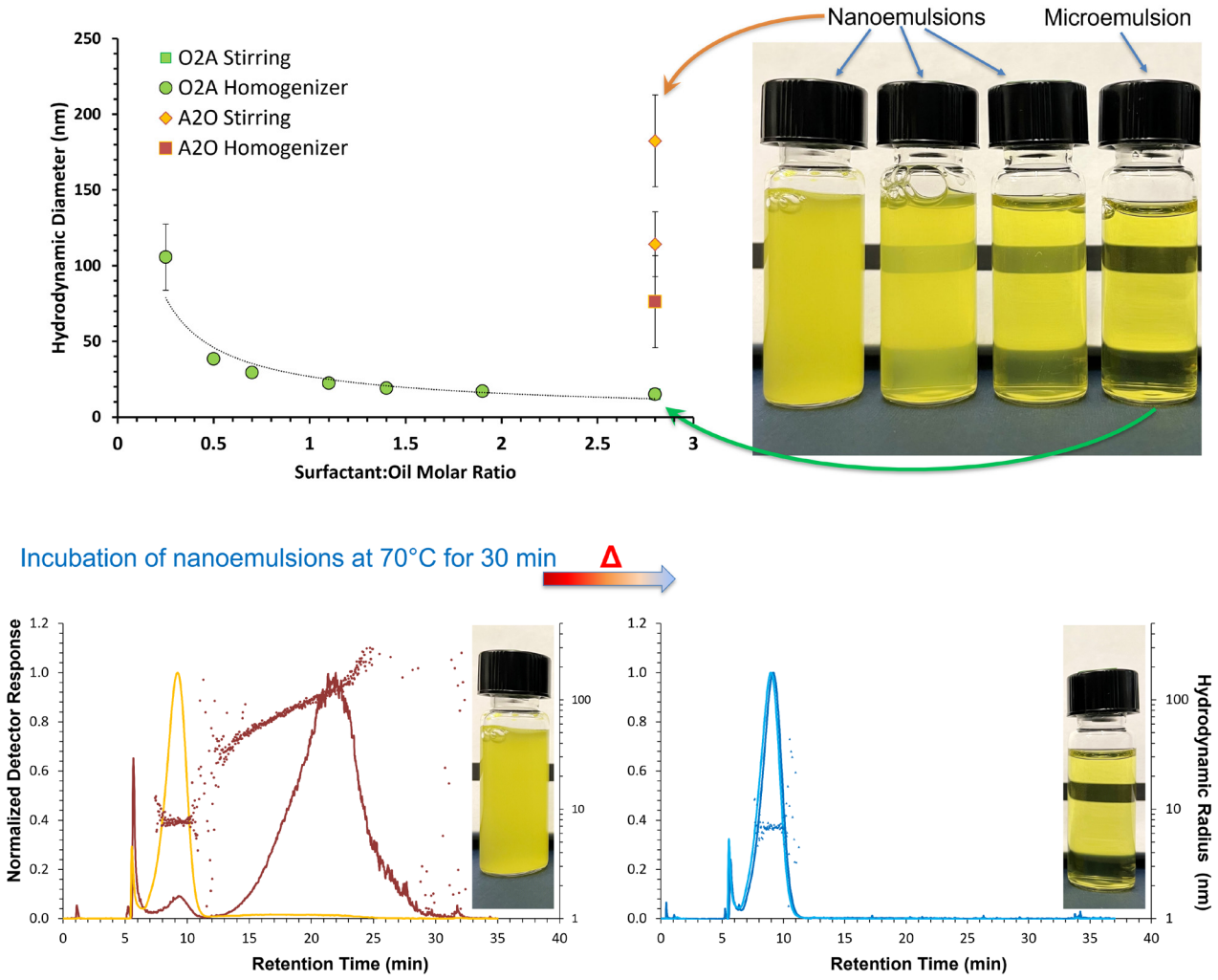


Figure 1. Particle sizes (top left) for formulations prepared at different compositions (surfactant to oil ratio, S:O) and using different component orders of addition (Aqueous to Oil; "A2O", or Oil to Aqueous; "O2A") and mixing procedures at S:O= 2.8 with accompanying representative images (top right). Asymmetric flow field flow fractionation (AF4) fractograms for nanoemulsion formulation before and after incubation at 70°C for 30 minutes (bottom panels); UV-Vis detector response (shown in yellow and light blue) with light scattering intensity at 90° from MALS (brown and dark blue) are overlaid with hydrodynamic radius from online DLS (scatter). *Insets: Still images of formulations before (left) and after (right).*

Continuing Grants and Contracts

- Grant (5U01FD005946-04) *Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics* with Taylor Woehl at the University of Maryland, College Park.
- Grant (1U01FD007363) *Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex - Ferric Derisomaltose* with Sarah L. Michel at the University of Maryland, Baltimore.
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long-Acting Injectable Drug Products to Accelerate their Generic Development* with Diane J. Burgess at the University of Connecticut.
- Contract (75F40119S30028) *Nanofluidic Slit Devices for Measuring Nan-Particle Drug Concentration to Improve Complex Drug Regulation* at NIST/CNST.
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie Au at IQSP - Institute of Quantitative Systems Pharmacology.
- Contract (75F40121C00189) *Characterization of Carboxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes* with Eric J. Munson at Purdue University.

Active FDA Research

- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Complex Generic Drug Bioequivalence*
- *In Vitro Characterization and Development of In Vitro Release Testing Method for Bupivacaine Multivesicular Liposomes*
- *In Vitro Performance Characterizations of Sucroferric Oxyhydroxide to Establish Bioequivalence Methods*

Product-Specific Guidances

There were four new and seven revised PSGs published in FY 2022 related to *Complex Injectables* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Bupivacaine Solution, Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Cyclosporine Emulsion.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Cytarabine; Daunorubicin Powder.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Dantrolene Sodium for Suspension.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Doxorubicin Hydrochloride Injectable Liposomal Injection.* (May 2022) Link to Posting
- *New Draft Guidance on Irinotecan Hydrochloride Injectable, Liposomal Intravenous.* (Feb. 2022) Link to Posting
- *Revised Draft Guidance for Medroxyprogesterone Acetate Injectable, Injection, 400 mg/ml.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Medroxyprogesterone Acetate Injectable, Injection, 150 mg/ml.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Meloxicam Solution, Intravenous.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Methylprednisolone Acetate Injectable Injection.* (Feb. 2022) Link to Posting
- *Revised Draft Guidance for Triamcinolone Acetate Injection Injectable.* (Nov. 2021) Link to Posting

Articles

- Ansar S, Jiang W, and Mudalige T. *Analysis of Verteporfin Liposomal Formulations for Phospholipids and Phospholipid Degradation Products by Liquid Chromatography-mass Spectrometry (LC-MS).* Journal of Pharmaceutical and Biomedical Analysis. (2022) 208: 114473. https://doi.org/10.1016/j.jpba.2021.114473. PMID: 34814079.
- Koo B, Liu Y, Abboud M, Qin B, Wu Y, Choi S, Kozak D, and Zheng J. *Characterizing How Size Distribution and Concentration Affect Echogenicity of Ultrasound Contrast Agents.* Ultrasonics. (2023) 127: 106827. https://doi.org/10.1016/j.ultras.2022.106827. PMID: 36063769.

- Liang J, Koo B, Wu Y, Manna S, N, Patel M, Park J, Kozak D, Wang Y, and Zheng J. *Characterization of Complex Drug Formulations using Cryogenic Scanning Electron Microscopy (Cryo-SEM).* Current protocols. (2022) 2(4): e406. https://doi.org/10.1002/cpz1.406. PMID: 35384403.

- Marx R, Lee J, Svirkin Y, Yoon S, Landrau N, Kaisar M, Qin B, Park J, Alam K, Kozak D, Wang Y, Xu X, Zheng J, and Rivnay B. *Physicochemical Surrogates for In Vitro Toxicity Assessment of Liposomal Amphotericin B. International Journal of Pharmaceutics.* (2022) 628: 122273. https://doi.org/10.1016/j.ijpharm.2022.122273. PMID: 36228881.

- Svirkin Y, Lee J, Marx R, Seongkyu Y, Landrau N, Kaisar M, Qin B, Park J, Alam K, Kozak D, Wang Y, Xu X, Zheng J, and Rivnay B. *Amphotericin B Release Rate is the Link between Drug Status in the Liposomal Bilayer and Toxicity.* Asian Journal of Pharmaceutical Sciences. (2022) 17(4): 544-556. https://doi.org/10.1016/j.ajps.2022.04.007. PMID: 36105314.

- Wang D, Park J, Zheng J, Cai B, Keire D, and Chen K. *Multiphase Drug Distribution and Exchange in Oil-in-Water Nanoemulsion Revealed by High-Resolution ^{19}F qNMR.* Molecular Pharmaceutics. (2022) 19(7): 2142-2150. https://doi.org/10.1021/acs.molpharmaceut.2c00025. PMID: 35657300.

Posters

- Smith W, Liu H, Wang Y, Kozak D, and Xu X. *Evaluation of Formulation Processes for Dosage Form Determination of Phytonadione Injectables.* Poster Presentation at the 22nd International Symposium on Field- and Flow-Based Separations. Riverside, California, Sep. 11, 2022.

- Gamage P, Yurtsever F, Jiang W, and Mudalige T. *Novel Drug Release Profiling Method for Albumin-Bound Paclitaxel Nanoparticle Drug Products.* Poster Presentation at the 5th FDA/PQRI Conference on Advancing Product Quality: Advancing Quality Technology of Future Pharmaceuticals. Virtual Meeting, Dec. 01, 2021.

- Ahmed S, Yilmaz H, and Willett D. *Simultaneous cryogenic Scanning Electron Microscopy (Cryo-SEM) and Raman Analysis for Characterization of Nanomedicine.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 17, 2021.

- Smith W, Bae J, Zhang Y, Wang Y, Qin B, Kozak D, Ashraf M, and Xu X. *Impact of Particle Flocculation on Dissolution and Implications on Bioavailability of Injectable Suspensions.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: A Novel In Vitro Drug Release Testing Method for Complex Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Ahmed S, Yilmaz H, and Willett D. *Comparative Study of Cryofixation Methods on Size and Morphology of Nanoparticle Albumin Paclitaxel (NAP) via cryogenic Scanning Electron Microscopy (Cryo-SEM).* Poster Presentation at the Great Scientific Exchange (SCIX) 2021. Virtual Meeting, Oct. 01, 2021.

Presentations

- Alam K. *Mechanistic Modeling of Complex Injectables: Recommendations to Navigate Regulatory Challenges.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Smith W. *Challenges and Considerations in Developing In Vitro Release Testing Methods for Parenteral Suspensions.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Xu X. *Thinking Outside the Box: A Regulatory Perspective on Innovation through Flow Processes.* Presentation at the 22nd International Symposium on Field- and Flow-Based Separations. Riverside, California, Sep. 12, 2022.
- Smith W. *Assessing Morphological Variation in Liposomal Drug Products using Asymmetrical Flow Field-Flow Fractionation.* Presentation at the 22nd International Symposium on Field- and Flow-Based Separations. Riverside, California, Sep. 11, 2022.
- Kozak D. *A Scientific and Regulatory Overview of IVRT: Current Considerations and Challenges.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.
- Qin B. *Regulatory Uses of IVRT Studies on Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.
- Smith W. *Developing Discriminatory IVRT Methods for Injectable Suspensions: Start with Why.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.

- Xu X. *Thinking Outside the Box: Adaptive Perfusion Method to Study Drug Release from Emulsions.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop on In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products. Virtual Meeting, Jun. 29, 2022.
- Smith W. *Impact of Particle Flocculation on Particle Size Determination and Implications on Dissolution and Bioavailability of Injectable Suspensions.* Presentation at the International Forum on Process Analytical Chemistry (IFPAC) 2022. Virtual Meeting, Jun. 14, 2022.
- O'Connor T. *Characterization of Excipients in Complex Dosage Forms – FDA Research Highlights.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 9, 2022.
- Kozak D, and Xu X. *Approaches Using Proactive Research in Support of Product-Specific Guidance (PSG) Development.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Generic Drugs Forum: The Current State of Generic Drugs. Virtual Meeting, Apr. 27, 2022.
- Xu X. *In Vitro Drug Release Test for Complex Formulations.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) Student Chapter – University of Connecticut (UConn)'s Seminar. Virtual Meeting, Mar. 11, 2022.
- Xu X. *Regulatory Perspective and Quality Considerations on Drug Products Containing Nanomaterials: Guidance and Research.* Presentation at the ACS POLY Workshop. Virtual Meeting, Feb. 21, 2022.
- Xu X. *In Vitro Release Test for Complex Drug Products: Start with Why.* Presentation at the 2021 National Institute for Pharmaceutical Technology and Education (NIPTE) Annual Research Conference: Accelerating the Drug Development Process. Virtual Meeting, Dec. 02, 2021.
- Srinivasan C, and Li Y. *Research Fueling Approval: A Case Study of Ferumoxytol.* Presentation at the Small Business and Industry Assistance (SBIA) 2021: Pharmaceutical Quality Symposium: Innovations in a Changing World. Virtual Meeting, Oct. 27, 2021.
- Chen K. *High Resolution ^{19}F qNMR Reveals Mass-balanced Drug Phase Distribution in Oil-in-Water Nano-Emulsion Formulations.* Presentation at the 6th International qNMR Summit 2021. Virtual Meeting, Oct. 06, 2021.

INHALATION AND NASAL PRODUCTS

Summary of FY 2022 Activities

In FY 2022, research efforts for inhalation and nasal products continued to focus on evaluating potential bioequivalence (BE) methods as alternatives to conducting a comparative clinical endpoint (CCEP) BE study.

Building off their previous research, University of Florida (contract #75F40119C10154) researchers found that the type of anatomical mouth-throat model and inhalation profile used significantly contributed to the deposition performance of the solution and suspension-based metered dose inhalers (MDIs) tested. Interestingly, the limited correlation between the two studies demonstrated that aerosol droplet size assessment using laser diffraction serves as an additional characterization method rather than an alternative to cascade impactor-based realistic in vitro methods for the estimation of MDI lung deposition. Additional research at the University of Florida (grant #U01FD004943) found a limited correlation between certain MDI spray velocity parameters and spray shape and actuator device characteristics, illustrating the challenges with understanding the complex relationships governing MDI performance. Research conducted at the University of Texas Austin (contract #HHSF223201710169C) identified surface energy characterization methods, like inverse gas chromatography, as potential predictive tools for detecting variability in dry powder inhaler (DPI) aerosol performance.

For nasal drug products, Virginia Commonwealth University researchers continued their efforts developing in vitro nasal models that can represent the inter-subject variability of posterior nasal deposition following nasal suspension spray administration, with their current models representing pediatric patients (contract #75F40120C00172). So far, three adult models have been selected while the testing of the pediatric models is ongoing, with results showing a range of 43.5 - 94% in posterior deposition[1,2].

Several in silico modeling studies were completed that predicted DPI and nasal product behavior. Princeton University (grant #1U01FD006514) researchers used both a computational fluid dynamics (CFD) and discrete element method (DEM) model to investigate the influence of dose loading and device characteristics on reservoir-based DPI aerosolization properties[3]. North Carolina State University (grant #1U01FD006537) workers studied mucociliary clearance effects on drug absorption in a new CFD model that, when combined with a physiologically based pharmacokinetic (PBPK) model, explored the intersubject variability influence on deposition and absorption[4] and predicted systemic pharmacokinetics (PK)[5]. In addition, previously obtained nasal deposition data aided the assessment of including cloud effects and the effects of post-deposition liquid motion and spray-wall interactions in CFD models of nasal suspension spray behavior to improve model validation and prediction[6,7,8].

---

1 Alfaifi A, Hosseini S, Esmaeili AR, Walenga R, Babiskin A, Schuman T, Longest W, Hindle M, and Golshahi L. *Anatomically Realistic Nasal Replicas Capturing the Range of Nasal Spray Drug Delivery in Adults.* International Journal of Pharmaceutics. (2022) 622: 121858. https://doi.org/10.1016/j.ijpharm.2022.121858. PMID: 35643344.

2 Esmaeili AR, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga R, Newman B, Schuman T, Edwards D, Longest W, Hindle M and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 493-498.

3 Sulaiman M, Liu X, and Sundaresan S. *Effects of Dose Loading Conditions and Device Geometry on the Transport and Aerosolization in Dry Powder Inhalers: A Simulation Study.* International Journal of Pharmaceutics. (2021) 610: 121219. https://doi.org/10.1016/j.ijpharm.2021.121219. PMID: 34699949.

4 Chari S, Sridhar K, and Kleinstreuer C. *Effects of Subject-Variability on Nasally Inhaled Drug Deposition, Uptake, and Clearance.* Journal of Aerosol Science. (2022) 28: 106021.

5 Dave S, Kleinstreuer C, and Chari S. *An Effective PBPK Model Predicting Dissolved Drug Transfer from a Representative Nasal Cavity to the Blood Stream.* Journal of Aerosol Science. (2022) 160: 105898.

6 Kolanjiyil AV, Alfaifi A, Aladwani G, Golshahi L, and Longest W. *Importance of Spray–Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays.* Pharmaceutics. (2022) 14(5): 956. https://doi.org/10.3390/pharmaceutics14050956. PMID: 35631539.

7 Kolanjiyil A, Hosseini S, Alfaifi A, Farkas D, Walenga R, Babiskin A, Hindle M, Golshahi L, and Longest P. *Validating CFD Predictions of Nasal Spray Deposition: Inclusion of Cloud Motion Effects for Two Spray Pump Designs.* Aerosol Science and Technology. (2022) 56(4): 305 - 322. https://doi.org/10.1080/02786826.2021.2011830.

8 Kolanjiyil A, Golshahi L, and Longest P. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 515-520.

For nasal suspension products, the particle size distribution (PSD) of the drug substance has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation. Therefore, while FDA has recommended CCEP BE studies for such products, more recently, FDA has also recommended an alternative to the CCEP BE studies that includes advanced in vitro PSD characterization methods, among others, to evaluate potential differences in PSD and to support a demonstration of BE between test and reference nasal suspensions. While PK BE studies are recommended to evaluate the equivalence of systemic exposures for nasal suspensions, there is uncertainty about whether PK studies could detect differences in drug substance PSD that may impact the BE of a test and reference nasal suspension. Through two research contracts (HHSF223201310220C and 75F40120C00036), two mometasone furoate nasal suspension formulations with different drug substance PSDs were developed and tested using both in vitro (i.e., dissolution, morphology directed Raman spectroscopy) and crossover PK studies. Results from the PK study showed that healthy subjects administered approximately 200 mcg of the nasal suspensions under charcoal block had significantly higher nasal absorption (i.e., larger C_{max} and $AUC_{0\text{-}inf}$) when given the MF-1 formulation as compared with MF-2 (**Figure 1**). These clinical results agreed with those obtained from dissolution and MDRS studies, which suggested that particle size was a significant contributor to the higher absorption observed in the PK study with the MF-1 nasal suspension. Notably, dissolution results between the reference listed drug (RLD) Nasonex® and the MF-2 formulation were similar despite the RLD's PSD being closer to that found in the MF-1 nasal suspension. Taken together, PK studies were shown to be sensitive to differences in PSD between nasal suspensions, suggesting that these studies may have the potential to serve as alternative BE methods that could detect the potential for PSD differences between nasal suspension products to impact BE.

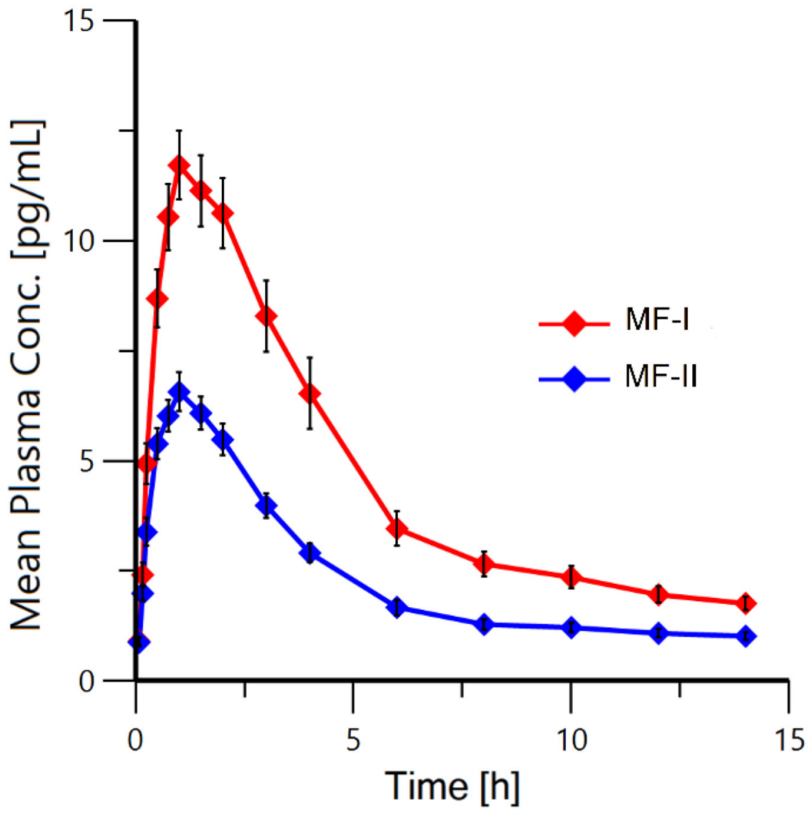


Figure 1. Mean plasma concentration – time profiles for mometasone furoate nasal suspension formulations MF-I and MF-II. Data points represent the mean ± SE. N = 45 (MF-I) and 47 (MF-II). Adapted with permission from Respiratory Drug Delivery 2022, RDD Online.

Table 1. Morphologically Directed Raman Spectroscopy (MDRS) based volume median diameter (VMD), mean dissolution times (MDT), apparent VMD based on USP dissolution tests, and systemic availability for the MF-I, MF-II nasal suspension formulations and Nasonex® (mometasone furoate) metered nasal spray. SD = Standard Deviation, GSD = Geometric Standard Deviation. N = 3. Adapted with permission from Respiratory Drug Delivery 2022, RDD Online.

Formulation	MDRS based VMD [µm]	MDT (SD) Transwell [h]	MDT (SD) USP Apparatus V [h]	VMD (GSD) USP Apparatus V [µm]	Systemic Availability (F) [%]
MF-I	3.17	1.67 (0.06)	0.14 (0.02)	5.55 (1.44)	2.7
MF-II	5.5	3.58 (0.33)	0.56 (0.06)	10.42 (1.76)	1.45
Nasonex®	3.20*	4.64 (0.53)	0.52 (0.06)	9.12 (2.56)	1.20**

*Data obtained from Farias et al. AAPS J. 2021. 23, 73. https://doi.org/10.1208/s12248-021-00605-w
** Based on EMA public assessment report DE/H/5907/001/DC. Applicant: Teva B.V., 2020. 1-12

New Grants and Contracts

- Grant (1U01FD007657) *Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data* at the University of Manchester.
- Contract (75F40122C00202) *Identification of Drug Distribution In Aerosols a Nanospectroscopy and Nanothermal Analysis* at the University of Sydney.
- Contract (75F40122C00197) Dissolvit® – *An in Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution- and Absorption of Drugs Administered via the Inhalation Route* at Inhalation Sciences Sweden AB (ISAB).
- Contract (75F40122C00182) *Advancing In Vitro and (patho)Physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs* at the University of Florida.

Continuing Grants and Contracts

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at the University of North Carolina at Chapel Hill.
- Grant (1U01FD007348) *Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics* with Jill Barber at the University of Manchester.
- Grant (1U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University.
- Contract (75F40119C10154) *Systematic Evaluation of the Ex-Throat Plume Properties of MDI Formulations* with Guenther Hochhaus at the University of Florida and S5 Consulting.
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at the Imperial College of Science and Technology, London.
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University.
- Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and its Origins In Dry Powder Inhalers* with Hugh Smyth at the University of Texas at Austin, College of Pharmacy.

Completed Grants and Contracts

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at the University of Iowa.
- Grant (1U01FD006514) *Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery* with Sankaran Sundaresan at Princeton University.
- Grant (1U01FD006537) *Nasal Mucociliary Clearance Affecting Local Drug-Absorption in Subject-Specific Geometries* with Clement Kleinstreuer at North Carolina State University.
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation (CFDRC).
- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Prediction of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffry Schroeter at Applied Research Associates, Inc.
- Contract (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price at the University of Bath.
- Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches* with Robert Price (PI), Jag Shur (CI) at the University of Bath.

Active FDA Research

- *Batch to Batch Variability of Inhalation Products*
- *CFD Models of Droplet Formulation from MDI*
- *CFD Models of Soft Mist Inhalers*
- *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*
- *Development of a Nasal PBPK Modeling Platform*
- *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*
- *Orally Inhaled Drug Product (OIDP) Data Collection and Analysis from Drug Product Submissions*

Product-Specific Guidances

There were eight new and four revised PSGs published in FY 2022 related to *Inhalation and Nasal* products. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Aclidinium Bromide; Formoterol Fumarate Powder, Metered.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Azelastine Hydrochloride Spray, Metered.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Azelastine Hydrochloride Nasal Spray, Metered.* (NDA 020114) (Aug. 2022) Link to Posting
- *New Draft Guidance for Beclomethasone Dipropionate Monohydrate Spray, Metered.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Ciclesonide Spray, Metered.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Cocaine Hydrochloride Nasal Solution. (May 2022)* Link to Posting
- *New Draft Guidance for Flunisolide Spray, Metered.* (May 2022) Link to Posting
- *New Draft Guidance for Mometasone Furoate and Olopatadine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride Nasal Spray.* (May 2022) Link to Posting
- *Revised Draft Guidance for Nicotine Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Olopatadine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Oxymetazoline Hydrochloride and Tetracaine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting

Articles

- Alfaifi A, Hosseini S, Esmaeili A, Walenga R, Babiskin A, Schuman T, Longest W, Hindle M, and Golshahi L. *Anatomically Realistic Nasal Replicas Capturing the Range of Nasal Spray Drug Delivery in Adults.* International Journal of Pharmaceutics. (2022) 622: 121858. https://doi.org/10.1016/j.ijpharm.2022.121858. PMID: 35643344.

- Bachhav S, Sheth P, Sandell D, Svensson M, Bhagwat S, Conti D, Oguntimein O, Dhapare S, Saluja B, Winner L, Bulitta J, and Hochhaus G. *Systematic Evaluation of the Effect of Formulation Variables on In Vitro Performance of Mometasone Furoate Suspension-Metered Dose Inhalers.* The AAPS Journal. (2021) 24(1): 9. https://doi.org/10.1208/s12248-021-00638-1. PMID: 34874508.

- Chari S, Sridhar K, and Kleinstreuer C. *Effects of Subject-Variability on Nasally Inhaled Drug Deposition, Uptake, and Clearance.* Journal of Aerosol Science. (2022) 165: 106021. https://doi.org/10.1016/j.jaerosci.2022.106021.

- Dave S, Kleinstreuer C, and Chari S. *An Effective PBPK Model Predicting Dissolved Drug Transfer from a Representative Nasal Cavity to the Blood Stream.* Journal of Aerosol Science. (2022) 160: 105898. https://doi.org/10.1016/j.jaerosci.2021.105898.

- Dhapare S, Mohan A, Newman B, Svensson M, Elfman P, Sandell D, Winner L, Berger S, Bulitta J, and Hochhaus G. *Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers (MDIs).* Drug Delivery to the Lungs. (2021) 32. https://ddl-conference.com/wp-content/uploads/2021/11/03.Dhapare.Final_.pdf.

- Dhapare S, Murphy S, Sandell D, Winner L, Sheth P, Hallinger M, Svensson M, Conti D, Oguntimein O, Bulitta J, and Hochhaus G. *Effects of Formulation and Actuator Design on Spray Velocity of Mometasone Furoate Metered Dose Inhalers.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 411-416.

- Dutta R, Kolanjiyil A, Golshahi L, and Longest P. *Development of a CFD-PK Nasal Spray Model with In Vivo Human Subject Validation.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 483-488.

- El-Gendy N, Bertha C, El-Shafy M, Gaglani D, Babiskin A, Bielski E, Boc S, Dhapare S, Fang L, Feibus K, Kaviratna A, Li B, Luke M, Ma T, Newman B, Walenga R, and Zhao L. *Scientific and Regulatory Activities Initiated by the U.S. Food and Drug Administration to Foster Approvals of Generic Dry Powder Inhalers: Quality Perspective.* Advanced Drug Delivery Reviews. (2022) 189: 114519. https://doi.org/10.1016/j.addr.2022.114519. PMID: 36038083.

- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga R, Newman B, Schuman T, Longest P, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 493-498.

- Golshahi L, Alfaifi A, Hosseini S, Esmaeili A, Hindle M, Longest P, and Schuman T. *Leveraging In Vitro Bioequivalence Tests for Locally-Acting Suspension Nasal Sprays with Three Anatomically-Correct Replicas of Human Nasal Airways Representing Intersubject Variability.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 37-46.

- Hochhaus G, Amini E, Berger S, Shur J, Kurumaddali A, Schilling U, Jiao Y, Drescher S, Seay B, Baumstein S, Abu-Hasan M, Oguntimein O, Carrasco C, Winner L, Delvadia R, Saluja B, Price R, Conti D, Dhapare S, Newman B, and Bulitta J. *Evaluating Particle Size Differences of Suspension-Based Nasal Sprays Through In Vitro and Pharmacokinetic Approaches.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 47-53.

- Kolanjiyil A, Alfaifi A, Aladwani G, Golshahi L, and Longest W. *Importance of Spray-Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays.* Pharmaceutics. (2022) 14(5): 956. https://doi.org/10.3390/pharmaceutics14050956. PMID: 35631539.

- Kolanjiyil A, Hosseini S, Alfaifi A, Farkas D, Walenga R, Babiskin A, Hindle M, Golshahi L, and Longest P. *Validating CFD Predictions of Nasal Spray Deposition: Inclusion of Cloud Motion Effects for Two Spray Pump Designs.* Aerosol Science and Technology. (2022) 56(4): 305 - 322. https://doi.org/10.1080/02786826.2021.2011830.

- Kolanjiyil A, Golshahi L, and Longest P. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 515-520.

- Lee J, Feng K, Conti D, Walenga R, Wientijes M, Wang H, Newman B, Han L, Dhapare S, Bielski E, Babiskin A, Wu F, Donnelly M, Kim M, Jiang W, Luke M, Fang L, and Zhao L. *Considerations for the Forced Expiratory Volume in 1 Second-Based Comparative Clinical Endpoint Bioequivalence Studies for Orally Inhaled Drug Products.* Clinical Pharmacology and Therapeutics. (2022) 112(5): 982–989 https://doi.org/10.1002/cpt.2553. PMID: 35133652.

- Mohan A, Dhapare S, Newman B, Svensson M, Elfman P, Winner L, Bulitta J, and Hochhaus G. *The Effects of Inhalation Flow Rate on Aerodynamic Particle Size Distribution of Commercial Solution and Suspension Metered Dose Inhalers.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 417-422.

- Newman B, Babiskin A, Bielski E, Boc S, Dhapare S, Fang L, Feibus K, Kaviratna A, Li B, Luke M, Ma T, Walenga R, Wang Z, Zhao L, El-Gendy N, Bertha C, El-Shafy M, and Gaglani D. *Scientific and Regulatory Activities Initiated by the U.S. Food and Drug Administration to Foster Approvals of Generic Dry Powder Inhalers: Bioequivalence Perspective.* Advanced Drug Delivery Reviews. (2022) 190: 114526. https://doi.org/10.1016/j.addr.2022.114526. PMID: 36067967.

- Schroeter JD, Rose M, Kimbell JS, Chopski S, and Walenga R. *A Physiologically-Based Pharmacokinetic Model to Estimate Absorption and Bioavailability of Corticosteroid Nasal Sprays.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 197-200.

- Singh N, Kannan R, Arey R, Walenga R, Babiskin A, and Przekwas A. *Predicting Systemic and Pulmonary Tissue Barrier Concentration of Orally Inhaled Drug Products.* bioRxiv. (2022) 2022.03.10.483633. https://doi.org/10.1101/2022.03.10.483633.

- Sulaiman M, Liu X, and Sundaresan S. *Effects of Dose Loading Conditions and Device Geometry on the Transport and a Aerosolization in Dry Powder Inhalers: A Simulation Study.* International Journal of Pharmaceutics. (2021) 610: 121219. https://doi.org/10.1016/j.ijpharm.2021.121219. PMID: 34699949.

- Wang Z, Ahluwalia S, Newman B, Dhapare S, Zhao L, and Luke M. *Medication Cost-Savings and Utilization of Generic Inhaled Corticosteroid (ICS) and Long-Acting Beta-Agonist (LABA) Drug Products in the USA.* Therapeutic Innovation & Regulatory Science. (2022) 56(2): 346-357. https://doi.org/10.1007/s43441-021-00372-y. PMID: 35118630.

Posters

- Quarterman J, Al-Ghabeish M, Newman B, Walenga R, Chopski S, Zidan A, Pavuluri V, Shakleya D, Li M, and Ashraf M. *Development of a Biopredictive and Biorelevant In-Vitro Permeation Test for the Nasal Bioavailability of Naloxone Hydrochloride Nasal Sprays.* Poster Presentation at the 2022 American College of Clinical Pharmacology (ACCP) Annual Meeting. Bethesda, Maryland, Sep. 25, 2022.

- Chakma M, Meah S, Biddiscombe M, Murnane D, Bielski E, Feibus K, Natarajan K, Li K, Kinoj M, Illoh O, Han L, Newman B, and Usmani O. *Dry Powder Inhaler (DPI) Resistance: Human Behaviour and Psychology of Patient Inspiratory Effort.* Poster Presentation at the European Respiratory Society 2022. Barcelona, Spain, Sep. 05, 2022.

- Dhapare S, Murphy S, Sandell D, Winner L, Sheth P, Hallinger M, Svensson M, Conti D, Oguntimein M, Bulitta J, and Hochhaus G. *Effects of Formulation and Actuator Design on Spray Velocity of Mometasone Furoate Metered Dose Inhalers.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Dutta R, Kolanjiyil A, Golshahi L, and Longest W. *Development of a CFD PK Nasal Spray Model with In Vivo Human Subject Validation.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Kolanjiyil A, Golshahi L, and Longest W. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Mohan A, Dhapare S, Newman B, Svensson M, Elfman P, Winner L, Bulitta J, and Hochhaus G. *The Effects of Inhalation Flow Rate on Aerodynamic Particle Size Distribution of Commercial Solution and Suspension Metered Dose Inhalers.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Schroeter J, Rose M, Kimbell J, Chopski S, and Walenga R. *A Physiologically-Based Pharmacokinetic Model to Estimate Absorption and Bioavailability of Corticosteroid Nasal Sprays.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga R, Newman B, Schuman T, Edwards D, Longest W, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 01, 2022.

- Berger S, Amini E, and Hochhaus G. *Dissolution Testing for Supporting Bioequivalence Assessment of Nasal Suspensions.* Poster Presentation at the 2021 American College of Clinical Pharmacology (ACCP) Annual Meeting. Phoenix, Arizona, Oct. 19, 2021.

- Hefnawy A, Herpin M, Nair V, Lee J, Feng K, Bielski E, Dhapare S, Newman B, Conti D, Boc S, and Smyth H. *Investigation of the Effects of Physicochemical Properties of Dry Powder Inhalers on Batch-to-Batch Variability.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Nair V, Hefnawy A, Smyth H, Lee J, Feng K, Bielski E, Dhapare S, Newman B, Conti D, Boc S, and Herpin M. *In Vitro Batch-to-Batch Variability of Fluticasone Propionate and Salmeterol Dry Powder Inhalers.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Boc S. *Alternative BE Approaches and Considerations for Nasal Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Holtgrewe N. *In Vitro Characterization of Nasal Powder Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Newman B. *Nasal Products: Current Landscape and Recent Advancements.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Walenga R. *Mechanistic Modeling and Realistic In Vitro Models to Facilitate Development of Generic Nasal Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Dutta R, Kolanjiyil A, Golshahi L, and Longest W. *Development of a CFD PK Nasal Spray Model with In Vivo Human Subject Validation.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga , Newman B, Schuman T, Edwards D, Longest W, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Golshahi L, Alfaifi A, Hosseini S, Esmaeili A, Hindle M, Longest W, and Schuman T. *Leveraging In Vitro Bioequivalence Tests for Locally-Acting Suspension Nasal Sprays with Three Anatomically-Correct Replicas of Human Nasal Airways Representing Intersubject Variability.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Florida, Orlando, May 02, 2022.
- Hochhaus G, Amini E, Berger S, Shur J, Kurumaddali A, Schilling U, Jiao Y, Drescher S, Seay B, Baumstein S, Abu Hasan M, Oguntimein O, Carrasco C, Winner L, Delvadia R, Saluja B, Price R, Conti D, Dhapare S, Newman B, and Bulitta J. *Evaluating Particle Size Differences of Suspension-based Nasal Sprays Through In Vitro and Pharmacokinetic Approaches.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Kolanjiyil A, Golshahi L, and Longest W. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Mohan A, Dhapare S, Newman B, Svensson M, Elfman P, Winner L, Bulitta J, and Hochhaus G. *The Effects of Inhalation Flow Rate on Aerodynamic Particle Size Distribution of Commercial Solution and Suspension Metered Dose Inhalers.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.

- Dhapare S, Murphy S, Sandell D, Winner L, Sheth P, Hallinger M, Svensson M, Conti D, Oguntimein O, Bulitta J, and Hochhaus G. *Effects of Formulation and Actuator Design on Spray Velocity of Mometasone Furoate Metered Dose Inhalers.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 01, 2022.

- Mohan A. *The Effects of Inhalation Flow Rate on Aerodynamic Particle Size Distribution of Commercial Solution and Suspension Metered Dose Inhalers (MDIs).* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 01, 2022.

- Walenga R. *Modeling of CNS Delivery for Nose-to-Brain Targeted Drug Products.* Presentation at the Society for Computational Fluid Dynamics of the Nose Airway (SCONA) 2022 Virtual Meeting. Virtual Meeting, Jan. 28, 2022.

- Dhapare S. *Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers (MDIs).* Presentation at the Drug Delivery to the Lungs (DDL) 2021. Virtual Meeting, Dec. 08, 2021.

TOPICAL PRODUCTS

Summary of FY 2022 Activities

During FY 2022, FDA's Generic Drug User Fee Amendments (GDUFA)-funded research continued to support the development of efficient bioequivalence (BE) approaches for topical drug products, as part of an effort to facilitate generic drug development and enhance patient access to these important medicines.

One goal of this research program is to continue to aid in the development of efficient characterization-based BE approaches for prospective generic products when the formulation composition is well matched to that of the reference standard. During FY 2022, data from FDA-funded research studies supported the development of generalized recommendations for comparative physicochemical and structural (Q3) characterization tests, in vitro release test (IVRT) studies as well as in vitro permeation test (IVPT) studies. These test methods are often recommended as components of efficient characterization-based BE approaches, with the ultimate goal of increasing the efficiency of product development programs for generic topical products applied to the skin, as well as those that are dosed using the vaginal, rectal, or anal routes of administration.

Additionally, FDA sought to understand the safe space and mechanisms that allow prospective generic products and reference standards to be bioequivalent when they are not the same in formulation, but are similar in components, composition, and/or Q3 attributes. To elucidate these mechanisms, in vitro experiments and in silico modeling and simulation were performed through collaborations with the University of South Australia (grant# 1U01FD006496) and the University of Mississippi (grant# 1U01FD006507). These research collaborations sought to elucidate when compositional changes in inactive ingredients can change the thermodynamic activity of the drug in a topical formulation, and how changes in thermodynamic activity correlate with bioavailability. Additionally, a research collaboration with the University of Queensland (grant# 1U01FD006700)

studied how differences in specific Q3 attributes that can impact sensorial properties of topical products (e.g., a cooling sensation) may be perceived by human subjects. Ongoing research at the University of Rhode Island (grant# 1U01FD006721) to develop characterization-based BE approaches for vaginal and rectal products produced insights into methodologies for assessing local bioavailability for such products (see **Research Highlight** below). Additionally, FDA initiated a research collaboration with the University of Rhode Island (grant# 1U01FD007656) to further efforts in this area.

Another goal was to develop efficient pharmacokinetics (PK)-based methods to directly monitor the drug's bioavailability at or near its site(s) of action in the skin. During FY 2022, in vivo BE studies in human subjects with diclofenac topical products were successfully completed at Joanneum Research (grant# 1U01FD005861) using dermal open flow microperfusion (dOFM) and in vivo studies in animal models were performed at Long Island University (grant# 1U01FD006930) to elucidate how PK principles should be applied when assessing local bioavailability in the dermis. Additionally, new research was initiated with Joanneum Research during FY 2022 (grant# 1U01FD007669) to optimize the clinical study design for cutaneous PK-based BE approaches. Independently, research at the University of Bath (grant# 1U01FD006533) and Massachusetts General Hospital/Harvard Medical School (grant# 1U01FD006698) developed sensitive and discriminating non-invasive cutaneous PK-based methods using advanced confocal Raman imaging techniques.

FDA recently started developing efficient characterization-based BE approaches for generic locally acting products that are dosed using the vaginal, rectal, and anal routes of administration. Based on an assessment of the Q3 attributes of reference standard products for these routes of administration, and the corresponding potential failure modes for BE, single-phase gels were determined to have among the fewest failure modes for BE among the dosage forms evaluated. In comparison, emulsion-based drug products (e.g., creams) and encapsulated drug products (e.g., certain suppositories/inserts, where the release of the drug from the dosage form, and thereby bioavailability, may be influenced by the rate of disintegration of a "shell") generally appeared to have more failure modes for BE compared to single phase gels. As the complexity of the dosage form increased, so did the number of potential failure modes for BE with such products.

Thus, while efficient characterization-based BE approaches are currently recommended for metronidazole vaginal gels[1],[2], among other gels, efficient characterization-based BE approaches for emulsion-based and/or encapsulated topical drug products are currently under development. This is being orchestrated through research internally at FDA laboratories and externally at the University of Rhode Island (grant# 1U01FD006721). This research is advancing the development of comparative Q3 characterization tests, IVRT studies, and other biorelevant comparative assessments of product performance (e.g., IVPT studies) for these classes of complex topical drug products dosed via vaginal, rectal, or anal routes of administration.

Recent research using clindamycin phosphate (CP) vaginal creams demonstrated that methodologies routinely utilized to validate IVRT methods for semisolid topical products applied to the skin can be extrapolated to vaginal drug products (with certain adjustments, e.g., study temperature based on the route of administration). Following initial IVRT method development, simulated vaginal fluid (pH 4.2) containing 3% Brij® O20 was selected as the receptor solution and a polyethersulfone (PES) membrane (0.45 µm) was chosen as the membrane in a vertical diffusion cell apparatus. The discriminatory ability of such methods was demonstrated using three laboratory-made vaginal creams of different nominal strengths (**Figure 1**).

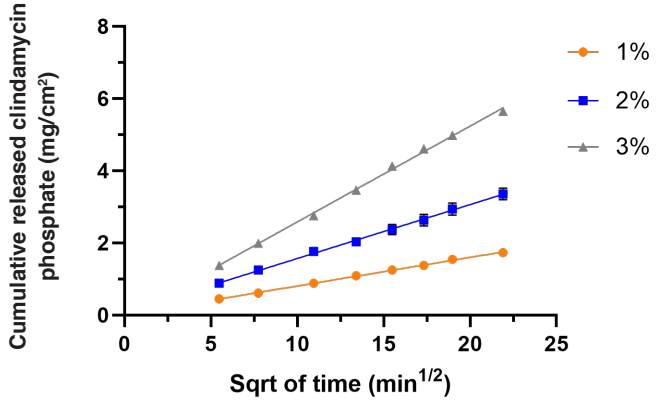


Figure 1. Mean (± SD) in vitro release profiles of three laboratory-made CP vaginal creams of different nominal strengths (n=3 per strength).

[1] Draft Guidance on Metronidazole, Gel; Vaginal. October 2022 Link to Posting

[2] Draft Guidance on Metronidazole, Gel; Vaginal. October 2022 Link to Posting

Additionally, IVPT studies were conducted by mounting excised porcine vaginal tissues in a vertical diffusion cell apparatus with a surface temperature of 37°C and simulated vaginal fluid (pH 4.2) containing 3% Brij O20 as the receptor solution. The intra- and inter-day IVPT flux profiles for a marketed 2% w/w CP vaginal cream using tissue from the same donor demonstrated good reproducibility and precision among tissue replicates (**Figure 2A**). The reproducibility of IVPT flux profiles among different donors was also found to be reasonable (**Figure 2B**). The method was able to differentiate the flux profiles of the laboratory-made formulations of different strengths of CP vaginal creams when compared in the same donor (**Figure 2C**). Similarly, results for mesalamine rectal suppositories (a model dosage form for rectal administration) suggest that it may also be feasible to develop sensitive and discriminatory IVRT methods and IVPT methods (using porcine rectal tissue) for the rectal route of administration.

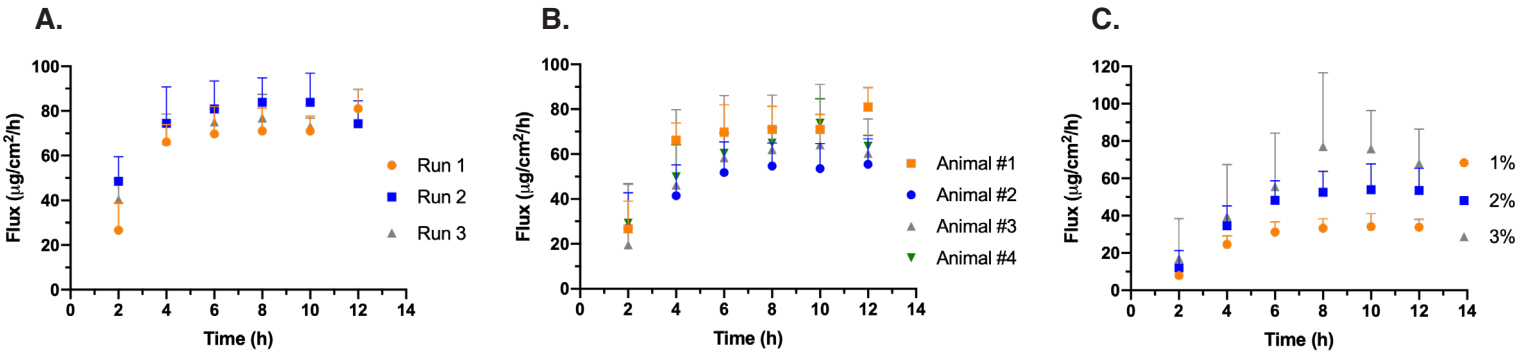


Figure 2: A) Intra- and inter-day method reproducibility was assessed using a marketed 2% w/w CP vaginal cream (n=3 cells/run, 3 independent runs (days); mean (± SD)). B) The impact of variation in vaginal tissue between donors on drug permeation was examined using tissues from four different donors (n=3 cells/donor; mean (± SD)). C) The discriminatory ability of the method was evaluated using three strengths of laboratory-made CP creams with the same components (n=3 cells/strength; mean (± SD)).

New Grants and Contracts

- Grant (1U01FD007656-01) *In Vitro Based Approaches to Evaluate the Bioequivalence of Locally-Acting Rectal and Vaginal Semi-Solid Drug Products* at the University of Rhode Island.
- Grant (1U01FD007669-01) *Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics* at Johanneum Research.

Continuing Grants and Contracts

- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at Simulations Plus, Inc.
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterisation, Release and Permeation Data to the Next Level - PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK Limited.
- Grant (1U01FD006700) *Bioequivalence of Topical Products: Elucidating the Sensorial and Functional Characteristics of Compositionally Different Topical Formulations* with Yousuf Hussain Mohammed at the University of Queensland.
- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School.
- Grant (1U01FD006521) *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations* with Sebastian Polak at Certara UK, LTD.
- Grant (1U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products using Non-Invasive Techniques (U01)* with Richard Guy at the University of Bath.
- Grant (1U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at the University of South Australia.
- Grant (1U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Sathyanarayana Murthy at the University of Mississippi.
- Grant (1U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with Grazia Stagni at Long Island University, Brooklyn Campus.

Completed Grants and Contracts

- Grant (1U01FD006721) *Federal Award Project Title Bioequivalence Considerations of Topical Rectal and Vaginal Suppositories* with Jie Shen at the University of Rhode Island.
- Grant (1U01FD005861) *Development of a Universal Bioequivalence Test Method for Topical Drugs using dOFM* with Frank Sinner at Joanneum Research.

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *Characterization of Product Quality Attributes of Imvexxy® (estradiol) Vaginal Insert*
- *Development of a Novel Bio-Relevant In Vitro Skin Permeation Test (IVPT) for Hydrophobic Drugs using In-Line Flow Through Diffusion Cells (FTC)*
- *Feasibility of IVRT and IVPT Studies to Support Product Specific Guidance Development for Several Locally Acting Topical Products (Gels, Creams, Ointments)*
- *Physicochemical and Structural Characterization of Several Multiphasic Locally Acting Topical Products (Gels, Creams, Ointments)*

Product-Specific Guidances

There were four new PSGs published in FY 2022 related to *Topical* products. Among those, the PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Acetaminophen Suppository.* (May 2022) Link to Posting
- *New Draft Guidance for Halobetasol Propionate Aerosol, Foam.* (May 2022) Link to Posting
- *New Draft Guidance for Minocycline Hydrochloride Aerosol, Foam,* NDA 212379. (Nov. 2021). Link to Posting
- *New Draft Guidance for Minocycline Hydrochloride Aerosol, Foam,* NDA 213690. (Nov. 2021). Link to Posting

Articles

- Arora S, Clarke J, Tsakalozou E, Ghosh P, Alam K, Grice J, Roberts M, Jamei M, and Polak S. *Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model.* Molecular pharmaceutics. (2022) 19(9): 3139–3152. https://doi.org/10.1021/acs.molpharmaceut.2c00229. PMID: 35969125.
- Burrows V, and Luke M. *The History of Dermatology and Dermatologists at the US Food and Drug Administration.* Dermatologic Clinics. (2022) 40(3): 237-248. https://doi.org/10.1016/j.det.2022.03.001. PMID: 35750408.
- Elfakhri K, Niu M, Ghosh P, Ramezanli T, Raney S, Ahmed S, Willett D, Yilmaz H, Ashraf M, and Zidan A. *Physicochemical and Structural Evaluation of Microparticles in Tretinoin Topical Gels.* International Journal of Pharmaceutics. (2022) 620: 121748. https://doi.org/10.1016/j.ijpharm.2022.121748. PMID: 35427749.
- Ghosh P, Raney S, and Luke M. *How Does the Food and Drug Administration Approve Topical Generic Drugs Applied to the Skin?* Dermatologic Clinics. (2022) 40(3): 279-287. https://doi.org/10.1016/j.det.2022.02.003. PMID: 35750411.
- Jung N, Namjoshi S, Mohammed Y, Grice J, Benson H, Raney S, Roberts M, and Windbergs M. *Application of Confocal Raman Microscopy for the Characterization of Topical Semisolid Formulations and their Penetration into Human Skin Ex Vivo.* Pharmaceutical research. (2022) 39(5): 935-948. https://doi.org/10.1007/s11095-022-03245-7. PMID: 35411509.
- Kuzma B, Senemar S, Ramezanli T, Ghosh P, Raney S, and Stagni G. *The Dose-Duration Effect on Cutaneous Pharmacokinetics of Metronidazole from Topical Dermatological Formulations in Yucatan Mini-Pigs.* European Journal of Pharmaceutics and Biopharmaceutics. (2022) 175: 43-52. https://doi.org/10.1016/j.ejpb.2022.05.001. PMID: 35526809.

- Liu X, Cheruvu H, Anissimov Y, Van Der Hoek J, Tsakalozou E, Ni Z, Ghosh P, Grice J, and Roberts M. *Percutaneous Absorption of Steroids from Finite Doses: Predicting Urinary Excretion from In Vitro Skin Permeation Testing.* International Journal of Pharmaceutics. (2022) 625: 122095. https://doi.org/10.1016/j.ijpharm.2022.122095. PMID: 35961420.

- Patel N, Clarke J, Salem F, Abdulla T, Martins F, Arora S, Tsakalozou E, Hodgkinson A, Arjmandi-Tash O, Cristea S, Gosh P, Alam K, Raney S, Jamei M, and Polak S. *Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) Model to Predict Local and Systemic Exposure of Drug Products Applied on Skin.* CPT: Pharmacometrics & Systems Pharmacology. (2022) 11(8): 1060–1084. https://doi.org/10.1002/psp4.12814. PMID: 35670226.

- Raney S, Ghosh P, Ramezanli T, Lehman P, and Franz T. *Cutaneous Pharmacokinetic Approaches to Compare Bioavailability and/or Bioequivalence for Topical Drug Products.* Dermatologic Clinics. (2022) 40(3): 319-332. https://doi.org/10.1016/j.det.2022.02.007. PMID: 35750415.

- Roberts M, Cheruvu M, Mangion S, Alinaghi A, Benson H, Mohammed Y, Holmes A, Van Der Hoek J, Pastore M, and Grice J. *Topical Drug Delivery: History, Percutaneous Absorption, and Product Development.* Advanced Drug Delivery Reviews. (2021) 177: 113929. https://doi.org/10.1016/j.addr.2021.113929. PMID: 34403750.

- Shukla, S., Bunge, A. L., Hassan, H. E., & Stinchcomb, A. L. *Investigator Impact on Reproducibility of Drug Bioavailability in Stratum Corneum Sampling by Tape Stripping.* Pharmaceutical research. (2022). 39(4): 703–719. https://doi.org/10.1007/s11095-022-03199-w PMID: 35411510.

- Tiffner K, Kanfer I, Augustin T, Raml R, Raney S, and Sinner F. *Comparative In Vitro Release Testing (IVRT) of Acyclovir Products.* International Journal of Pharmaceutics. (2021) 609: 121186. https://doi.org/10.1016/j.ijpharm.2021.121186. PMID: 34655706.

Posters

- Tsakalozou E, Alam K, Babiskin A, Fang L, and Zhao L. *Development and Application of a Dermal PBPK Modeling for Ethinyl Estradiol-Containing Transdermal Delivery Systems to Predict Exposure for Different Application Sites.* Poster Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 27, 2022.

- Xie L, Yue W, Kelchen M, Ghosh P, Niu M, Raney S, and Shen J. *Development of An In Vitro Permeation Test (IVPT) Method for Vaginal Creams.* Poster Presentation at the Controlled Release Society (CRS) 2022 Annual Meeting. Montreal, Canada, Jul. 12, 2022.

- Silva S, Mohammad Y, Roberts M, Ramezanli T, Lian G, and Chen T. *In-Silico and Experimental Investigation of the Thermodynamic Change of Topical Formulations due to Evaporation and the Impact on Skin Permeation.* Poster Presentation at the 18th Skin Forum Annual Conference 2022. Malmo, Sweden, Jun. 21, 2022.

- Tiffner K, Ramezanli T, Birngruber T, Bodenlenz M, Lackner B, Raml R, Raney S, and Sinner F. *Clinical Study to Assess the Cutaneous Bioequivalence of Topically Applied Lidocaine and Prilocaine Products Using Dermal Open Flow Microperfusion.* Poster Presentation at the 18th Skin Forum Annual Conference 2022. Malmo, Sweden, Jun. 21, 2022.

- Bodenlenz M, Augustin T, Birngruber T, Tiffner K, Raml R, and Sinner F. *Dermal OFM Indicates Differences in Acyclovir Skin Penetration between Males and Females.* Poster Presentation at the 17th International Perspectives in Percutaneous Penetration Conference (PPP2022). La Grande Motte, France, Apr. 20, 2022.

- Belsey N, Tsikritsis D, Zarmpi P, Tyagi V, Maciel-Tabosa A, Vorng J, Dexter A, Delgado-Charro M, and Guy R. *Characterization of Topical Products and Their Fate Post-Application with Label-Free Chemical Imaging.* Poster Presentation at the 17th International Perspectives in Percutaneous Penetration Conference (PPP2022). La Grande Motte, France, Apr. 19, 2022.

- Zarmpi P, Maciel-Tabosa A, Vitry P, Tsikritsis D, Belsey N, Vorng J, Woodman T, Bunge A, White K, Delgado-Charro M, and Guy R. *Assessing Dermatological Product Bioequivalence with Raman Spectroscopy.* Poster Presentation at the 17th International Perspectives in Percutaneous Penetration Conference (PPP2022). La Grande Motte, France, Apr. 19, 2022.

- Senemar S, Kuzma B, Ramezanli T, Ghosh P, Raney S, and Stagni G. *Dermal Clearance, Elimination Half-life, and Apparent Volume of Distribution of Lidocaine and Prilocaine are Independent of the Dose Delivered Directly in Dermis Using a Dermal Infusion Technique.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

- Shukla S, Ramezanli T, Rantou E, Tiffner K, Birngruber T, Sinner F, and Raney S. *Quantitative Discrimination of Cutaneous Pharmacokinetic Profiles for Topical Drug Products.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

- Zarmpi P, Maciel-Tabosa MA, Vitry P, Belsey NA, Vorng JL, Tsikritis D, Woodman TJ, White KAJ, Bunge AL, Delgado-Charro MB, and Guy R. *Validation of a Confocal Raman Spectroscopy Approach to Quantify Drug Delivery into the Skin.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 20, 2021.

- Rangappa S, Kolimi P, Shankar V, Wang Y, Ghosh P, Raney S, Repka M, Maibach H, and Murthy N. *Influence of Drying Profile on the Performance of Diclofenac Sodium Gels.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 20, 2021.

- Yue W, Xie L, Kelchen M, Ghosh P, Niu M, Raney S, and Shen J. *Development of a Reproducible In Vitro Release Test Method for Vaginal Creams.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 20, 2021.

- Haq A and Ghosh P. *Evaluation of COSMO-RS as a Tool to Predict the Liquid Phase Thermodynamic Properties of Active Ingredients in Topical Dermatological Drug Products.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 19, 2021.

- Xie L, Kelchen M, Ghosh P, Niu M, Raney S, and Shen J. *Development of an In Vitro Permeation Test Method for Rectal Suppositories.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 19, 2021.

- Rangappa S, Kolimi P, Shankar V, Wang Y, Ghosh P, Raney S, Repka M, and Maibach H. *Determination of Water Content during Metamorphosis in Topical Gels with Different Amounts of PEG-200.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.

- Senemar S, Kuzma B, and Stagni G. *Comparison of Metronidazole Dermal Pharmacokinetics Between Mini-pig and Rabbit.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.

- Senemar S, Kuzma B, and Stagni G. *A Cross-Species Retrospective Percutaneous IVIVR for Topical Dermatological Products Containing Metronidazole.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.

- Alam K, Tsakalozou E, Babiskin A, Ghosh P, Ramezanli T, Jiang Y, Niu M, and Zhao L. *Does Vehicle Evaporation Affect Drug Distribution within Different Phases of Topically Applied Emulsion? A Modeling Case Study with Clindamycin Phosphate Lotion.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Hamad G, Niu M, Ghosh P, Ramezanli T, Raney S., Ashraf M, and Zidan A. *Drug Release from Porous Microparticle-Based Tretinoin Topical Gels: Proportionality of Release Across Various Strengths.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 17, 2021.

- Telaprolu K, Polak S, Tsakalozou E, Ghosh P, Alam K, Dabbaghi M, Namjoshi S, Mohammed Y, Grice J, and Roberts M. *Modeling In Vitro and In Vivo Human Skin Permeation of Eutectic Mixtures of Local Anesthetics Using PBPK Modeling: Development of Dermal IVIVE for Lidocaine 2.5% w/w and Prilocaine 2.5% w/w Cream (EMLA® Cream).* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Ghosh P, and Luke M. *Characterization Based Approaches for Establishing Bioequivalence Locally Acting Drug Products Applied to the Skin.* Presentation at the 5th Annual Global Bioequivalence Harmonization Initiative Meeting. Amsterdam, Netherlands, Sep. 29, 2022.
- Ghosh P, and Luke M. *Cutaneous Pharmacokinetic Based Approaches for Establishing Bioequivalence Locally Acting Drug Products Applied to the Skin.* Presentation at the 5th Annual Global Bioequivalence Harmonization Initiative Meeting. Amsterdam, Netherlands, Sep. 29, 2022.
- Tiffner K, Boulgaropoulos B, Birngruber T, Bodenlenz M, Lackner B, Raml R, and Sinner F. *Promising Technologies: Continuous Skin Sampling Methods for Cutaneous PK-Based Bioequivalence Assessment.* Presentation at the 5th Annual Global Bioequivalence Harmonization Initiative Meeting. Amsterdam, Netherlands, Sep. 29, 2022.
- Ghosh P. *Translating Scientific Advances to Regulatory Methods Assessment of Cutaneous Pharmacokinetics.* Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 29, 2022.
- Guy R. *Dermatopharmacokinetics: Modelling, Assessment and Optimization.* Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 29, 2022.
- Kuzma B. *Novel Methodologies to Assess Cutaneous Bioavailability and Bioequivalence: Dermal Microdialysis and Coherent Raman Imaging.* Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 29, 2022.
- Ramezanli T. *Therapeutic Equivalence of Compositionally Different Topical Products: Correlation of Product Characteristics with Sensorial Attributes.* Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 29, 2022.
- Tsakalozou E. *Dermal PBPK Modeling for a Transdermal Delivery System to Assess the Impact of the Application Site on In Vivo Performance.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.

- Patel H. *Practical Considerations Related to IVPT Studies for Topical Products Submitted in ANDAs.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Best Practices for Topical Generic Product Development and ANDA Submission. Virtual Meeting, Aug. 11, 2022.
- Ramezanli T. *Practical Considerations for IVRT Studies with Topical Drug Products Submitted in ANDAs.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Best Practices for Topical Generic Product Development and ANDA Submission. Virtual Meeting, Aug. 11, 2022.
- Raney S. *Scientific and Regulatory Considerations for Q3 Characterization of Topical Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Best Practices for Topical Generic Product Development and ANDA Submission. Virtual Meeting, Aug. 11, 2022.
- Luke M. *Advancing the Science of how Topically Applied Drugs Penetrate the Skin and Clinical Relevance - the Viewpoint of an FDA Dermatologist.* Presentation at the Dermatology Innovation Forum - an Advancing Innovation in Dermatology Conference. Virtual Meeting, Jun. 24, 2022.
- Ghosh P. *Product Development Considerations and Bioequivalence Strategies for Generic Topical Products.* Presentation at the Drug Information Association (DIA) 2022 Annual Meeting. Chicago, Illinois, Jun. 22, 2022.
- Raney S. *GDUFA Funded Development of Efficient Bioequivalence Approaches for Topical Generics.* Presentation at the Drug Information Association (DIA) 2022 Annual Meeting. Chicago, Illinois, Jun. 22, 2022.
- Zidan A. *Research and innovation to support the availability of topical dermatological products in the US.* Presentation at the Drug Information Association (DIA) 2022 Annual Meeting. Chicago, Illinois, Jun. 22, 2022.
- Senemar S. *New developments in the Assessment of Cutaneous Bioavailability and Bioequivalence of Topical Dermatological Drug Products Using Dermal Microdialysis.* Presentation at The Center for Dermal Research. Virtual Meeting, Jun. 06, 2022.
- Evans C. *Advanced Techniques for Measuring Cutaneous Pharmacokinetics Using Pharmacokinetic Tomography.* Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. Portland, Oregon, May 20, 2022.
- Ghosh P. *Overview FDA's Generic Drug Research Topical Dermatological Drug Products.* Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. Portland, Oregon, May 20, 2022.
- Raney S. *GDUFA Science and Research Program.* Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. Portland, Oregon, May 20, 2022.
- Sinner F. *Advanced Techniques for Measuring Cutaneous Pharmacokinetics In Vivo Using Microdialysis & Dermal Open Flow Microperfusion.* Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. Portland, Oregon, May 20, 2022.

- Roberts M. *Advanced Techniques for Characterizing the Form & Function of Topical Dermatological Drug Products.* Presentation at the Society for Investigative Dermatology (SID) Annual Meeting. Portland, Oregon, May 20, 2022.
- Ghosh P. *Identification of Research Needs During Product Development Prior to ANDA Submission.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 09, 2022.
- Niu M. *The Role of Microparticles and Other Excipients in the Complexity of Certain Topical Drug Products.* Presentation at the Excipient World Conference & Expo 2022. Kissimmee, Florida, May 03, 2022.
- Raney S. *The Critical Impact of Excipients on the Physicochemical and Structural Characteristics of Topical Drug Products.* Presentation at the Excipient World Conference & Expo 2022. Kissimmee, Florida, May 03, 2022.
- Raney S. *A Regulatory Perspective on Physicochemical, Structural, and Performance Characterization of Topical Semisolid Products.* Presentation at the 17th International Perspectives in Percutaneous Penetration Conference (PPP2022). La Grande Motte, France, Apr. 20, 2022.
- Sinner F. *Learnings from Accessing the Dermis Vivo: from Topical Bioequivalence to Biomarker Research.* Presentation at the 17th International Perspectives in Percutaneous Penetration Conference (PPP2022). La Grande Motte, France, Apr. 20, 2022.
- Luke M. *FDA and the Dermatologist - The Basics about FDA and a New Paradigm for Generic Topical Drug Bioequivalence.* Presentation at the American Academy of Dermatology Annual Meeting 2022. Boston, Massachusetts, Mar. 27, 2022.
- Van Osdol B, and Spires J. *In Silico QbD for Dermal Topical Formulations via TCAT Model Simulations.* Presentation at the Simulations Plus 2022 Model-Informed Drug Development (MIDD+) Scientific Conference. Virtual Meeting, Feb. 17, 2022.
- Tsakalozou E. *Leveraging Dermal Physiologically-based Pharmacokinetic Modeling and Simulation Approaches for the Approval of a Generic Diclofenac Sodium Topical Gel.* Presentation at the Simcyp Scientific Webinar Series. Virtual Meeting, Dec. 08, 2021.
- Luke M. *FDA and Dermatology - Topical Drug Products: New Paradigm for Generics.* Presentation at the International Dermatology Outcome Measures (IDEOM) 2021 Annual Meeting. Virtual Meeting, Nov. 19, 2021.
- Kozak D. *Formulation Considerations for In Vitro Characterization Based Approaches of Locally Acting Complex Generic Drug Products.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 08, 2021.
- Zidan A. *Microstructure (Q3) Characterization Approaches for Demonstration of BE of Locally Acting Drug Products.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 08, 2021.

LOCALLY-ACTING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

Summary of FY 2022 Activities

In FY 2022, research activities including 19 contracts and grants (that were either active or completed during FY 2022), as well as internal modeling projects, continued the development of mechanistic in silico tools alongside relevant in vitro tests for the prediction of local drug concentrations at the site of administration/action for the purposes of bioequivalence (BE).

- For products delivered via oral inhalation, research was conducted to improve the validation of computational fluid dynamics (CFD) predictions for regional deposition in metered dose inhalers (MDI) and dry powder inhalers (DPI), and to explore the influence of device modifications on product performance.

- Nasal drug product research was directed toward improving the ability of CFD and physiologically based pharmacokinetic (PBPK) models to accurately predict regional dose and absorption, and to investigate the impact of in vitro metric variations on the delivery of a drug to the target site.

- For ophthalmic products, one research area was to integrate dissolution and tear film blinking models with a whole eye model to simulate fluid dynamics in the eye and to predict drug concentrations in ocular tissues using an integrated multiscale computational modeling approach. Another area of focus was on the development of preclinical models, interspecies extrapolation to humans, and validation of this model development and extrapolation.

- For dermal products, research focused on understanding the impact on drug permeation into the skin of formulation attributes in multi-phase, semisolid dosage forms, and of metamorphosis following product application. In addition to modeling in vivo skin absorption, models to describe the study data generated from in vitro permeation tests (IVPT) were developed (See **Research Highlight**). Furthermore, ongoing research and development of in silico tool capabilities is focused on modeling metabolism and protein-mediated transport processes during skin permeation.

- In addition, research conducted in FY 2022 included the development of PBPK models of the female reproductive tract; parameterization (through in vitro studies) of a mechanistic model developed for liposomal delivery systems; and development of long-acting injectable, insertable, or implantable (collectively, LAI) formulation variants - in each case, focused on building an in vitro-in vitro correlation (IVIVC) approach.

In FY 2022, two new extramural research projects were funded — one contract in the oral inhalation area and one grant in the nasal area. The new contract with the University of Florida (75F40122C00182) aims to build upon the Pulmonary Compartmental Absorption & Transit™ model (within GastroPlus®). Physicochemical parameter and in vitro permeability data will be collected to address model parameterization, and separate lamina propria compartments will be added to the model as well as the ability to consider variations in pH. The improved model will then be validated using existing in vivo pharmacokinetics (PK) data. In the emerging area of nose-to-brain drug delivery for nasal drug products, a PBPK model for this delivery mechanism in humans will be developed as part of a new grant to the University of Manchester (1U01FD007657). To support PBPK model development, proteomics data will be collected from the olfactory region of the brain as well as in vitro permeability and transport kinetic data. The new model will be validated with three drug products using in vivo systemic PK data collected for this study and positron emission tomography data of brain concentration available from literature.

Some other noteworthy and/or published accomplishments during FY 2022 (in addition to the **Research Highlight**) include the following:

- Particle behavior following actuation of a reservoir-based DPI was modeled using a combined CFD and discrete element method (DEM) approach, as part of grant #1U01FD006514 awarded to Princeton University[1]. Results suggested that certain device modifications improved aerosolization quality without greatly increasing the pressure drop, and that the average slip velocity between air and carrier particles had a greater influence on the quality of aerosolization compared to collisions between carrier particles or collisions with carrier particles and the wall. The model developed for this study may be useful for predicting the influence of DPI device changes during product development.

[1] Sulaiman M, Liu X, and Sundaresan S. *Effects of Dose Loading Conditions and Device Geometry on the Transport and a Aerosolization in Dry Powder Inhalers: A Simulation Study.* International Journal of Pharmaceutics. (2021) 610: 121219. https://doi.org/10.1016/j.ijpharm.2021.121219. PMID: 34699949.

- Further analyses were conducted with a CFD model previously developed for grant #1U01FD006537 awarded to North Carolina State University that simultaneously predicts particle transit, dissolution, and absorption for deposited particles in a moving nasal mucus layer geometry. The effects of inter-subject variability were explored in one study using three different nasal cavity geometries[2], and PK predictions were produced in another study that combined a PBPK model with the existing CFD model[3].

- A novel CFD model was developed in FY 2021 to explain spray-wall interaction and post-deposition liquid motion following the deposition of droplets from a nasal spray in a nasal cavity, in support of contract HHSF223201810144C awarded to Virginia Commonwealth University, and the results of this research were published in FY 2022[4]. Discrepancies between CFD predictions and actual measurements of regional deposition with in vitro nasal models motivated the creation of this new model, to better understand how the regional distribution of drug on the surface may change following deposition.

- A validated PBPK model of drug exposure in rabbits from levofloxacin, moxifloxacin, and gatifloxacin ophthalmic solutions (previously developed under grant #1U01FD006927 awarded to Simulations Plus, Inc.) which accounted for nasolacrimal drainage, ocular absorption, and distribution, was extrapolated to predict ocular exposure in humans by considering the interspecies differences in anatomy and physiology. The results of this research were published during FY 2022[5].

- A multiphase, multilayer mechanistic dermal absorption (MPML MechDermA) model available within the Simcyp™ Simulator has been developed under grant #U01FD006521. The model is capable of simulating the permeation of drugs into human skin following product application by accounting for formulation characteristics as well as body site- and sex-population variability. The published report[6] outlines the structure and assumptions of the MPML MechDermA model and includes results from simulations on exemplary drug products to demonstrate the model's capabilities. The reported model was utilized to establish an in vitro-in vivo extrapolation leveraging IVPT study and drug

---

[2] Chari S, Sridhar K, and Kleinstreuer C. *Effects of Subject-Variability on Nasally Inhaled Drug Deposition, Uptake, and Clearance.* Journal of Aerosol Science. (2022) 165: 106021. https://doi.org/10.1016/j.jaerosci.2022.106021.

[3] Dave S, Kleinstreuer C, and Chari S. *An Effective PBPK Model Predicting Dissolved Drug Transfer from a Representative Nasal Cavity to the Blood Stream.* Journal of Aerosol Science. (2022) 160: 105898. https:/doi.org/10.1016/j.jaerosci.2021.105898.

[4] Kolanjiyil A, Alfaifi A, Aladwani G, Golshahi L, and Longest W. *Importance of Spray-Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays.* Pharmaceutics. (2022) 14(5): 956. https://doi.org/10.3390/pharmaceutics14050956. PMID: 35631539.

[5] Le Merdy M, Alqaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2022) Online ahead of Print. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444.

[6] Patel N, Clarke J, Salem F, Abdulla T, Martins F, Arora S, Tsakalozou E, Hodgkinson A, Arjmandi-Tash O, Cristea S, Gosh P, Alam K, Raney S, Jamei M, and Polak S. *Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) Model to Predict Local and Systemic Exposure of Drug Products Applied on Skin.* CPT: Pharmacometrics & Systems Pharmacology. (2022) 11(8): 1060-1084. https://doi.org/10.1002/psp4.12814. PMID: 35670226.

product in vitro characterization data for multiple metronidazole semisolid dosage forms and to predict metronidazole amounts in the stratum corneum of virtual subjects[7].

- Enhancements on a published PBPK model for vaginal delivery[8] are being performed under contract HHSF223201810188C. Data on the female anatomy/physiology and the in vivo kinetics of carefully selected drugs and drug products, not currently available in the literature, are being collected through a series of in vitro, ex vivo, and in vivo studies. These data will fill critical gaps needed to develop and validate a generalized PBPK modeling platform for complex products delivered through the female reproductive tract (**Figure 1**). This research may be useful during the development of generic versions of these complex drug products by potentially assisting product development, supporting alternative approaches to establish bioequivalence, and/or reducing the burden of comparative clinical endpoint BE studies[9].

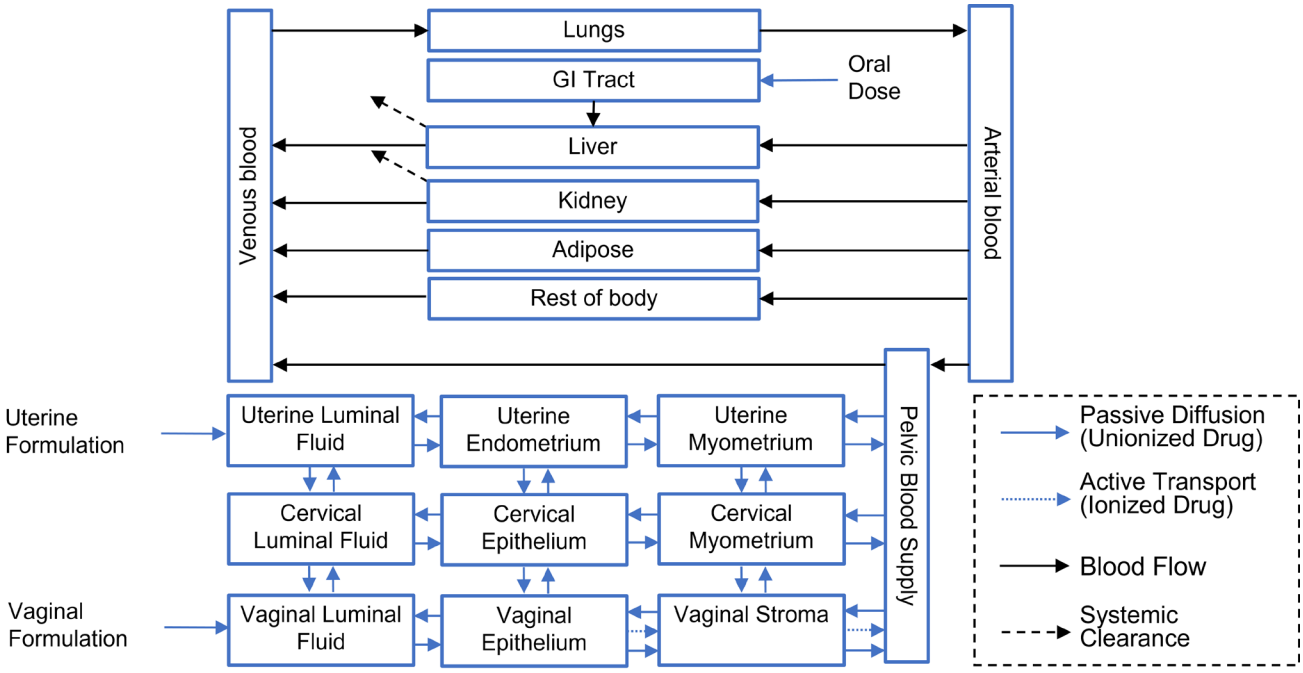


Figure 1: Proposed PBPK structural model (developed under contract HHSF223201810188C) for complex drug products delivered through the female reproductive tract.

---

[7] Arora S, Clarke J, Tsakalozou E, Ghosh P, Alam K, Grice J, Roberts M, Jamei M, and Polak S. Mechanistic Modeling of *In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model.* Molecular Pharmaceutics. (2022) 19(9): 3139–3152. https://doi.org/10.1021/acs.molpharmaceut.2c00229. PMID: 35969125.

[8] Kay K, Shah DK, Rohan L, and Bies, R. *Physiologically-Based Pharmacokinetic Model Of Vaginally Administered Dapivirine Ring and Film Formulations.* British Journal of Clinical Pharmacology. (2018) 84(9): 1950-1969. https://doi.org/10.1111/bcp.13625. PMID: 29714824

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

During FY 2022, research related to the development of in silico tools to model drug permeation into and through the skin has focused on the development of mechanistic models to describe and predict IVPT study data (**Figure 2**). An IVPT is a methodology typically employed to inform the development of dermatological drug products. Additionally, an IVPT is recommended within the scope certain in vitro characterization-based approaches for establishing the BE of topical dermatological drug products. Under grants with Certara® (#1U01FD007323, utilizing Simcyp™ Simulator), Children's Hospital of Los Angeles (#1U01FD006549, utilizing Open Systems Pharmacology Suite), and Simulations Plus (#1U01FD006526 and #1U01FD007320 utilizing GastroPlus®), in silico IVPT modeling and simulation tools have been further developed to capture key parameters of IVPT experimental design as accurately as possible, such as:

1. Describing the type of apparatus used for the IVPT study (e.g., static cells vs flow through cells) and relevant experimental conditions including donor chamber volume and composition;

2. Accounting for the type of the skin sample used (dermatomed skin, heat separated epidermis, full thickness, etc.) and any available demographic information (sex, age, anatomical site);

3. Considering the specific characteristics of a drug product that may differ between a prospective generic product and its reference standard.

The integration of this breadth of information within the in silico IVPT tools is expected to facilitate increasingly reliable predictions of the rate and extent to which topically applied drugs permeate into and through the skin, including predictions of the amount of drug in different skin layers when desired. Although still under development, when these in silico IVPT models are adequately verified/validated for their intended purpose, they may be used to support the development of safe and effective generic dermatological drug products by supporting the design of IVPT studies whose experimental parameters can be efficiently optimized in silico, and in developing and validating dermal PBPK models used for drug product development and approval.

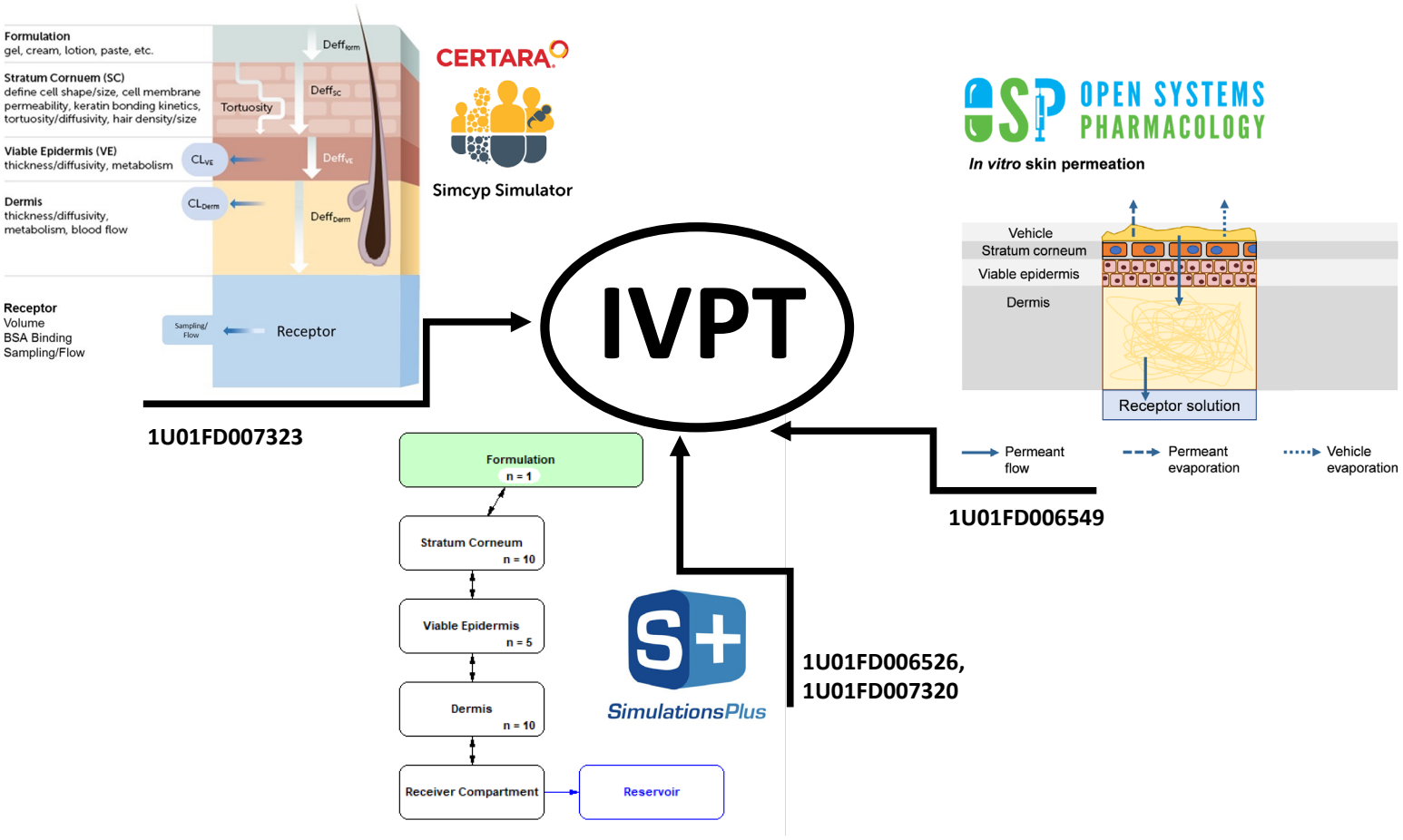


Figure 2. Prediction of in vitro permeation testing (IVPT) study data using IVPT in silico models implemented in several software platforms including (in alphabetical order of awardee name) the Multi-Phase, Multi-Layer MechDermA model within the Simcyp™ Simulator by Certara® (grant #1U01FD007323); a skin model within PK-Sim®/MoBi® developed by Children's Hospital of Los Angeles (grant #1U01FD006549) and available with the Open Systems Pharmacology Suite[10]; and the Transdermal Compartmental Absorption & Transit™ within GastroPlus® by Simulations Plus (grants #1U01FD006526, #1U01FD007320). The development of these in silico tools allows for a mechanistic understanding of the processes that govern permeation through the skin of drug substances applied on the skin within the scope of IVPT studies. Inset figures are published with permission from the owners.

[10] Hamadeh A, Troutman J, Najjar A, and Edginton A. *A Mechanistic Bayesian Inferential Workflow for Estimation of In Vivo Skin Permeation from In Vitro Measurements.* Journal of Pharmaceutical Sciences. (2022) 111(3): 838-851. https://doi.org/10.1016/j.xphs.2021.11.028. PMID: 34871561.

New Grants and Contracts

- Grant (1U01FD007657) *Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data* at the University of Manchester.
- Contract (75F40122C00182) *Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs* at the University of Florida.

Continuing Grants and Contracts

- Grant (1U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University.
- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at Simulations Plus, Inc.
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterisation, Release and Permeation Data to the Next Level - PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK Limited.
- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at the University of North Carolina at Chapel Hill.
- Grant (1U01FD007348) *Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics* with Jill Barber at the University of Manchester.
- Grant (1U01FD006521) *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations* with Sebastian Polak at Certara UK, LTD.
- Grant (1U01FD006929) *Computational Biology (Cobi) Tools as a Framework for Physiologically-Based Pharmacokinetic/Pharmacodynamic Model Extrapolation from Rabbit to Human for Ophthalmic Drug Products* with Carrie German at CFD Research Corporation.
- Grant (1U01FD006927) *Development and Validation of a PBPK/PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human* with Jessica Spires at Simulations Plus, Inc.
- Contract (75F40119C10139) MIDD *Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie Au at IQSP - Institute of Quantitative Systems Pharmacology.
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate Their Generic Development* with Dianne Burgess at the University of Connecticut.

- Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert Bies at State University of New York at Buffalo.
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University.

Completed Grants and Contracts

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at the University of Iowa.
- Grant (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael N. Neely at Children's Hospital of Los Angeles.
- Grant (1U01FD006514) *Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery* with Sankaran Sundaresan at Princeton University.
- Grant (1U01FD006537) *Nasal Mucociliary Clearance Affecting Local Drug-Absorption in Subject-Specific Geometries* with Clement Kleinstreuer at North Carolina State University.
- Contract (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation.
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation (CFDRC).
- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Prediction of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffry Schroeter at Applied Research Associates, Inc.

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *CFD Models of Droplet Formulation from MDI*
- *CFD Models of Soft Mist Inhalers*
- *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*
- *Development of a Nasal PBPK Modeling Platform*
- *Development of an Ophthalmic PBPK Modeling Platform*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

Articles

- Alfaifi A, Hosseini S, Esmaeili A, Walenga R, Babiskin A, Schuman T, Longest W, Hindle M, and Golshahi L. *Anatomically Realistic Nasal Replicas Capturing the Range of Nasal Spray Drug Delivery in Adults.* International Journal of Pharmaceutics. (2022) 622: 121858. https://doi.org/10.1016/j.ijpharm.2022.121858. PMID: 35643344.

- Arora S, Clarke J, Tsakalozou E, Ghosh P, Alam K, Grice J, Roberts M, Jamei M, and Polak S. *Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model.* Molecular pharmaceutics. (2022) 19(9): 3139-3152. https://doi.org/10.1021/acs.molpharmaceut.2c00229. PMID: 35969125.

- Capecelatro J, Longest W, Boerman C, Sulaiman M, and Sundaresan S. Recent *Developments in the Computational Simulation of Dry Powder Inhalers.* Advanced Drug Delivery Reviews. (2022) 188: 114461. https://doi.org/10.1016/j.addr.2022.114461. PMID: 35868587.

- Chari S, Sridhar K, and Kleinstreuer C. *Effects of Subject-Variability on Nasally Inhaled Drug Deposition, Uptake, and Clearance.* Journal of Aerosol Science. (2022) 165: 106021. https://doi.org/10.1016/j.jaerosci.2022.106021.

- Dave S, Kleinstreuer C, and Chari S. *An Effective PBPK Model Predicting Dissolved Drug Transfer from a Representative Nasal Cavity to the Blood Stream.* Journal of Aerosol Science. (2022) 160: 105898. https:/doi.org/10.1016/j.jaerosci.2021.105898.

- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga R, Newman B, Schuman T, Longest P, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 493-498.

- Dutta R, Kolanjiyil A, Golshahi L, and Longest P. *Development of a CFD-PK Nasal Spray Model with In Vivo Human Subject Validation.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 483-488.

- Golshahi L, Alfaifi A, Hosseini S, Esmaeili A, Hindle M, Longest P, and Schuman T. *Leveraging In Vitro Bioequivalence Tests for Locally-Acting Suspension Nasal Sprays with Three Anatomically-Correct Replicas of Human Nasal Airways Representing Intersubject Variability.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 37-46.

- Hamadeh A, Troutman J, Najjar A, and Edginton A. *A Mechanistic Bayesian Inferential Workflow for Estimation of In Vivo Skin Permeation from In Vitro Measurements.* Journal of Pharmaceutical Sciences. (2022) 111(3): 838-851. https://doi.org/10.1016/j.xphs.2021.11.028. PMID: 34871561.

- Kolanjiyil A, Alfaifi A, Aladwani G, Golshahi L, and Longest W. *Importance of Spray-Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays.* Pharmaceutics. (2022) 14(5): 956. https://doi.org/10.3390/pharmaceutics14050956. PMID: 35631539.

- Kolanjiyil A, Golshahi L, and Longest P. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 515-520.

- Kolanjiyil A, Hosseini S, Alfaifi A, Farkas D, Walenga R, Babiskin A, Hindle M, Golshahi L, and Longest P. *Validating CFD Predictions of Nasal Spray Deposition: Inclusion of Cloud Motion Effects for Two Spray Pump Designs.* Aerosol Science and Technology. (2022) 56(4): 305-322. https://doi.org/10.1080/02786826.2021.2011830.

- Le Merdy M, Alqaraghuli F, Tan M-L, Walenga R, Babiskin A, Zhao L, and Lukacova V. *Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation.* Pharmaceutical Research. (2022) Online ahead of Print. https://doi.org/10.1007/s11095-022-03390-z. PMID: 36151444.

- Liu X, Cheruvu H, Anissimov Y, Van Der Hoek J, Tsakalozou E, Ni Z, Ghosh P, Grice J, and Roberts M. *Percutaneous Absorption of Steroids from Finite Doses: Predicting Urinary Excretion from In Vitro Skin Permeation Testing.* International Journal of Pharmaceutics. (2022) 625: 122095. https://doi.org/10.1016/j.ijpharm.2022.122095. PMID: 35961420.

- Newman B, Babiskin A, Bielski E, Boc S, Dhapare S, Fang L, Feibus K, Kaviratna A, Li B, Luke M, Ma T, Walenga R, Wang Z, Zhao L, El-Gendy N, Bertha C, El-Shafy M, and Gaglani D. *Scientific and Regulatory Activities Initiated by the U.S. Food and Drug Administration to Foster Approvals of Generic Dry Powder Inhalers: Bioequivalence Perspective.* Advanced Drug Delivery Reviews. (2022) 190: 114526. https://doi.org/10.1016/j.addr.2022.114526. PMID: 36067967.

- Patel N, Clarke J, Salem F, Abdulla T, Martins F, Arora S, Tsakalozou E, Hodgkinson A, Arjmandi-Tash O, Cristea S, Gosh P, Alam K, Raney S, Jamei M, and Polak S. *Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) Model to Predict Local and Systemic Exposure of Drug Products Applied on Skin.* CPT: Pharmacometrics & Systems Pharmacology. (2022) 11(8): 1060-1084. https://doi.org/10.1002/psp4.12814. PMID: 35670226.

- Roberts M, Cheruvu H, Mangion S, Alinaghi A, Benson H, Mohammed Y, Holmes A, Hoes J, Pastore M, and Grice J. *Topical Drug Delivery: History, Percutaneous Absorption, and Product Development.* Advanced Drug Delivery Reviews. (2021) 177: 113929. https://doi.org/10.1016/j.addr.2021.113929. PMID: 34403750.

- Schroeter J, Rose M, Kimbell J, Chopski S, and Walenga R. *A Physiologically-Based Pharmacokinetic Model to Estimate Absorption and Bioavailability of Corticosteroid Nasal Sprays.* Respiratory Drug Delivery (RDD) 2022. (2022) 1: 197-200.

- Singh N, Kannan R, Arey R, Walenga R, Babiskin A, and Przekwas A. *Predicting Systemic and Pulmonary Tissue Barrier Concentration of Orally Inhaled Drug Products.* bioRxiv. (2022) 2022.03.10.483633. https://doi.org/10.1101/2022.03.10.483633.

- Sulaiman M, Liu X, and Sundaresan S. *Effects of Dose Loading Conditions and Device Geometry on the Transport and a Aerosolization in Dry Powder Inhalers: A Simulation Study.* International Journal of Pharmaceutics. (2021) 610: 121219. https://doi.org/10.1016/j.ijpharm.2021.121219. PMID: 34699949.

Posters

- Tsakalozou E, Alam K, Babiskin A, Fang L, and Zhao L. *Development and Application of a Dermal PBPK Modeling for Ethinyl Estradiol-Containing Transdermal Delivery Systems to Predict Exposure for Different Application Sites.* Poster Presentation at the 2022 Innovations in Dermatological Sciences Conference. Virtual Meeting, Sep. 27, 2022.
- Kolanjiyil AV, Golshahi L, Longest W. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, FL, May 2, 2022.
- Dutta R, Kolanjiyil AV, Golshahi L, and Longest W. *Development of a CFD PK Nasal Spray Model with In Vivo Human Subject Validation.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, FL, May 2, 2022.
- Schroeter J, Rose M, Kimbell J, Chopski S, and Walenga R. *A Physiologically-Based Pharmacokinetic Model to Estimate Absorption and Bioavailability of Corticosteroid Nasal Sprays.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga R, Newman B, Schuman T, Edwards D, Longest W, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Poster Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 01, 2022.
- Le Merdy M, Lukacova V, Tan M-L, Babiskin A, and Zhao L. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Moxifloxacin Solution Case Study.* Poster Presentation at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Denver, Colorado, May 01, 2022.
- Alam K, Tsakalozou E, Babiskin A, Ghosh P, Ramezanli T, Jiang Y, Niu M, and Zhao L. *Does Vehicle Evaporation Affect Drug Distribution within Different Phases of Topically Applied Emulsion? A Modeling Case Study with Clindamycin Phosphate Lotion.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Le Merdy M, Zheng Y, Lukacova V, Tan M-L, Babiskin A, and Zhao L. *Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Levofloxacin Solution Case Study.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Telaprolu K, Polak S, Tsakalozou E, Ghosh P, Alam K, Dabbaghi M, Namjoshi S, Mohammed Y, Grice J, and Roberts M. *Modeling In Vitro and In Vivo Human Skin Permeation of Eutectic Mixtures of Local Anesthetics Using PBPK Modeling: Development of Dermal IVIVE for Lidocaine 2.5% w/w and Prilocaine 2.5% w/w Cream (EMLA® Cream).* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 17, 2021.

Presentations

- Edginton A, Yun E, and Hamadeh A. *Physiologically-Based Pharmacokinetic Pediatric Skin Model.* Presentation at the 14th European Paediatric Formulation Initiative (EuPFI) Conference 2022. Rome, Italy, Sep. 21, 2022.
- Tsakalozou E. *Dermal PBPK Modeling for a Transdermal Delivery System to Assess the Impact of the Application Site on In Vivo Performance.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Walenga R. *Mechanistic Modeling and Realistic In Vitro Models to Facilitate Development of Generic Nasal Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Alam K. Mechanistic *Modeling of Complex Injectables: Recommendations to Navigate Regulatory Challenges.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Pellowe M, and Sjogren E. *Virtual Bioequivalence Workflow.* Presentation at Population Approach Group Europe (PAGE) 2022 Annual Meeting. Ljubljana, Slovenia, Jun. 28, 2022.
- Dutta R, Kolanjiyil A, Golshahi L, and Longest W. *Development of a CFD PK Nasal Spray Model with In Vivo Human Subject Validation.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Esmaeili A, Hosseini S, Wilkins J, Alfaifi A, Dhapare S, Walenga , Newman B, Schuman T, Edwards D, Longest W, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Drug Deposition in Nasal Airways of Children Using Realistic Anatomical Replicas.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Golshahi L, Alfaifi A, Hosseini S, Esmaeili A, Hindle M, Longest W, and Schuman T. *Leveraging In Vitro Bioequivalence Tests for Locally-Acting Suspension Nasal Sprays with Three Anatomically-Correct Replicas of Human Nasal Airways Representing Intersubject Variability.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Florida, Orlando, May 02, 2022.
- Kolanjiyil A, Golshahi L, and Longest W. *On the Importance of Liquid Motion in Nasal Spray Delivery.* Presentation at the Respiratory Drug Delivery (RDD) 2022 Conference. Orlando, Florida, May 02, 2022.
- Hamadeh A, and Troutman J. *Mechanistic in Silico Inference of Dermal Absorption for Chemical Risk Assessment.* Presentation at the ScitoVation Webinar. Virtual Meeting, Mar. 08, 2022.

- Van Osdol B, and Spires J. *In Silico QbD for Dermal Topical Formulations via TCAT Model Simulations.* Presentation at the Simulations Plus 2022 Model-Informed Drug Development (MIDD+) Scientific Conference. Virtual Meeting, Feb. 17, 2022.
- Walenga R. *Modeling of CNS Delivery for Nose-to-Brain Targeted Drug Products.* Presentation at the Society for Computational Fluid Dynamics of the Nose Airway (SCONA) 2022 Virtual Meeting. Virtual Meeting, Jan. 28, 2022.
- Tsakalozou E. *Leveraging Dermal Physiologically-based Pharmacokinetic Modeling and Simulation Approaches for the Approval of a Generic Diclofenac Sodium Topical Gel.* Presentation at the Simcyp Scientific Webinar Series. Virtual Meeting, Dec. 08, 2021.

QUANTITATIVE CLINICAL PHARMACOLOGY

Summary of FY 2022 Activities

In FY 2022, FDA continued developing methodologies and disseminating innovative quantitative clinical pharmacology (QCP) approaches to help address challenges in development and assessment for certain generics such as long-acting injectable, insertable, or implantable (collectively, LAI), oncology, and orphan drug products. The outcomes from internal and external research positioned FDA to provide timely QCP-based advice during pre-ANDA interactions and helped applicants prepare ANDA submissions that incorporated innovative model-integrated evidence (MIE) for bioequivalence (BE). The research outcomes, thereby, facilitated more efficient BE approaches such as the use of alternative study designs with a shorter duration or a reduced sample size. To facilitate the implementation of MIE, FDA organized two public workshops with the Center for Research on Complex Generics (CRCG) to build a consensus on best practices in MIE for BE with experts including generic industry stakeholders[1]. The population pharmacokinetic (PK) MIE framework developed by FDA-Uppsala University collaboration (contract# 75F40119C10018) along with the associated R packages for easy implementation, supported the standardization of MIE and facilitated its implementation for regulatory use.

FDA invested in facilitating the adoption of advanced BE approaches and methodologies. A virtual BE trial simulation platform that integrates population PK and physiologically-based PK modeling approaches was developed (grant#1U01FD006549). Mechanistic models describing skin absorption and inhalation for dermatological and orally inhaled drug products, respectively, were developed and made available within the open-source platform, Open Systems Pharmacology

[1] FDA and the Center for Research on Complex Generics (CRCG) hosted two free public workshops, one on the Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products (Virtual Meeting, Nov. 30, 2021. https://complexgenerics.org/LAI2021/) and the other on the Best Practices for Utilizing Modeling Approaches to Support Generic Product Development (Virtual Meeting, Oct. 27-28, 2022. https://complexgenerics.org/modeling-approaches/).

Suite, which also houses the developed clinical trial simulation tool. The platform integrates QCP modeling and simulation tools in one place to generate BE evidence in silico, and is expected to help reduce or replace in vivo BE studies for complex locally acting drug products, ultimately improving the efficiency of their development and approval.

In FY 2022, FDA scientists and collaborators actively communicated research outcomes that supported the development of innovative methodologies for complex or emerging BE issues. For example, a model-based statistical approach was further evaluated as an alternative to a non-compartmental analysis (NCA) for patient PK BE studies with sparse sampling (contract #75F40119C10111). To help the adoption of the model-based BE analysis, an R package was developed (contract #HHSF223201710015C) that includes both NCA- or model-based BE analysis to assist the selection of an appropriate BE analysis for a patient PK BE study with sparse samples, such as for ophthalmic drug products. The University of Maryland (contract #75F40119C10068) developed a BE strategy to help address the high batch-to-batch variability for certain oral powder inhalation products using population PK modeling to identify relationships between the batch variability and formulation properties such as particle size, and to help select batches for in vivo BE studies.

FDA scientists and world experts collaboratively advanced the development of a model-based (MB) BE analysis framework to address challenges associated with patient PK BE studies where intensive PK sampling is challenging or impossible. This study highlights the application of the developed framework to ophthalmic drugs, where BE studies are typically conducted in patients using a parallel design with one sample of aqueous humor collected in one eye. The extremely sparse PK sampling precludes a traditional BE analysis, and an approach coupling non-compartmental analysis (NCA) with parametric or non-parametric bootstrap is typically recommended[2,3]. Recent research has focused on MB two one-sided test (TOST) methods in PK BE studies with sparse sampling[4,5].

A simulated PK BE study was performed using a published PK model for theophylline4 with 500 subjects assigned to 5 or 10 groups, each representing a single sampling time. Simulations were performed using parallel and crossover designs with a between-subject variability of 50% for both designs and a within-subject variability of 15% for the crossover design. Formulation differences were simulated to assess Type I error and power.

The non-parametric bootstrap NCA showed lower power for C_{max} and similar power for AUC when compared to MB TOST (**Figure 1**). The Type I error for C_{max} using non-parametric bootstrap NCA was well below 5% for both a parallel design (**Figure 2**) and crossover design (not shown). The conservative Type I error control for C_{max} resulted in lower power with the non-parametric bootstrap NCA for C_{max}, especially with 10 sampling times containing some uninformative time points.

These results suggest that MB-TOST may serve as an alternative BE analysis approach for single sample PK studies, but additional research is needed. Ultimately, this research may help promote the development of generic ophthalmic drug products and supports a key priority at FDA to establish a foundation for model-based BE study designs[3,6].

---

[2] Shen M, and Machado SG. *Bioequivalence Evaluation of Sparse Sampling Pharmacokinetics Data using Bootstrap Resampling Method.* Journal of biopharmaceutical statistics. (2017) 27(2): 257-264. https://doi.org/10.1080/10543406.2016.1265543. PMID: 27906608.

[3] Choi SH, and Lionberger RA. *Clinical, Pharmacokinetic, and In Vitro Studies to Support Bioequivalence of Ophthalmic Drug Products.* The AAPS journal. (2016). 18(4): 1032-1038. https://doi.org/10.1208/s12248-016-9932-z. PMID: 27184578.

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

[5] Möllenhoff K, Loingeville F, Bertrand J, Nguyen TT, Sharan S, Zhao L, Fang L, Sun G, Grosser S, Mentré F, and Dette H. *Efficient Model-Based Bioequivalence Testing.* Biostatistics (Oxford, England). (2022). 23(1): 314-327. https://doi.org/10.1093/biostatistics/kxaa026. PMID: 32696053.

[6] Generic Drug Research Priorities and Projects, Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year (FY) 2022, U.S. Food and Drug Administration (FDA), Current as of 06/01/2022, https://www.fda.gov/media/154487/download

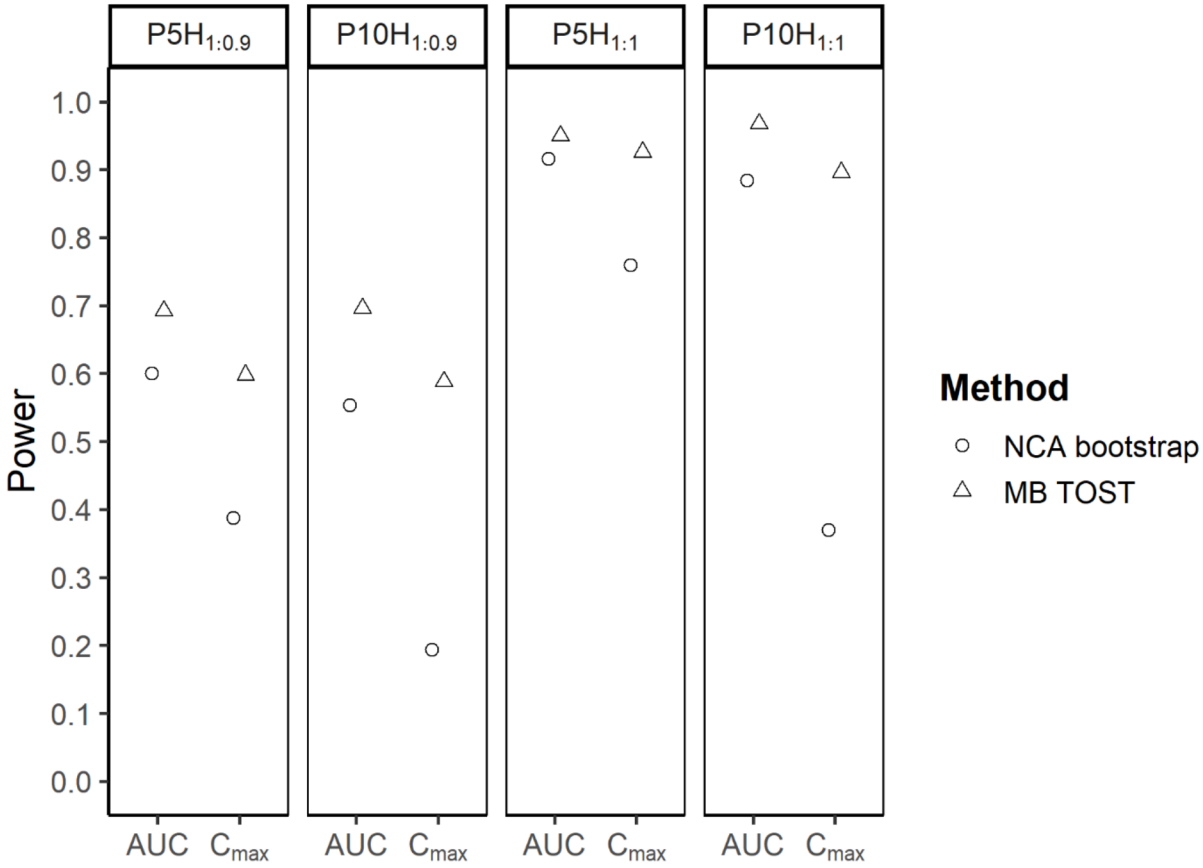


Figure 1. Power for a simulated geometric mean ratio (GMR) = 0.9 and 1.0 of non-parametric bootstrap NCA (○) and MB TOST (△) for AUC and C_{max} for a parallel design (P) when the subjects are assigned to 5 or 10 groups. Real and simulated data sets were analyzed using Monolix 2018R2 software. Estimates were not corrected for the departure from the nominal level of the test.

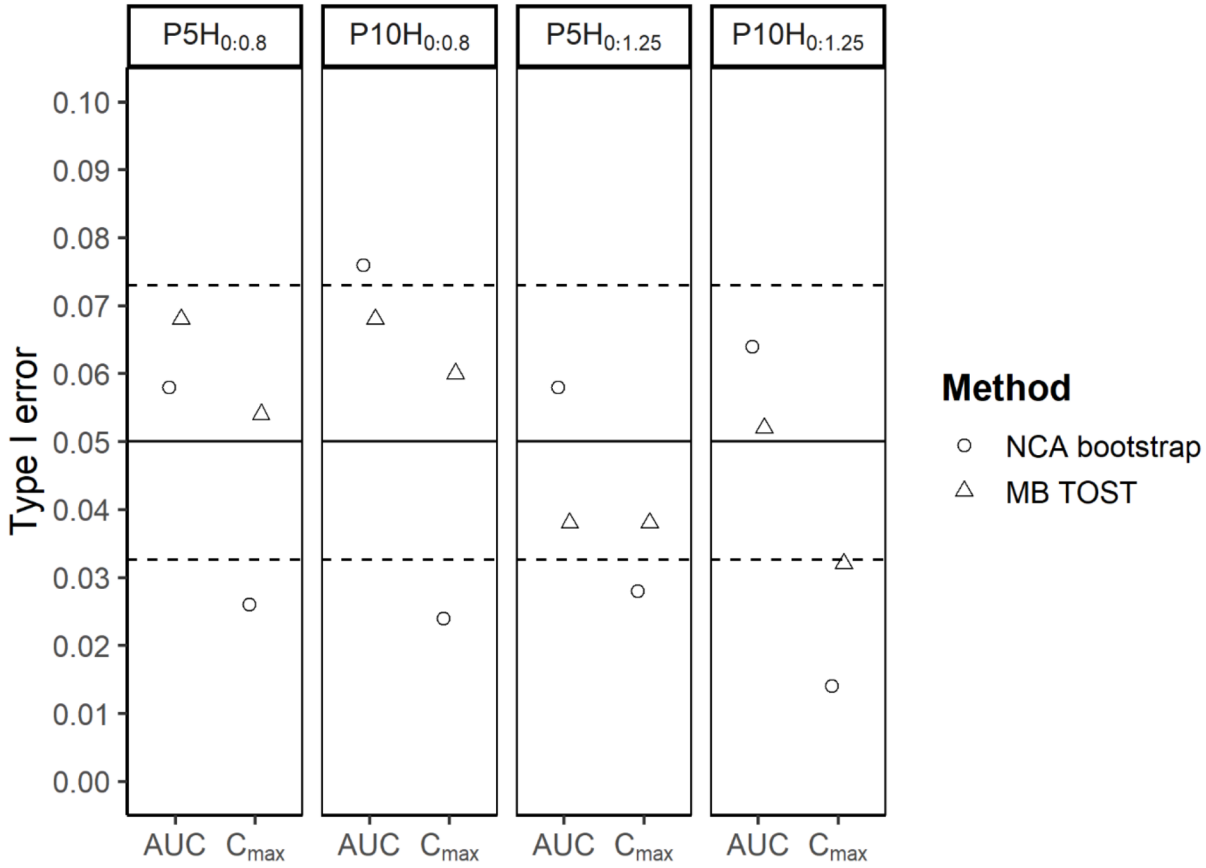


Figure 2. Type I error rate for a simulated geometric mean ratio (GMR) = 0.8 and 1.25 of non-parametric bootstrap NCA (○) and MB TOST (△) for AUC and C_{max} for a parallel design (P) when the subjects are assigned to 5 or 10 groups. Real and simulated data sets were analyzed using Monolix 2018R2 software.

New Grants and Contracts

- Contract (75F40122C00139) *Model-integrated strategies for bioequivalence evaluation of drugs with high variability and/or long half-life* at Uppsala University.

Continuing Grants and Contracts

- Grant (1U01FD007355) *Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis* with Mark Sale at Nuventra, Inc.

Completed Grants and Contracts

- Grant (1U01FD006549) *PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform* with Michael N. Neely at Children's Hospital of Los Angeles.
- Contract (HHSF223201610110C) *Evaluation of Model-Based Bioequivalence Statistical Approaches for Sparse Design PK Studies* with France Mentre at Inst Nat Sante Et La Recherche Medicale (INSERM).
- Contract (75F40119C10068) *Batch-to-Batch Variability: Exploring Solutions for Generic BE Pathway* at the University of Maryland.
- Contract (75F40119C10111) *Evaluation of Model-Based Bioequivalence (MBBE) statistical approaches for sparse designs PK studies* with France Mentre at Inst Nat Sante Et La Recherche Medicale (INSERM).

Active FDA Research

- *Batch to Batch Variability of Inhalation Products*
- *Clinical Trial Simulation for Clinical Endpoint Bioequivalence Studies*
- *Evaluation and Development of Model-Integrated Bioequivalence Analysis Strategies*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*
- *Model-based Assessment on Bioequivalence Limits for Anticoagulants*
- *New Approaches to Identify Clinically Relevant Partial AUC Measures for Bioequivalence*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based Supports for Bioequivalence Assessment During the COVID-19 Public Health Emergency*

Product-Specific Guidances

There were 12 new and 3 revised PSGs published in FY 2022 related to *Quantitative Clinical Pharmacology* products. Among those, the PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *Revised Draft Guidance for Acarbose Tablet.* (May 2022) Link to Posting
- *New Draft Guidance for Amphetamine; Amphetamine Aspartate/ Dextroamphetamine Sulfate Tablet, Extended Release.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Asenapine Transdermal System.* (May 2022) Link to Posting
- *New Draft Guidance for Capmatinib Hydrochloride Oral Tablet.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Carbamazepine Tablet, Chewable.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Etonogestrel Implant.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Exenatide Synthetic for Suspension, Extended Release.* (NDA 022200) (May 2022) Link to Posting
- *New Draft Guidance for Exenatide Synthetic for Suspension, Extended Release.* (NDA 209210) (May 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate for Subcutaneous Injection.* (NDA 021379 and NDA 021488) (Feb. 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate for Subcutaneous Injection.* (NDA 021731 and NDA 213150) (Feb. 2022) Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride Nasal Spray.* (May 2022) Link to Posting
- *New Draft Guidance for Progesterone Vaginal System.* (Feb. 2022) Link to Posting
- *Revised Draft Guidance for Testosterone Pellet.* (May 2022) Link to Posting
- *Revised Draft Guidance for Theophylline Tablet, Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Viloxazine Hydrochloride Oral Capsule, Extended Release.* (Feb. 2022) Link to Posting

Articles

- Gong Y, Feng K, Zhang P, Lee J, Pan Y, Zhang Z, Ni Z, Bai T, Yoon M, Li B, Kim C, Fang L, and Zhao L. *Quantitative Methods and Modeling to Assess COVID-19-Interrupted In Vivo Pharmacokinetic Bioequivalence Studies with Two Reference Batches.* CPT: Pharmacometrics & Systems Pharmacology. (2022) 11(7): 833-842. https://doi.org/10.1002/psp4.12795. PMID: 35411692.

- Guhl M, Mercier F, Hofmann C, Sharan S, Donnelly M, Feng K, Sun W, Sun G, Stella G, Zhao L, Fang L, Mentre F, Comets E, and Bertrand J. *Impact of Model Misspecification on Model-Based Tests in PK Studies with Parallel Design: Real Case and Simulation Studies.* Journal of Pharmacokinetics and Pharmacodynamics. (2022) 49(5): 557-577. https://doi.org/10.1007/s10928-022-09821-z. PMID: 36112338.

- Hamadeh A, Troutman J, Najjar A, and Edginton A. *A Mechanistic Bayesian Inferential Workflow for Estimation of In Vivo Skin Permeation from In Vitro Measurements.* Journal of Pharmaceutical Sciences. (2022) 111(3): 838-851. https://doi.org/10.1016/j.xphs.2021.11.028. PMID: 34871561.

- Lee J, Feng K, Conti D, Walenga R, Wientijes M, Wang H, Newman B, Han L, Dhapare S, Bielski E, Babiskin A, Wu F, Donnelly M, Kim M, Jiang W, Luke M, Fang L, and Zhao L. *Considerations for the Forced Expiratory Volume in 1 Second-Based Comparative Clinical Endpoint Bioequivalence Studies for Orally Inhaled Drug Products.* Clinical Pharmacology and Therapeutics. (2022) 112(5): 982-989 https://doi.org/10.1002/cpt.2553. PMID: 35133652.

- Mosley S, Kim S, Rouby N, Lingineni K, Vozmediano V, Gong Y, Chen Y, Estores D, Feng K, Kim H, Kinjo M, Langaee T, Li Z, Schmidt S, Johnson J, Frye R, Fang L, Zhao L, Binkley P, Schmidt S, and Cavallari L. A Randomized, *Cross-over Trial of Metoprolol Succinate Formulations to Evaluate PK and PD Endpoints for Therapeutic Equivalence.* Clinical and Transitional Science. (2022) 15(7): 1764-1775. https://doi.org/10.1111/cts.13294. PMID: 35488487.

- Sharan S, Choi S, Zou Y, Wang Y, Kim M, Fang L, Choi S, Makhlouf F, Grosser S, Zhang X, and Zhao L. *Application of Modeling and Simulation to Identify a Shortened Study Duration and Novel Bioequivalence Metric for a Long-Acting Intrauterine System.* The AAPS Journal. (2022) 24(3): 63. https://doi.org/10.1208/s12248-022-00715-z. PMID: 35501412.

Posters

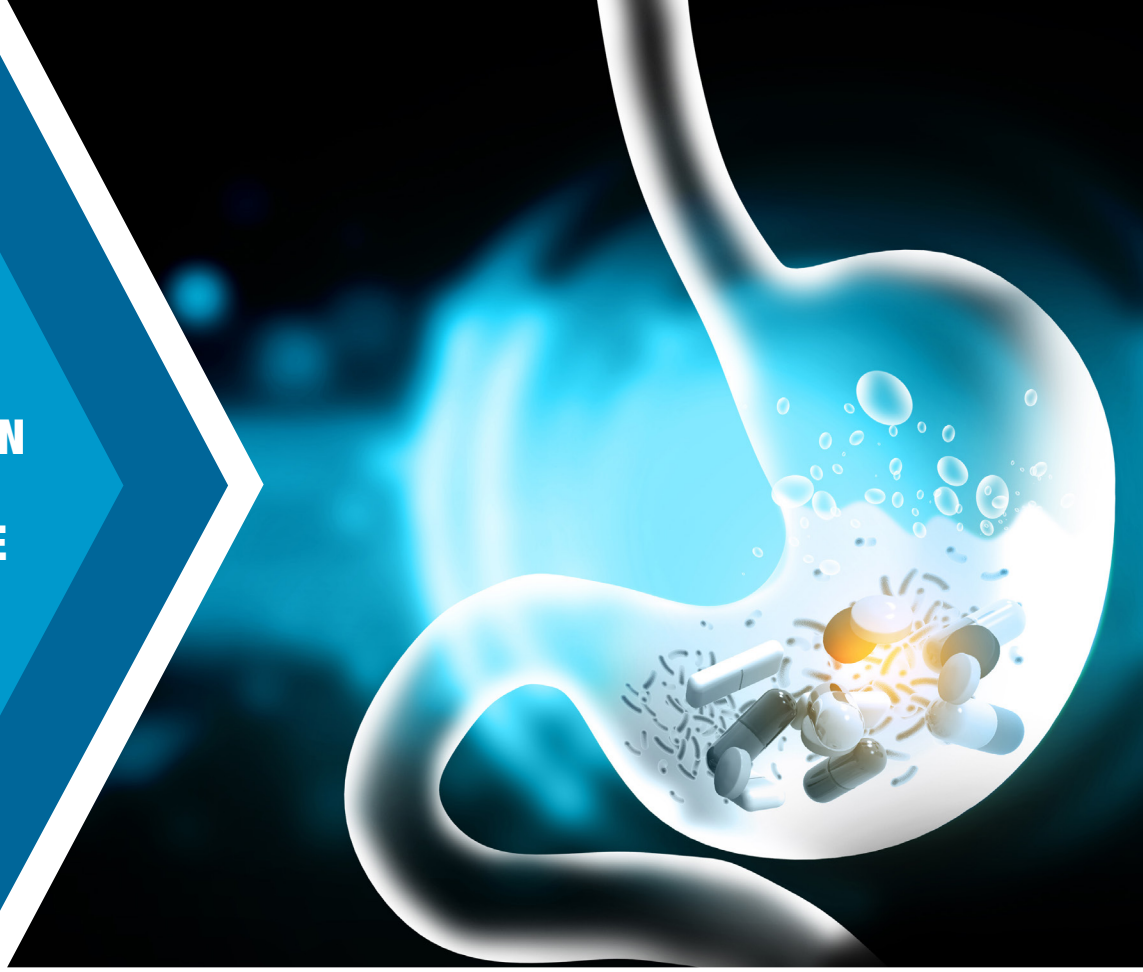
- Philipp M, Tessier A, Donnelly M, Fang L, Feng K, Zhao L, Grosser S, Sun G, Sun W, Mentre F, and Bertrand J. *Model-Based Bioequivalence Approach: Robustness to Model Misspecification for Sparse Pharmacokinetic Bioequivalence Studies.* Poster Presentation at the Population Approach Group Europe (PAGE) 2022 Annual Meeting. Ljubljana, Slovenia, Jun. 28, 2022.
- Sale M, Ismail M, Wang F, Feng K, Hu M, Zhao L, and Bies R. *Comparison of Robustness and Efficiency of Four Machine Learning Algorithms for Identification of Optimal Population Pharmacokinetic Models.* Poster Presentation at the Population Approach Group Europe (PAGE) 2022 Annual Meeting. Ljubljana, Slovenia, Jun. 28, 2022.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Evaluating Novel Pilot Pharmacokinetic Bioequivalence Study for Inhalation Powder Drug Products Exhibiting Batch-To-Batch Variability.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Exploration the Potential Impact of Batch-to-Batch Variability of Inhalation Powder Drug Products on Pharmacokinetic Bioequivalence Study Power.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Exploring the Relationship Between the In Vitro Properties and the Pharmacokinetic Parameters of Advair Diskus.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.
- Li S, Feng K, Lee J, Gong Y, Wu F, Newman B, Yoon M, Fang L, Zhao L, and Gobburu J. *Population Pharmacokinetic Modeling for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder in a Bioequivalence Study.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.
- Xie L, Kelchen M, Ghosh P, Niu M, Raney S, and Shen J. *Development of An In Vitro Permeation Test Method for Rectal Suppositories.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.
- Yue W, Xie L, Kelchen M, Ghosh P, Niu M, Raney S, and Shen J. *Development of an In Vitro Release Testing Method for Vaginal Creams.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Feng K. *Model-based Bridging to Establish Bioequivalence with a Discontinued Reference Listed Product.* Presentation at the 2022 American College of Clinical Pharmacology (ACCP) Annual Meeting. Bethesda, Maryland, Sep. 24, 2022.
- Edginton A, Yun E, and Hamadeh A. *Physiologically-Based Pharmacokinetic Pediatric Skin Model.* Presentation at the 14th European Paediatric Formulation Initiative (EuPFI) Conference 2022. Rome, Italy, Sep. 21, 2022.
- Gong Y. *Alternative Model-Based Data Analysis Approach to Demonstrate Bioequivalence.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Feng K. *Application of Quantitative Modeling and Simulations to Bioequivalence Determination for Long-Acting Injectables – Sharing Research Progress and Regulatory Experience.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Thomas S. *Recommendation of Partial Area Under the Curve (pAUC) Metrics in Product-Specific Guidance for Long-Acting Injectable (LAI) Drug Products.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Pellowe M, and Sjogren E. *Virtual bioequivalence workflow.* Presentation at the Population Approach Group Europe (PAGE) 2022 Annual Meeting. Ljubljana, Slovenia, Jun. 28, 2022.
- Hooker A. *Research Related to Model Master Files to Establish the Concept and Details for Practical Implementation of Model- Integrated BE Packages in Regulatory Submissions.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 09, 2022.
- Zhao L. *Best Practices to Leverage Model-Integrated Evidence and Model Master File Packages to Bring Complex Generics to Market.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 09, 2022.
- Donnelly M. *Regulatory Challenges with Pharmacokinetic (PK) Bioequivalence (BE) Studies for Drugs Containing Endogenous Compounds.* Presentation at the Scientists Advancing Affordable Medicines Workshop 2022. Virtual Meeting, Apr. 27, 2022.
- Hamadeh A, and Troutman J. *Mechanistic in Silico Inference of Dermal Absorption for Chemical Risk Assessment.* Presentation at the ScitoVation Webinar. Virtual Meeting, Mar. 08, 2022.

- Hooker A. *Model-Integrated Methods and Innovative Study Designs for Generic LAI Product Development and Regulatory Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products. Virtual Meeting, Nov. 30, 2021.
- Yoon M. *Model-Integrated Evidence for Bioequivalence Assessment of Long-Acting Injectables from a Generic Drug Perspective.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products. Virtual Meeting, Nov. 30, 2021.
- Yoon M. *Model-Integrated Bioequivalence Establishment: Long-Acting Injectable Drug Products.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 10, 2021.
- Batchelor H, Pawar G, Wu F, Zhao L, Fang L, Burckart G, Feng K, and Mousa Y. *Risk Factors Related to Relative Bioavailability Studies for Pediatric Products.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.
- Fang L. *Is Bioequivalence Established in Adults Relevant for Pediatrics?* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 17, 2021.
- Wu F. *Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 15, 2021.

ORAL ABSORPTION MODELS AND BIOEQUIVALENCE



Summary of FY 2022 Activities

In FY 2022, 12 contracts and grants as well as multiple internal research projects focused on the development of biorelevant/biopredictive in vitro testing and physiologically-based pharmacokinetics (PBPK) modeling to predict the impact of formulations (including excipients), food, and specific populations (e.g., pediatric) on bioequivalence (BE) assessment. The extramural and intramural projects related to oral absorption models and bioequivalence encompassed four scientific areas:

1. The potential expansion of biowaivers for Biopharmaceutics Classification System (BCS) Class III Drugs:

   Grant #3U01FD005978 continued to investigate the clinical significance of in vitro test results. Under this grant, an exploratory clinical study is being conducted to evaluate whether sodium lauryl sulfate (SLS) has the potential to impact the in vivo oral bioavailability of fexofenadine, a known OATP2B1 substrate. Another contract #75F40119C10127 “Expanding BCS Class III Waivers for Generic Drugs to Non-Q1/Q2 Formulations” used the in vitro dissolution absorption system (IDAS) to compare the dissolution and permeation of BCS Class III active pharmaceutical ingredients (APIs) in four pairs of commercial reference listed drug (RLD) products and generic drug products containing acyclovir, atenolol, hydroxychloroquine, or rasagiline. The IDAS testing demonstrated similar permeation data for four pairs of RLD and generic drug products, despite the differences observed in the initial release of acyclovir between the generic product and the RLD. The in vitro (IDAS) results, thereby, correlated with the clinical data for these generic products that had previously demonstrated bioequivalence to their corresponding RLDs in clinical studies.

2. Enhancement of physiologically based pharmacokinetics (PBPK) modeling capabilities:

   Under contract #HHSF223201810112C, a project exploring the biorelevant dissolution methods of four Narrow Therapeutic Index (NTI) drugs was completed and the dissolution profiles generated were integrated into PBPK modelling software to determine whether these methods provide discriminatory tools to better predict risks of bio-inequivalence in pediatric patients. The aim of ongoing contract #75F40120C00150 was to develop a predictive in silico modeling and simulation platform for drug products delivered via the oral cavity (e.g., buccal tablets, sublingual tablets, etc.). Under this project, a dynamic in vitro dissolution and absorption model (DIVDAM) will be developed, which will account for sequential dissolution/absorption processes in both the oral cavity and the upper gastrointestinal (GI) tract. Another ongoing contract #75F40120C00200 aimed to develop biopredictive methods for setting patient centric quality specifications using in vitro-in vivo correlation (IVIVC) models for modified release (MR) oral drug products. In this project, the in vivo release and dissolution of two MR drug products in different human GI tract regions (and the relevant GI physiological parameters) are being measured. The outcome from this research is expected to elucidate how in vitro differences may be associated with variable absorption in vivo.

3. Utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed conditions:

   Grant #1U01FD007352 focused on the development and validation of a best practices framework for PBPK analysis in support of model-informed biowaivers of fed state BE studies for BCS Class II drugs. In FY 2022, this project showed that accurate measurement of logP values is fundamental to predict the volume of distribution at steady state (V_{ss}) of highly lipophilic compounds. For drugs like itraconazole that show slow recrystallization, measuring the apparent solubility of the amorphous form is critical for PBPK modeling under fasting conditions. Another ongoing contract #75F40121C00020, aimed to identify important product quality attributes by focusing on formulation variables that influence the in vivo performance of such products in fasting and fed states. This project is expected to help determine when the performance of an excipient or a formulation may be highly dependent on food and, thereby, support the development of biopredictive disintegration and dissolution methods that mimic fed conditions.

4. Research on the swallowability of oral dosage forms:

   Contract (#75F40121C00132) aimed to develop an in vitro method to assess the comparative swallowability of a solid oral generic product from compared to its reference standard counterpart when they differ in size, shape, or other physical attributes.

RESEARCH HIGHLIGHT

During FY 2022, research into the bioavailability of poorly water-soluble drugs was highlighted on FDA's website in an article titled "Formulating Drug Products for Optimized Absorption: Elucidating Amorphous Solid Dispersions", describing the outcomes of a completed contract (#HHSF223201710137C) "Phase Behavior and Transformation Kinetics of a Poorly Water Soluble Weakly Basic Drug upon Transit from Low to High pH Conditions". That contract research explored the mechanistic basis for the supersaturation and precipitation behavior of poorly water-soluble compounds to facilitate predictions of the in vivo performance of amorphous solid dispersion (ASD) drug products. As part of the research, different extents of supersaturation were evaluated using physiologically relevant media. **Figure 1** shows the solubility of crystalline and amorphous forms for posaconazole in biorelevant media as a function of pH[1]. Since the driving force for passive diffusion through the intestinal membrane is proportional to the concentration of the uncharged molecule, the supersaturation ratio indicates the potential improvement in the absorption rate. Current insights based on these research outcomes create a valuable foundation for understanding the impact of biologically relevant media on the solution phase behavior of poorly soluble drugs, which can assist in the development of prospective generic drug products that use ASDs.

[1] Van Duong T, Ni Z, and Taylor L. *Phase Behavior and Crystallization Kinetics of a Poorly Water-Soluble Weakly Basic Drug as a Function of Supersaturation and Media Composition.* Molecular Pharmaceutics. (2022) 19(4): 1146-1159. https://doi.org/10.1021/acs.molpharmaceut.1c00927. PMID: 35319221.

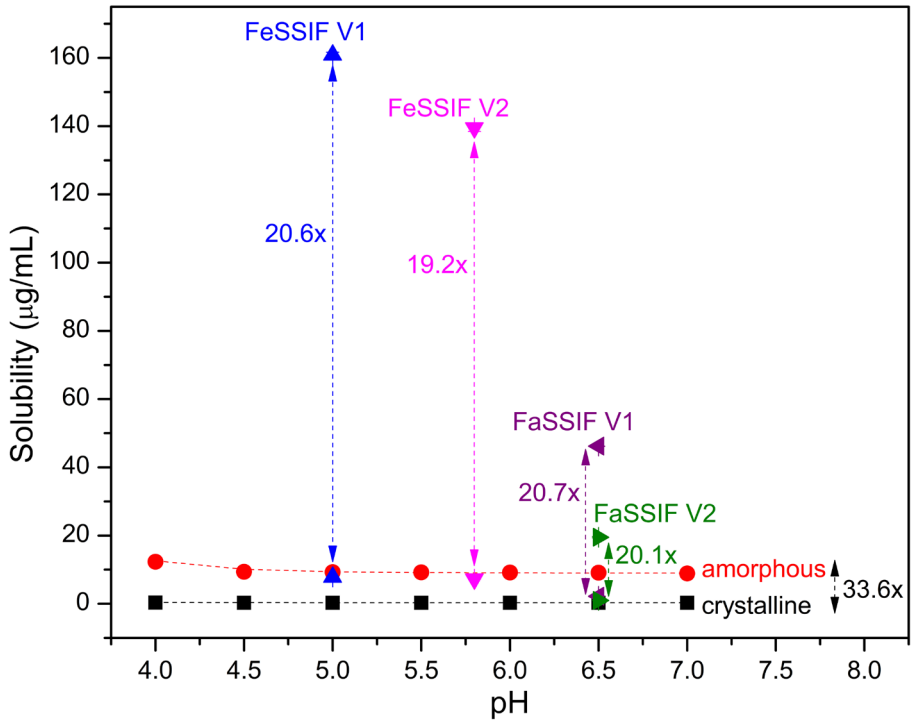


Figure 1. Solubility of crystalline and amorphous forms for posaconazole in media at different pHs, including biorelevant media. For each biorelevant medium (fasted or fed state simulated intestinal fluid), the lower and higher data points represent the crystalline and amorphous solubility, respectively.

In addition, during FY 2022 the research outcomes of a collaborative project between FDA and the University of Washington on whether BCS classes may be correlated with food effect (FE) and pH-dependent drug-drug interactions (DDIs) was published in the scientific literature, in an article titled "Exploring the Relationship of Drug BCS Classification, Food Effect, and Gastric pH-Dependent Drug Interactions". Specifically, trends in FE data were investigated for 170 drugs with clinical FE studies from the literature and new drugs approved from 2013 to 2019 by U.S. FDA. The research identified that drugs with significantly increased exposure FE (AUC ratio ≥2.0; N=14) were BCS Class II or IV, while drugs with significantly decreased exposure FE (AUC ratio ≤0.5; N=2) were BCS Class I/III or III (See **Figure 2**)[2]. This research outcome helps establish an important body of evidence that characterizes the influence of food on drug exposure as a function of the solubility classification of the drug, for drugs belonging to different BCS classes.

[2] Owens K, Argon S, Yu J, Yang X, Wu F, Lee S, Sun W, Ramamoorthy A, Zhang L, and Ragueneau-Majlessi I. *Exploring the Relationship of Drug BCS Classification, Food Effect, and Gastric pH-Dependent Drug Interactions.* The AAPS Journal. (2021) 24(1): 16. https://doi.org/10.1208/s12248-021-00667-w. PMID: 34961909.

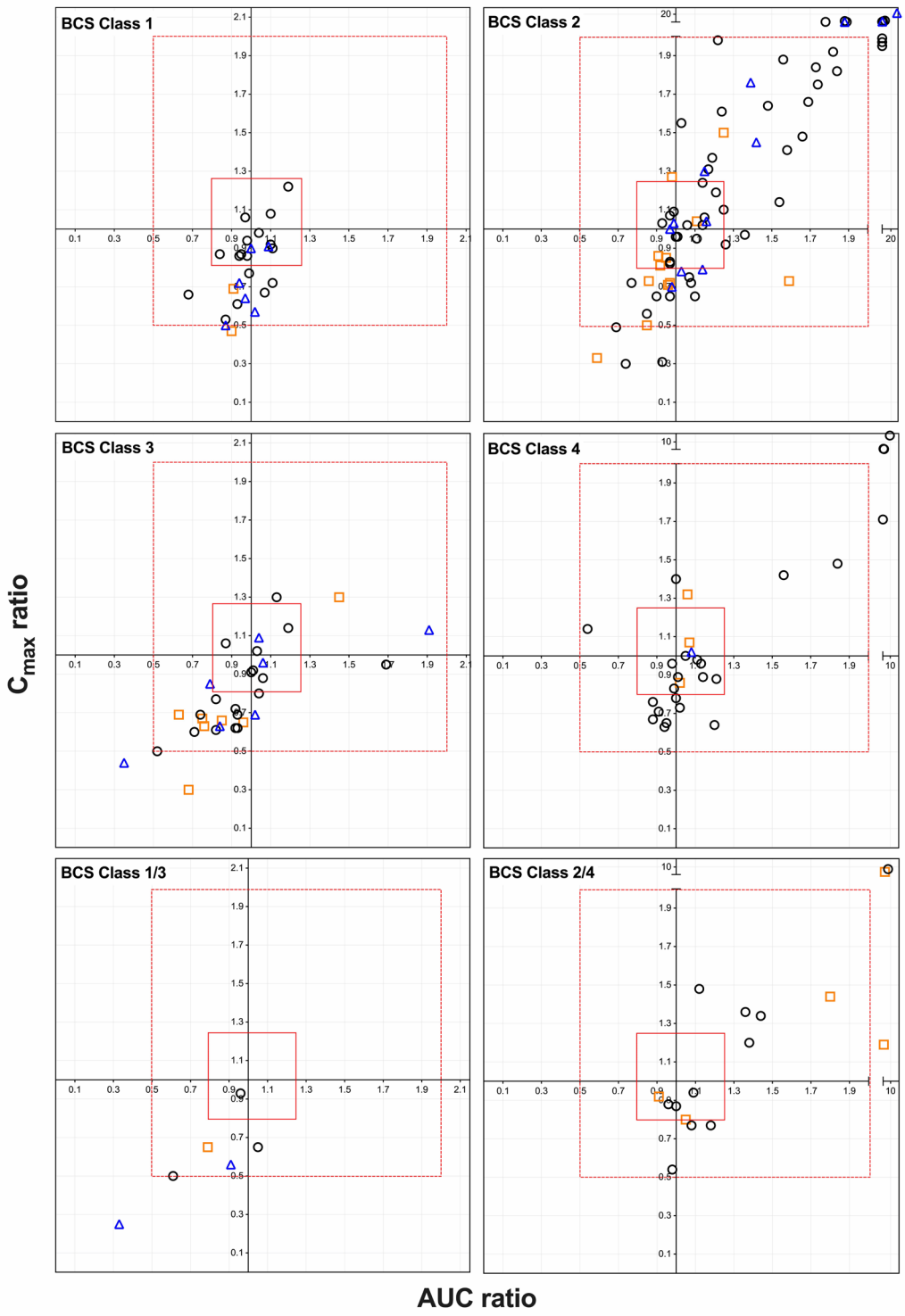


Figure 2. AUC and Cmax ratios for all drugs with FE studies, by BCS class: △ zwitterionic or neutral; ○ weak base; □ weak acid; — AUC and Cmax ratios within 0.8–1.25; — AUC and C_{max} ratios within 0.5–2.0. AUC and C_{max} ratios were retrieved from University of Washington (UW) Drug Interaction Database (DIDB) (https://www.druginteractionsolutions.org/)

New Grants and Contracts

- Grant (1U01FD007660) *Development of PBBM Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients* with Nikoletta Fotaki at the University of Bath.
- Grant (1U01FD007662) *Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract* with Rodrigo Cristofoletti at the University of Florida.
- Contract (75F40122C00139) *Model-Integrated Strategies for Bioequivalence Evaluation of Drugs with High Variability and/or Long Half-Life* with Mats Karlsson at Uppsala University.

Continuing Grants and Contracts

- Grant (3U01FD005978-04S3) *The Effect of Excipients on the Oral Absorption of Fexofenadine in Humans* with Kathleen Giacomini at the University of California, San Francisco.
- Grant (1U01FD007352) *Development and Validation of a Best Practices Framework for PBPK Analysis for Biopharmaceutic Applications in Support of Model-informed Biowaivers of Fed State BE Studies for BCS Class II Drugs* with Rodrigo Cristofoletti at 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 (75F40121C00132) *Applying a Robotic Soft Esophagus (Rose) to Assess the Swallowability of Opioid Drugs* with Peter Xu at the University of Auckland.
- Contract (75F40120C00150) *Robust in vitro/in silico Model to Accelerate Generic Drug Product Development for the Oral Cavity Route of Administration* with Giovanni Pauletti at University of Health Sciences and Pharmacy in St. Louis.
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive in Vitro Dissolution-Models* with Duxin Sun, Amit Pai Manjunath at the University of Michigan, College of Pharmacy.

Active FDA Research

- *Analysis of the Predictability of Bioequivalence in the Fed State*
- *Baseline Correction in Bioequivalence Studies for Drug Products Containing an Endogenous Compound*
- *Best Practice for Using Physiologically Based Pharmacokinetic (PBPK) Modeling for Orally Absorbed Generic Drug Products*
- *Develop a ML Model to Aid in Qualification of Formulation Differences across Strengths for Modified Release (MR) Drug Products*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *Evaluation of Formulation Dependence of Drug-Drug Interaction with Proton Pump Inhibitors (PPIs) for Oral Extended-Release Drug Products*
- *Evaluation of the Need for Sprinkle BE Studies*
- *Identification of Critical Factors for Oral Solution Bioequivalence*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *Prioritization and Optimization of Modified Release BE Guidances*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based Supports for Bioequivalence Assessment During the COVID-19 Public Health Emergency*

Product-Specific Guidances

There were 10 new and 27 revised PSGs published in FY 2022 that were supported by *Oral Absorption and BE* models/analyses. All of these PSGs, listed below, were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- Revised *Draft Guidance for Alprazolam Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Amoxicillin; Clavulanate Potassium Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Aripiprazole Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Carbidopa; Levodopa Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Cetirizine Hydrochloride Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Cetirizine Hydrochloride Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Cobicistat; Darunavir; Emtricitabine; Tenofovir Alafenamide Fumarate Tablet.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Colesevelam Hydrochloride Bar, Chewable.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Desloratadine Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Donepezil Hydrochloride Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Doxycycline Hyclate System, Extended Release.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Estradiol Gel.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Estradiol Gel, Metered.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Estradiol Spray.* (Feb. 2022) Link to Posting
- *Revised Draft Guidance for Ethinyl Estradiol; Norethindrone Acetate Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Ethinyl Estradiol; Norethindrone Tablet, Chewable.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Famotidine Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Lamotrigine Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Lansoprazole Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting

- *Revised Draft Guidance for Lanthanum carbonate Tablet, Chewable.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Loperamide Hydrochloride; Simethicone Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Loratadine Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Loratadine Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Methylphenidate Hydrochloride Tablet, Chewable.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Methylphenidate Tablet, Orally Disintegrating, Extended Release.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Metoclopramide Hydrochloride Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Mirtazapine Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Olanzapine Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Ondansetron Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Oseltamivir Phosphate Capsule.* (May 2022) Link to Posting
- *New Draft Guidance for Palbociclib Tablet.* (May 2022) Link to Posting
- *New Draft Guidance for Progesterone System.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Riluzole Suspension.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Risperidone Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Rizatriptan Benzoate Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting
- *Revised Draft Guidance for Solifenacin Succinate Tablet.* (May 2022) Link to Posting
- *Revised Draft Guidance for Zolmitriptan Tablet, Orally Disintegrating.* (Nov. 2021) Link to Posting

Articles

- Chen K. *2D NMR Peak Profiling to Compare Chemical Differences between Batches of Pentosan Polysulfate Sodium.* Journal of Pharmaceutical and Biomedical Analysis. (2022) 211: 114589. https://doi.org/10.1016/j.jpba.2022.114589. PMID: 35038672.

- Gong Y, Feng K, Zhang P, Lee J, Pan Y, Zhang Z, Ni Z, Bai T, Yoon M, Li B, Kim C, Fang L, and Zhao L. *Quantitative Methods and Modeling to Assess COVID-19-Interrupted In Vivo Pharmacokinetic Bioequivalence Studies with Two Reference Batches.* CPT Pharmacometrics & Systems Pharmacology. (2022) 11(7): 833-842. https://doi.org/10.1002/psp4.12795. PMID: 35411692.

- Lex T, Rodriguez J, Zhang L, Jiang W, and Gao Z. *Development of In Vitro Dissolution Testing Methods to Simulate Fed Conditions for Immediate Release Solid Oral Dosage Forms.* The AAPS Journal. (2022) 24: 40. https://doi.org/10.1208/s12248-022-00690-5. PMID: 35277760

- Martinez M, Sinko B, Wu F, Flanagan T, Borbas E, Tsakalozou E, and Giacomini K. *A Critical Overview of the Biological Effects of Excipients (Part I): Impact on Gastrointestinal Absorption.* American Association of Pharmaceutical Scientists. (2022) 24(3): 60. https://doi.org/10.1208/s12248-022-00711-3. PMID: 35501614.

- Martinez M, Wu F, Sinko B, Brayden D, Grass M, Kesisoglou F, Stewart A, and Sugano K. *A Critical Overview of the Biological Effects of Excipients (Part II): Scientific Considerations and Tools for Product Development.* The AAPS Journal. (2022) 24(3): 61. https://doi.org/10.1208/s12248-022-00713-1. PMID: 35501528.

- Miao L, Wu F, Yang X, Mousa Y, Ramamoorthy A, Lee S, Raines K, Zhang L, and Seo P. *Application of Solubility and Dissolution Profile Comparison for Prediction of Gastric pH-Mediated Drug-Drug Interactions.* The AAPS Journal. (2022) 24(1): 35. https://doi.org/10.1208/s12248-022-00684-3. PMID: 35165814.

- Owens K, Argon S, Yu J, Yang X, Wu F, Lee S, Sun W, Ramamoorthy A, Zhang L, and Ragueneau-Majlessi I. *Exploring the Relationship of Drug BCS Classification, Food Effect, and Gastric pH-Dependent Drug Interactions.* The AAPS Journal. (2021) 24(1): 16. https://doi.org/10.1208/s12248-021-00667-w. PMID: 34961909.

- Peck C, Campbell G, Yoo I, Feng K, Hu M, and Zhao L. *Comparing a Bayesian Approach (BEST) with the Two One Sided Tests (TOST) for Bioequivalence Studies.* The AAPS Journal. (2022) 24(5): 97. https://doi.org/10.1208/s12248-022-00746-6. PMID: 36050426.

- Van Duong T, Ni Z, and Taylor L. *Phase Behavior and Crystallization Kinetics of a Poorly Water-Soluble Weakly Basic Drug as a Function of Supersaturation and Media Composition.* Molecular Pharmaceutics. (2022) 19(4): 1146-1159. https://doi.org/10.1021/acs.molpharmaceut.1c00927. PMID: 35319221.

- Zhang L, Liu Q, Huang S, and Lionberger R. *Transporters in Regulatory Science: Notable Contributions from Dr. Giacomini in the Past Two Decades.* Drug Metabolism and Disposition. (2022) 50: 1211-1217. https://doi.org/10.1124/dmd.121.000706. PMID: 35768075.

Posters

- Cheng Y, Wu F, Yoon M, Fang L, and Zhao L. *Utilizing Physiologically Based Pharmacokinetic Modeling and Virtual Simulation to Evaluate the Sensitivity of Using Parent vs Metabolite as Analytes on Bioequivalence Assessment for Simvastatin.* Poster Presentation at the 2022 American College of Clinical Pharmacology (ACCP) Annual Meeting. North Bethesda, Maryland, Sep. 25, 2022.

- Nguyen D, Shon J, Frost M, Kim M, and Natarajan K. *Identifying High Drug Load Solid Oral Products with Swallowing-Related Adverse Events for In Vitro Swallowability Testing.* Poster Presentation at the 2022 American College of Clinical Pharmacology (ACCP) Annual Meeting. North Bethesda, Maryland, Sep. 25, 2022.

- Abdallah I, Gabal Y, Boyce H, Zhu J, and Kim M. *A Retrospective Analysis of Pharmacokinetic Variability Between Fasting and Fasting-Sprinkle Bioequivalence Studies of Generic Modified-Release Drug Products: A Case Study on Esomeprazole Magnesium.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

- Lim H, Sun W, Kim M, and Lee S. *Baseline Correction in Bioequivalence Studies for Drug Products Containing an Endogenous Compound.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

- Xi X. *Evaluation of Glucose Administration Recommendation in Bioequivalence Studies to Support Generic Oral Antidiabetic Drug Development.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

- Wu K, Rana M, Tian L, Sun W, Xia L, Nwakama P, Kim M, Tampal N, Xu X, Boyce H, and Feng X. *In Vitro Evaluation of an Extended-Release Methylphenidate Hydrochloride Product Sprinkled on Food Vehicles.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 19, 2021.

- Jordan L, Zheng K, Feng X, Mahjabeen S, Sun W, Xia L, Lee S, Hwang S, Nwakama P, Kim M, Tampal N, Boyce H, and Tian L. *In Vitro Evaluation of a Morphine Sulfate Extended-Release Formulation Sprinkled on Soft Foods.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Kotsybar J, Hakeem S, Zhang L, and Jiang W. *Solid Oral Immediate-Release Drug Product Landscape and Bioequivalence Recommendations.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Lex T, Rodriguez J, Zhang L, Jiang W, and Gao Z. *Utilizing Viscous Media to Assess Food-Induced Viscosity Effects on Immediate Release Tablet Disintegration and Drug Dissolution.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 17, 2021.

- Selaya D, Hunt R, Ren P, Li D, Qu H, Yang W, Wang J, Chan T, Kim M, Faustino P, and Zhang Y. *Evaluation of the Dissolution Drug Release Profiles of Approved Generic Formulations in Multiple pH Media for Putative Biopharmaceutics Classification System Class III Drugs, Atenolol Tablets and Acyclovir Tablets.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

- Zheng K, Jordan L, Tian L, Hoover A, Mahjabeen S, Sun W, Xia L, Lee S, Hwang S, Nwakama P, Xi X, Kim M, Tampal N, Boyce H, and Feng X. *Stability of Pantoprazole Sodium Delayed Release Granules When Sprinkled on Soft Foods.* Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 17, 2021.

Presentations

- Gong Y. *Alternative Model-Based Data Analysis Approach to Demonstrate Bioequivalence.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.

- Sun W. *In Vitro Binding Studies for Bioequivalence Demonstration.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.

- Wu F. *Challenges and Opportunities when Using Oral PBPK to Support Risk Assessment and Biowaiver in Regulatory Submissions.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.

- Zhang Y. *Essential Elements of BCS III-Based Biowaiver Request.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Regulatory Best Practices for Global Access to Medicines Workshop. Virtual Meeting, Aug. 18, 2022.

- Donnelly M. *Regulatory Challenges with Pharmacokinetic (PK) Bioequivalence (BE) Studies for Drugs Containing Endogenous Compounds.* Presentation at the Scientists Advancing Affordable Medicines Workshop 2022. Virtual Meeting, Apr. 27, 2022.
- Zhang L. *Regulatory Research on the Effect of Excipients on Drug Absorption.* Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2021 Membrane Transporter Community Meeting. Virtual Meeting, Jan. 11, 2022.
- Wu F. *Bioequivalence Evaluation of Pediatric Products Using Physiologically Based Pharmacokinetic Modeling.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, PA, Oct. 18, 2021.
- Shakleya D. *Analytical Regulatory Considerations for Different Pharmaceutical Drug Matrices.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Virtual Meeting, Oct. 17, 2021.
- Wu F. *Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Philadelphia, Pennsylvania, Oct. 15, 2021.
- Bode C. *Impact of Excipients on Drug Permeation to Support Biowaivers for Non-Q1/Q2 Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches. Virtual Meeting, Oct. 1, 2021.
- Mousa Y. *Modeling for Success: A Case Example for Oseltamivir Phosphate.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches. Virtual Meeting, Oct. 1, 2021.
- Shoyaib Al A. *Development of PBPK Model for Predicting Food Impact on BE Assessment.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches. Virtual Meeting, Oct. 1, 2021.
- Wu F. *PBPK Absorption Modeling to Support Risk Assessment and Biowaiver for Generic Oral Products.* Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches. Virtual Meeting, Oct. 1, 2021.

PATIENT SUBSTITUTION OF GENERIC DRUGS

Summary of FY 2022 Activities

As part of Generic Drug User Fee Amendments (GDUFA) science and research program, FDA has advanced research to evaluate the substitutability of generic drug products for patients, including clinical studies evaluating generic substitution in patients or pharmacokinetic (PK) bioequivalence (BE) studies in healthy subjects, analyzing clinical databases on the utilization and substitution of generic drugs, and assessing patients' and health care providers' perceptions impacting generic substitution.

Since FY 2021, the substitutability among approved generic levothyroxine products has been evaluated in collaboration with the Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI) (grant# 1U01FD005938-A2). The study demonstrated that there were no clinically significant differences in serum thyrotropic concentration between patients taking different generic levothyroxine products, as summarized in the Research Highlight below.

A contract with BioPharma Services USA, Inc. (contract# HHSF223201610004I-75F40120F19005) was awarded to investigate the BE between a generic tacrolimus oral capsule product and its reference listed drug (Prograf®) in healthy subjects. FDA completed PK parameters and statistical analysis for the BE assessment. In collaboration with the Office of Testing and Research in the Office of Pharmaceutical Quality, in vitro studies were performed to evaluate the quality of that generic product and of Prograf®. The same manufacturing lots of drug products used in the BE study were tested in these in vitro studies.

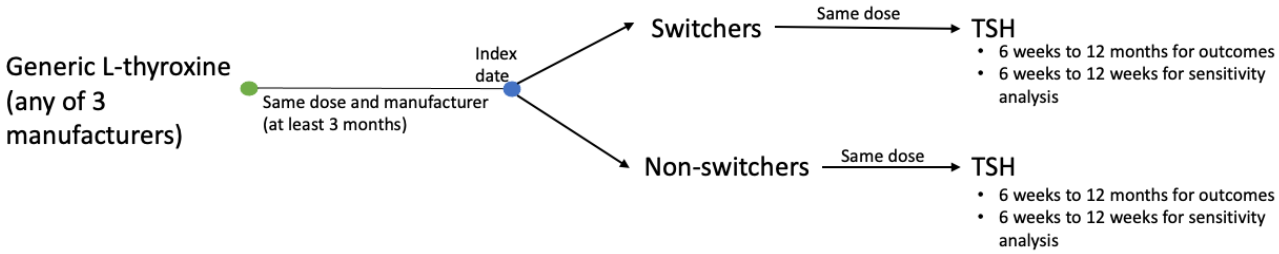
As a part of ongoing internal efforts to monitor post-market products, a cross-disciplinary research team has been actively engaged in assessing the substitutability of generic mixed amphetamine sulphate (MAS) products for the treatment of attention-deficit/hyperactivity disorder (ADHD). FDA had received reports suggesting a potentially inadequate therapeutic effect when switching from the reference listed drug to generic products, primarily in the adult ADHD population. Thus, during FY 2022, a dedicated research team at FDA worked to investigate this potential issue through an active research contract (75F40121P00621) with Avomeen, LLC to assess whether there may be differences among recently manufactured lots of any of these products, which may have the potential to impact their therapeutic effectiveness.

RESEARCH HIGHLIGHT

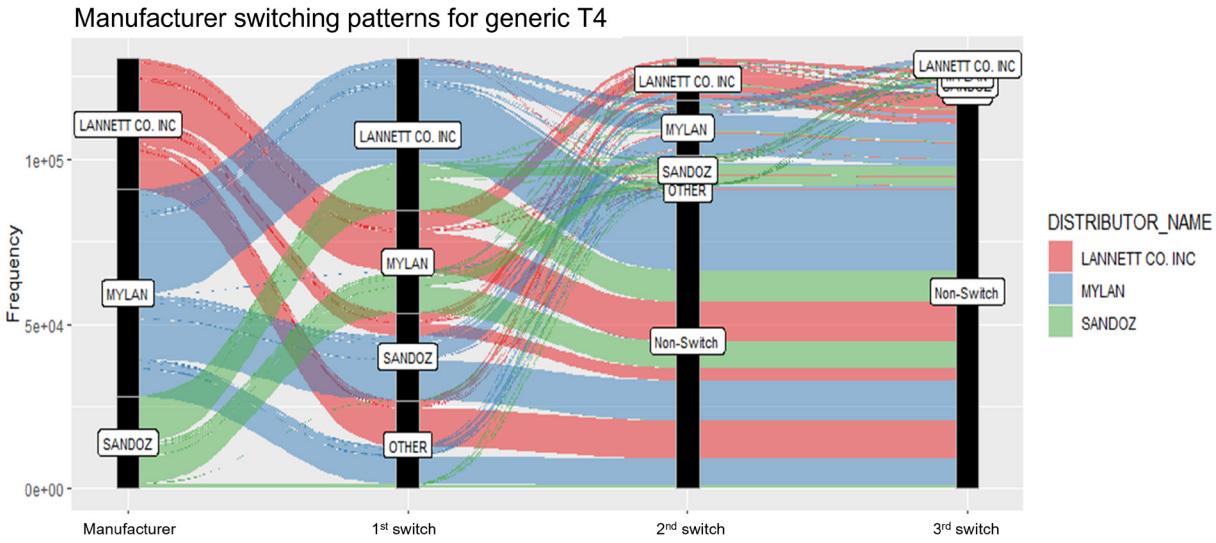
Based upon limited allegorical evidence, certain clinical practice guidelines recently recommended against switching among generic levothyroxine products due to the possibility that serum thyrotropin (TSH) concentrations may be affected by switching from one product to another[1]. To assess this potential issue, a retrospective comparative effectiveness study was conducted using information in the OptumLabs Data Warehouse (national administrative claims database) to compare TSH concentrations between patients who continued taking the same sourced generic levothyroxine product and those who switched. Outcomes included the proportion of patients with normal, abnormal, or markedly abnormal TSH concentrations, mean TSH concentration, and mean TSH concentration change from the baseline. Out of a total of 15,829 patients who filled generic levothyroxine products, 2,780 (17.6%) switched among generic levothyroxine products. Among 2,780 propensity-matched (1:1) patient pairs, the proportion of patients with a normal TSH concentration after the index date was 82.7% among non-switchers and 84.5% among switchers (risk difference: -0.018; 95% CI: -0.038 to 0.002; P=0.07). The proportion of patients with a markedly abnormal TSH concentration after the index date was 3.1% among non-switchers and 2.5% among switchers (risk difference: 0.007; 95% CI: -0.002 to 0.015; P=0.14). The mean (SD) TSH concentrations after the index date were 2.7 (2.3) mIU/L among non-switchers and 2.7 (3.3) mIU/L among switchers (P=0.94). These results suggest that switching among different generic levothyroxine products was not associated with clinically significant changes in TSH concentration, which does not support the aforementioned clinical practice guidelines.

[1] Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM, and American Thyroid Association Task Force on Thyroid Hormone Replacement. *Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement.* Thyroid. (2014) 24(12): 1670-1751. https://doi.org/10.1089/thy.2014.0028. PMID: 25266247.

A.



B.



C.

	Patients, No. (%)			
	Non-switchers (n=2780)	Switchers (n=2780)	Risk or mean difference (95% CI)	P value
TSH level				
Normal (0.3-4.4 mIU/L)	2298 (82.7)	2348 (84.5)	Risk difference: -0.018 (-0.038 to 0.002)	0.07
Abnormal (<0.3 or >4.4 mIU/L)	482 (17.3)	432 (15.5)	Risk difference: 0.018 (-0.002 to 0.038)	0.07
Markedly abnormal (<0.1 or >10 mIU/L)	87 (3.1)	69 (2.5)	Risk difference: 0.007 (-0.002 to 0.015)	0.14
Mean TSH level, (SD), mIU/L	2.7 (2.3)	2.7 (3.3)	Mean difference: 0.01 (-0.14 to 0.16)	0.94
Mean TSH level change from baseline, (SD), mIU/L	0.51 (2.28)	0.53 (3.25)	Mean difference: -0.02 (-0.16 to 0.13)	0.84
Abbreviation: TSH, thyrotropin				

Figure 1: (A) Study design. Adults aged 18 years or older were included if they filled a generic levothyroxine prescription between 01/01/2008 and 06/30/2019, and had a stable dose, the same manufacturer, and a normal TSH concentration (0.3-4.4 mIU/L) for at least 3 months before continuing to take the same product or switching among generic levothyroxine products (index date). (B) Alluvial plot of switching patterns for switchers who completed the first switch as shown in second column at 100% and followed for possible 2nd and 3rd switches. (C) Comparison of outcomes between switchers and non-switchers.

Continuing Grants and Contracts

- Grant (1U01FD005938-A10) *Use of Instrumental Variable Approaches to Assess the Safety and Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross, Nilay Shah at Yale-Mayo CERSI.
- Grant (1U01FD005938-A2) *Characterizing Use, Safety and Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross, Nilay Shah at Yale-Mayo CERSI.
- Contract (75F40121P00621) *In Vitro Assessment of Mixed Amphetamine Salt (MAS) Products* at Avomeen, LLC.

Completed Grants and Contracts

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

Active FDA Research

- *Bioequivalence of an Approved Tacrolimus Product*
- *COVID-19 Generic Drug Utilization*
- *Postmarketing Surveillance of Generic Drugs Using Sentinel*

Articles

- Brito J, Deng Y, Ross J, Choi N, Graham D, Qiang Y, Rantou E, Wang Z, Zhao L, Shah N, and Lipska K. *Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults.* JAMA Internal Medicine. (2022) 182(4): 418-425. https://doi.org/10.1001/jamainternmed.2022.0045. PMID: 35226058.

- Brito J, Wang Z, and Lipska K. *Considerations for Generic-to-Generic Levothyroxine Switching-Reply.* JAMA Internal Medicine. (2022) 182(8): 887. https://doi.org/10.1001/jamainternmed.2022.1990. PMID: 35666533.

- Mosley S, Kim S, Rouby N, Lingineni K, Vozmediano V, Gong Y, Chen Y, Estores D, Feng K, Kim H, Kinjo M, Langaee T, Li Z, Schmidt S, Johnson J, Frye R, Fang L, Zhao L, Binkley P, Schmidt S, and Cavallari L. *A Randomized, Cross-over Trial of Metoprolol Succinate Formulations to Evaluate PK and PD Endpoints for Therapeutic Equivalence.* Clinical and Transitional Science. (2022) 15(7): 1764-1775. https://doi.org/10.1111/cts.13294. PMID: 35488487.

- Wang Z, Ahluwalia S, Newman B, Dhapare S, Zhao L, and Luke M. *Medication Cost-Savings and Utilization of Generic Inhaled Corticosteroid (ICS) and Long-Acting Beta-Agonist (LABA) Drug Products in the USA.* Therapeutic Innovation & Regulatory Science. (2022) 56(2): 346-357. https://doi.org/10.1007/s43441-021-00372-y. PMID: 35118630.

ABUSE-DETERRENT OPIOID DRUG PRODUCTS

Summary of FY 2022 Activities

In FY 2022, research efforts for abuse-deterrent formulations (ADF) of opioid drug products focused on: 1) safety concerns associated with the non-intended use (abuse) of opioid products; 2) assessment of the abuse deterrent (AD) potential of ADFs when chewed; 3) assessment of the AD potential of ADFs when insufflated; 4) development of an anatomical in vitro nasal model to quantify regional deposition following insufflation of manipulated opioid ADFs; and (5) physiologically based pharmacokinetics (PBPK) modeling of manipulated ADFs after nasal insufflation (see **Research Highlight**).

The relationship between excipients, manufacturing manipulation methods, and toxicological outcomes associated with non-intended use of ADF opioids continued to be an active area of FDA research during FY 2022. These collaborative studies provided insights into the molecular size dependent acute toxicity of polyethylene oxide (PEO). In addition, two in vitro models were developed to evaluate the safety of PEO: a needle model and a microfluidic model.

Contract #HHSF223201610004I-75F40119F19004 investigated AD performance against chewing of hydrocodone bitartrate extended-release (ER) tablets. The effect of chewing time (2, 7, and 10 min) of Hysingla® (New Drug Application [NDA] 206627; hydrocodone bitartrate extended release tablet) on pharmacokinetics (PK) parameters was evaluated. These research outcomes will help establish critical study design parameters for PK studies in which the product is chewed before swallowing and evaluate if an in vitro chewing method can predict the in vivo impact of chewing on this opioid drug product.

Contract #75F40121C00178 developed and utilized a new chewing robot to evaluate the inter- and intra-subject variability of human chewing, determine the critical human chewing variables that impact the extent of drug release from a chewed pharmaceutical dosage form, and predict the extent of drug release in vivo for different types of AD products when chewed. The data obtained is expected to support further development of in vitro approaches to assess the non-inferiority (at deterring abuse) of generic ADF opioid products relative to reference standard opioid products.

Contract #HHSF223201610004I-HHSF22301002T investigated the PK and pharmacodynamics of oxycodone hydrochloride (HCl), naloxone HCl (ER tablets) following nasal insufflation of tablets milled to different particle size ranges. The results will be used to verify an in silico model developed by FDA to predict in vivo AD behavior.

An anatomical in vitro nasal model was created to quantify the regional deposition of insufflated sumatriptan succinate powders. Initial results for the regional deposition of sumatriptan succinate matched available in vivo gamma scintigraphy data. A PBPK model was developed to predict the absorption of crushed naloxone HCl tablets administered intranasally. Model predictions demonstrated that the PK response of naloxone is dependent on the particle size distribution (PSD). This model will be used to understand the performance of naloxone HCl nasal spray and to support a hybrid combined computational fluid dynamics and PBPK model for an ADF product containing both, an opioid agonist and an antagonist.

As part of an internal FDA research project titled "Physiologically-based pharmacokinetic (PBPK) modeling of crushed Embeda® (NDA 022321, morphine sulfate/naltrexone HCl ER capsules) capsules for nasal insufflation," PBPK models were developed to predict the absorption of crushed morphine sulfate and naltrexone HCl ER microspheres administered intranasally. The drugs were modeled using the pulmonary compartmental absorption and transit (PCAT) module in GastroPlus™ (Simulations Plus, Inc., Lancaster, CA, USA). Morphine sulfate was modeled using a 30 mg dose and naltrexone HCl was modeled using a 1.2 mg dose. Both drugs were administered as an intranasal dose with a mean particle size of 50 μm for a fine powder. The results of the individual PBPK models were validated against morphine and naltrexone concentration data from a nasal insufflation clinical study of a crushed morphine sulfate and naltrexone HCl ER capsule published in the literature. The models were then used to investigate the effect of PSD ranges between 100 and 500 μm on PK parameters. The model predicted that the PK response of morphine, but not naltrexone, was dependent on PSD when particles were in a range between 100 and 500 µm. The nasal absorption of both drugs with varying PSDs of 100-500 µm was compared in **Figure 1**. It was found that 0.51 mg (42.5%) of the naltrexone dose and 0.39 mg (1.3%) of the morphine dose were absorbed through the nasal mucosa. The remaining drug substance is expected to be absorbed via the oral route through deposition of particles in the stomach by nasal mucociliary clearance. These results elucidated how PSDs below 500 µm affect the intranasal absorption of morphine and naltrexone.

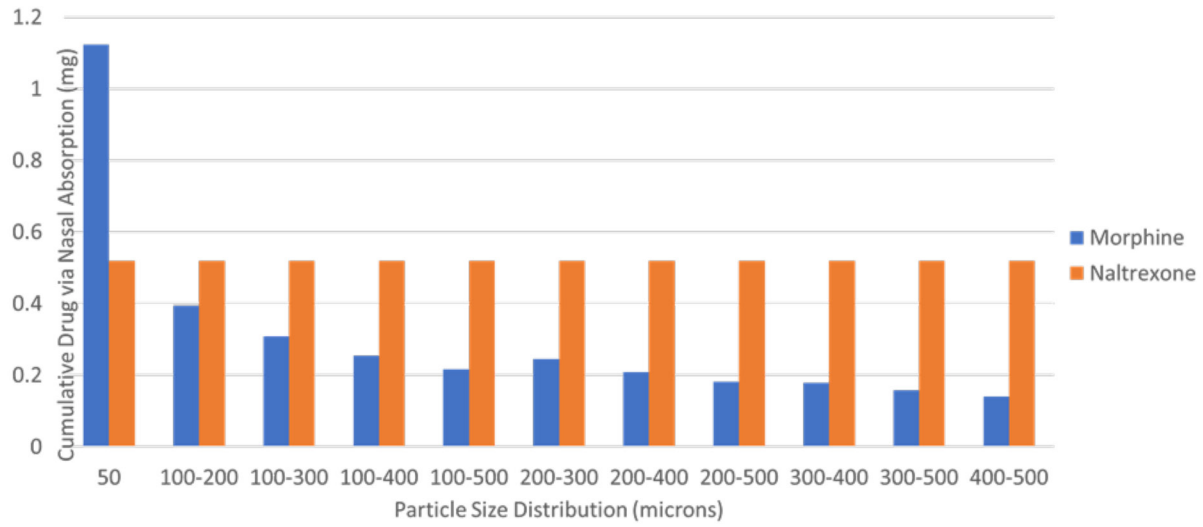


Figure 1. Plot of predicted nasal absorption versus input particle size distribution for a 30 mg morphine and 1.2 mg naltrexone powder prepared for nasal administration.

Continuing Grants and Contracts

- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic (PK) /Pharmacodynamic (PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Artan Markollari at Biopharma.
- Contract (HHSF223201610004I-75F40119F19004) *Pharmacokinetic (PK) Study of Opioid Drug Products Following Oral Ingestion of Chewed Products* with Artan Markollari at Biopharma.

Completed Grants and Contracts

- Grant (3U01FD004275-07S1) *Formulation of Hydrocodone Bitartrate Opioid Tablet* with National Institute for Pharmaceutical Technology & Education (NIPTE).
- Contract (75F40119C10112) *Assessment of Smoking and Vaping Risk of Opioids and Commercial Products, and Standardization of Methods to Assess these Properties* with National Institute for Pharmaceutical Technology & Education (NIPTE).

Active FDA Research

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

Posters

- Qu H, Smith W, Feng X, Wang J, Xu X, and Faustino P. *Challenges and Opportunities of using Asymmetrical Flow Field Flow Fractionation for the Characterization of High Molecular Mass Polyethylene Oxide in Abuse-Deterrent Formulation.* Poster Presentation at the 22nd International Symposium on Field- and Flow-Based Separations. Riverside, California, Sep. 11, 2022.
- Kim D, Herbertson L, Natu R, Malinauskas R, Baek J, Buehler P, Pinto J, Feng X, Qu H, and Xu X. *Effect of High Molecular Weight Polyethylene Oxide on Thrombosis Under High Shear Blood Flow Conditions.* Poster Presentation at the International Society on Thrombosis and Haemostasis (ISTH) 2022. Virtual Meeting, Jul. 09, 2022.
- Gabal Y, Boyce H, Sun W, Al Ghabeish M, Ibrahim A, Hollenbeck G, Hoag S, Mostofa A, and Kim M. *Preparation and Characterization of Physically Manipulated Abuse-Deterrent Formulation of an Opioid Product Prepared for Nasal Insufflation Studies.* Poster Presentation at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.

Presentations

- Qu H. *Challenges and Opportunities of using AF4 for Characterizing High Molecular Mass PEO in Abuse-Deterrent Formulations.* Presentation at the 22nd International Symposium on Field- and Flow-Based Separations. Riverside, California, Sep. 12, 2022.

DATA ANALYTICS

Summary of FY 2022 Activities

Artificial intelligence (AI), including machine learning, natural language processing (NLP), etc., has been used to develop automation tools and promote business intelligence and efficiency at FDA. For example, a user-friendly automation tool was recently developed to assist bioequivalence (BE) assessments, named 'BE Assessment Mate' (BEAM). In FY 2022, the BEAM tool was substantially improved by connecting it with other components of FDA's information technology infrastructure, thereby facilitating efficient and high-quality BE assessments by streamlining labor-intensive work during the BE assessment process. As another example, during FY 2022 ongoing work under contract (#75F40119C10106) further developed data analytics tools to expedite the development of product-specific guidances (PSGs); specifically, an NLP pipeline was developed to automatically retrieve supportive information from drug labeling to optimize the efficiency of PSG development. Current research efforts are focused on improving the performance of the established pipeline and developing additional functionalities to retrieve information from internal review documents.

Notably, during FY 2022, a heterogeneous treatment effect (HTE) method based on a machine learning methodology was developed to differentiate sub-groups with different treatment effects from among the whole population (see **Research Highlight**). The developed HTE method represents a promising AI tool to provide business intelligence and promote operational efficiency within FDA. For example, by considering the availability of a PSG to be a 'treatment' and considering the subsequent submission of Abbreviated New Drug Applications (ANDAs) for that specific product as potential outcomes of that treatment, this AI tool could provide insights about the impact of new or revised PSGs that could help prioritize FDA's development of PSGs.

Similarly, ongoing work during FY 2022 under grant #U01FD007355, *Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis*, developed a python package "pyDarwin" (version 1.0) as a machine learning solution for NONMEM model selection that is conveniently supported on Windows, Linux, and Sun Grid engines. This python package has been released to the public (https://github.com/certara/pyDarwin) and should maximize the value of models used to support drug development decision-making and accelerate the timeline for developing population pharmacokinetic (PK) models for generic drug development.

During FY 2022, data analytics tools also supported regulatory assessments and helped to address questions regarding bioassays, in vitro release testing (IVRT), active pharmaceutical ingredient (API) sameness, particle size distribution, sample size estimation, data imputation, etc. For example, an analysis of real-world evidence was performed using the IQVIA data system to evaluate the cost savings associated with the availability of generic inhaled corticosteroid (ICS) and long acting β agonist (LABA) combination products. The results showed that more than 20% of prescription drug cost savings was achieved for the ICS/LABA dry powder inhalers in the first year following the introduction of the first approved generic[1].

[1] Wang Z, Ahluwalia S, Newman B, Dhapare S, Zhao L, and Luke M. *Medication Cost-Savings and Utilization of Generic Inhaled Corticosteroid (ICS) and Long-Acting Beta-Agonist (LABA) Drug Products in the USA.* Therapeutic Innovation & Regulatory Science. (2022) 56(2): 346-357. https://doi.org/10.1007/s43441-021-00372-y. PMID: 35118630.

An HTE analysis focuses on examining varying treatment effects for individuals or subgroups in a population (**Figure 1**). The treatment effect information obtained by an HTE analysis can substantially improve a trial study design during the drug development process and can potentially guide personalized medicine. In addition, with a well-defined treatment and outcome, an HTE analysis can also be a powerful tool for enhancing business intelligence and efficiency within the FDA. For example, if the publication of a PSG release is considered treatment, the FDA can quantitatively evaluate its impact on the timing and the number of ANDA submissions by an HTE analysis. The utilization of HTE analyses in this manner has not been widely recognized or adopted, even despite the explosive increase in the availability of data, attributed to the arrival of the 'Big Data' era. A part of the reason for its underuse is likely that data are often of high dimension and high complexity, which pose substantial challenges for applying conventional HTE analysis methods (e.g., a two-step method). To overcome such challenges, a newly developed causal forest HTE method has been derived from the random forest ML algorithm. In this work, scenarios with different levels of complexity in terms of HTE were simulated to fully characterize the capabilities of the causal forest method and the conventional two-step method, in identifying effect heterogeneity. The simulation approach was used because it allows the explicit specification of HTE and maintains ground truth information for a model performance check. The results showed that the causal forest method outperforms the conventional HTE method in assessing treatment effect, especially when data are complex (e.g., nonlinear) and high dimensional (**Figure 2**). Given its resilience in handling complex data (e.g., nonlinear and/or high-dimensional data), the causal forest HTE method, an ML approach derived from a random forest algorithm, provides a unique opportunity for scientists to assess and predict heterogeneity for treatment effect for real-world applications.

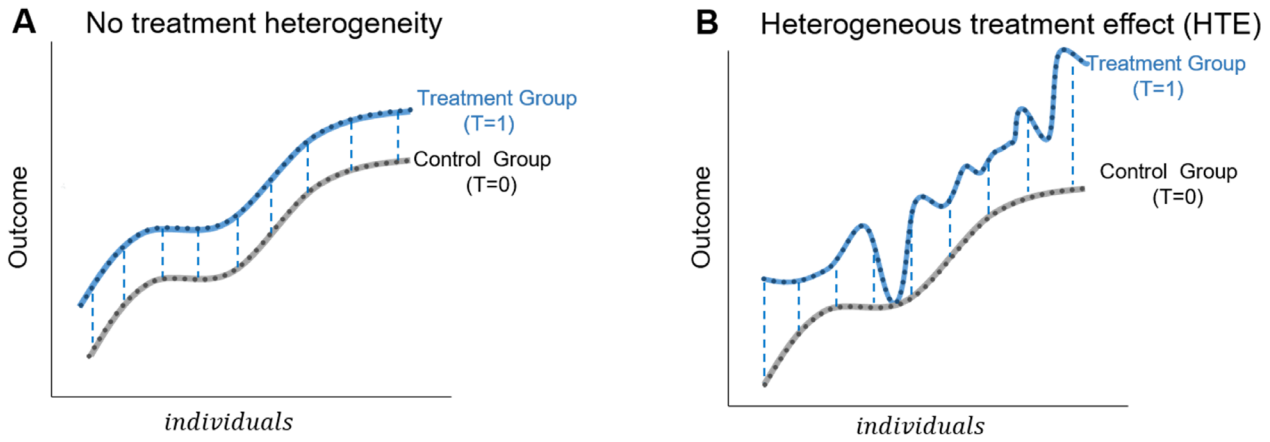


Figure 1. (A) Homogenous treatment effect (no treatment heterogeneity): the outcome of the treatment shows variation across the individuals and between treatment groups, but the treatment effect (i.e., the difference of the outcomes depicted by the dotted lines between the two treatment outcome curves) is the same for every individual. (B) Heterogeneous treatment effect (HTE): treatment effect varies among individuals. Some individuals benefit more, some less, and some might not benefit at all from the treatment.

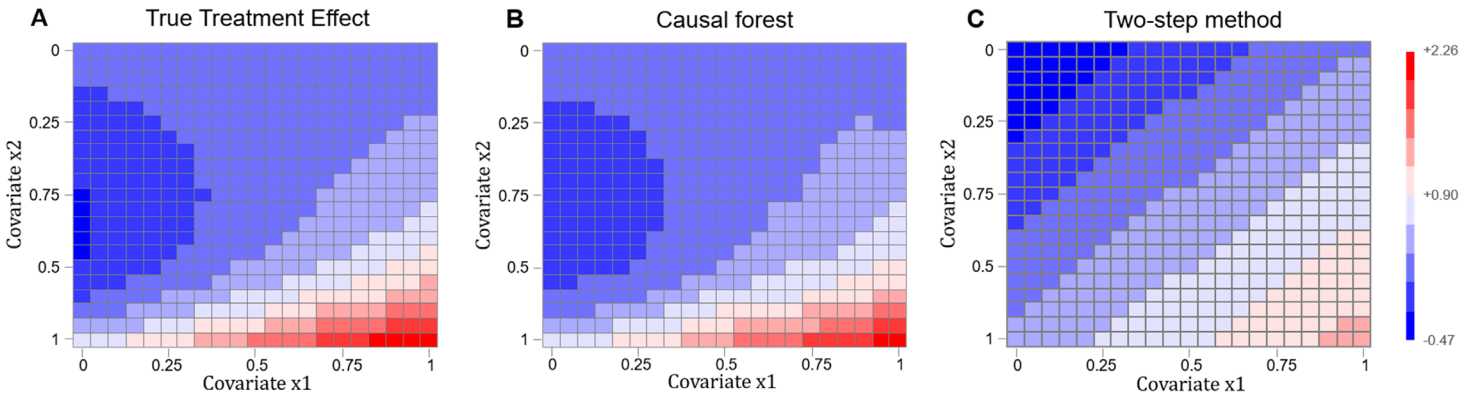


Figure 2. Treatment effect in a data set where the relationship between the two covariates (e.g., x1, x2) and treatment effect is nonlinear. (A): the "true" treatment effect with varying values of x1 and x2; (B): the predicted treatment effect using a causal forest method; (C): the predicted treatment effect using the conventional two-step method. The treatment effect is denoted by color from blue (low) to red (high).

New Grants and Contracts

- Contract (75F40122C00121) *Machine-Learning based Heterogeneous Treatment Effect Models for Informing Product-Specific Guidance Development* with Dr. Hualou Liang at Drexel University.

Continuing Grants and Contracts

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

Active FDA Research

- *Develop a ML Model to Aid in Qualification of Formulation Differences across Strengths for Modified Release (MR)* Drug Products
- *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency*
- *Development and Analysis of a Complex Product Database*
- *Development of PK Data Warehouse for BE Analysis*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Machine Learning for Generic Drug Analysis*
- *Postmarketing Surveillance of Generic Drugs Using Sentinel*

Articles

- Brito J, Deng Y, Ross J, Choi N, Graham D, Qiang Y, Rantou E, Wang Z, Zhao L, Shah N, and Lipska K. *Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults.* JAMA Internal Medicine. (2022) 182(4): 418-425. https://doi.org/10.1001/jamainternmed.2022.0045. PMID: 35226058.

- Brito J, Wang Z, and Lipska K. *Considerations for Generic-to-Generic Levothyroxine Switching-Reply.* JAMA Internal Medicine. (2022) 182(8): 887. https://doi.org/10.1001/jamainternmed.2022.1990. PMID: 35666533.

- Gong X, Hu M, Basu M, and Zhao L. *Heterogeneous Treatment Effect Analysis Based on Machine-Learning Methodology.* CPT: Pharmacometrics & Systems Pharmacology. (2021) 10(11): 1433-1443. https://doi.org/10.1002/psp4.12715. PMID: 34716669.

- Gong X, Hu M, Liu J, Kim G, Xu J, McKee A, Palmby T, Claro R, and Zhao L. *Decoding Kinase-Adverse Event Associations for Small Molecule Kinase Inhibitors.* Nature Communications. (2022) 13(1): 4349. https://doi.org/10.1038/s41467-022-32033-5. PMID: 35896580.

- Shi Y, ValizadehAslani T, Wang J, Ren P, Zhang Y, Hu M, Zhao L, and Liang H. *Improving Imbalanced Learning by Pre-finetuning with Data Augment.* Proceedings of the Fourth International Workshop on Learning with Imbalanced Domains: Theory and Applications. (2022). PMLR 183:68-82.

- Shi Y, Wang J, Ren P, ValizadehAslani T, Zhang Y, Hu M, and Liang H. *Fine-Tuning BERT for Automatic ADME Semantic Labeling in FDA Drug Labeling to Enhance Product-Specific Guidance Assessment.* (2022) *arXiv:2207.12376* https:/doi.org/10.48550/arXiv.2207.12376.

- Wang Z, Ahluwalia S, Newman B, Dhapare S, Zhao L, and Luke M. *Medication Cost-Savings and Utilization of Generic Inhaled Corticosteroid (ICS) and Long-Acting Beta-Agonist (LABA) Drug Products in the USA.* Therapeutic Innovation & Regulatory Science. (2022) 56(2): 346-357. https://doi.org/10.1007/s43441-021-00372-y. PMID: 35118630.

- Wang J, Gong X, Hu M, and Zhao L. *Improved GSimp: A Flexible Missing Value Imputation Method to Support Regulatory Bioequivalence Assessment.* Annals of Biomedical Engineering. (2022). Online Ahead of Print. https://doi.org/10.1007/s10439-022-03070-4. PMID: 36107365.

Posters

- Sale M, Ismail M, Wang F, Feng K, Hu M, Zhao L, and Bies R. *Comparison of Robustness and Efficiency of Four Machine Learning Algorithms for Identification of Optimal Population Pharmacokinetic Models.* Poster Presentation at the Population Approach Group Europe (PAGE) 2022 Annual Meeting. Ljubljana, Slovenia, Jun. 28, 2022.
- Wang J, Gong X, Zhao L, and Hu M. *Improved GSimp - a Flexible Missing Value Imputation Method to Support Generic Drug Development and Regulatory Assessment.* Poster Presentation at American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2022 Annual Meeting. Virtual Meeting, Mar. 16, 2022.
- Wang J, Gong X, Zhao L, and Hu M. *Improved GSimp - a Flexible Missing Value Imputation Method to Support Generic Drug Development and Regulatory Assessment.* Poster Presentation at the American Conference on Pharmacometrics (ACoP) 12 Conference. Virtual Meeting, Nov. 08, 2021.

Presentations

- Wang J. *Advance in Data Imputation Approach to Support BE Assessment.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 21, 2022.
- Hu M. *Leveraging Artificial Intelligence (AI) and Machine Learning (ML) to Support Generic Drug Development and Regulatory Efficiency.* Presentation at the International Consortium for Innovation and Quality in Pharmaceutical Development - Workshop 2022. Virtual Meeting, Sep. 15, 2022.
- Hu M. *Leveraging Artificial Intelligence (AI) and Machine Learning (ML) to Support Regulatory Efficiency – Current Progress.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 09, 2022.

DRUG-DEVICE COMBINATION PRODUCTS

Summary of FY 2022 Activities

The development of complex generic drug-device combination products (DDCPs) involves unique challenges across a variety of drug and device constituent parts, indications, and user populations. FDA's key research priority initiatives for FY 2022[1] included a focus on patient perceptions, user interface (UI) considerations, and development of in vitro techniques to assist in the development and evaluation of complex DDCPs. Research conducted both, in FDA laboratories and with external collaborators supported these research initiatives.

To enhance FDA's understanding of patient and caregiver perspectives on generic substitution and differences between the UIs of generic DDCPs as compared to their reference listed drugs, contracts #HHSF223201710072C and #HHSF223201810113C (awarded in FY 2018 and FY 2019, respectively) continued their progress in FY 2022. Contract #HHSF223201710072C, with the Imperial College of Science Technology & Medicine (London, UK), aimed to develop a standardized questionnaire that can provide a quantitative evaluation of a patient's perception of airflow resistance from a dry powder inhaler (DPI) device. In FY 2022, an airflow resistance assessment across multiple DPI products was completed to categorize resistance levels for use in an engineered inhaler resistance simulator. This inhaler resistance simulator will assist in establishing the relationship between questionnaire responses on airflow resistance with airflow measurements at different resistance categories. Outcomes from several focus groups and cognitive interview sessions with asthma and chronic obstructive pulmonary disease (COPD) patients guided the identification and development of the themes and language that will be used in the finalized airflow resistance questionnaire.

[1] U.S. Food and Drug Administration (FDA). GDUFA Regulatory Science Priority Initiatives for Fiscal Year 2021, Link: https://www.fda.gov/media/154487/download.

Contract #HHSF223201810113C, with the Research Triangle Institute (RTI) International (NC, US), focused on examining patient and caregiver attitudes toward complex generic DDCP substitution, and on building evidence to inform regulatory policy. During FY 2022, FDA and RTI published a manuscript documenting the results from focus groups conducted with DPI users. Overall, positive feelings about financial savings were mixed with some anticipatory anxiety about understanding how to use the new DPI device, and about whether the generic DPI would perform as well as the brand name product. Additionally, research with autoinjector user focus groups was completed virtually. Currently, RTI and FDA are reviewing data from prior in-person testing and the virtual autoinjector focus groups, which will be submitted for publication in FY 2023. The outcomes of these two contracts are expected to provide valuable insights about patient and caregiver experiences with complex generic DDCP substitution and use.

FDA had awarded grants #1U01FD007359 and #1U01FD007360 in late FY 2021 to develop new methodologies and techniques to assess UI design differences, and this work continued throughout FY 2022. Grant #1U01FD007359 with Battelle Memorial Institute completed an initial literature review, identified current research gaps for generic UI assessment, and initiated the first assessment of injectable devices utilizing their new proposed methodologies. Research staff for grant #1U01FD007360 with the University of Detroit, Mercy developed a summary of key stakeholder perspectives on existing strategies in assessing UIs of generic DDCPs, and are currently developing a visual taxonomy to systematically analyze and categorize UI differences. The outcomes of these two grants are expected to advance FDA's understanding of critical UI design differences that may impact the substitutability of a generic DDCP for its brand name product.

To understand device performance and applicable in vitro bioequivalence (BE) testing for complex generic DDCPs, two projects were conducted in FDA laboratories. An FDA laboratory investigation to evaluate the electronic componentry and mobile application software in three FDA-approved metered dose inhalers was completed during FY 2022. The investigations revealed good agreement between classification of peak inspiratory flows (PIFs) by the software and experimental measurements, an understanding of when misclassifications generally occur, and impacts on software outputs when the air vents were blocked. These outcomes provided critical device and software data that should be considered for generic drug development and assessment. In another FDA-initiated laboratory project, FDA continued its investigation of critical material and process parameters of microneedle arrays that affect critical quality attributes (CQAs) such as needle integrity, mechanical properties (hardness and piercing ability), and the development of clinically relevant disintegration and dissolution methods for the dissolving microneedles. The knowledge gained through this project is expected to inform FDA's assessment of brand name and generic microneedle products.

During FY 2022, an ongoing grant #11U01FD007360 awarded to the University of Detroit, Mercy endeavored to develop improved strategies to identify and analyze UI differences that may impact the substitutability of a generic for its brand name product through three aims: 1) to develop a body of knowledge of key stakeholder perspectives of existing strategies, 2) to develop a visual taxonomy to systematically analyze UI design attributes and identify minor and other design differences, and 3) to develop improved comparative use human factors (CUHF) study methodology related to UI design differences that have the potential for introducing critical task use errors that could result in harm or compromised medical care. In FY 2022, progress was made on Aims 1 and 2. For Aim 1, interviews were completed with medical device manufacturers and human factors experts from academia and industry whose experience working with comparative (threshold) analyses and/or CUHF studies for DDCPs ranged from 5-25 years and spanned a variety of device types including autoinjectors, pen injectors, nasal sprays, and inhalers. Additionally, current scientific literature, FDA guidance documents, and public comments related to UI assessment were reviewed and assessed. For Aim 2, a taxonomy design was chosen as the method to organize and create a shared vocabulary for DDCP subject-specific concepts. A content library for DDCPs, a visual classification system, and a database of known potential use errors was initiated and expected to continue into FY 2023. Initial concepts for a visual DDCP classification system based on device design (**Figure 1**) and type (**Figure 2**) are being developed. Additionally, the potential for classifying devices and device UI designs by identifying key design features is being explored (**Figure 3**).

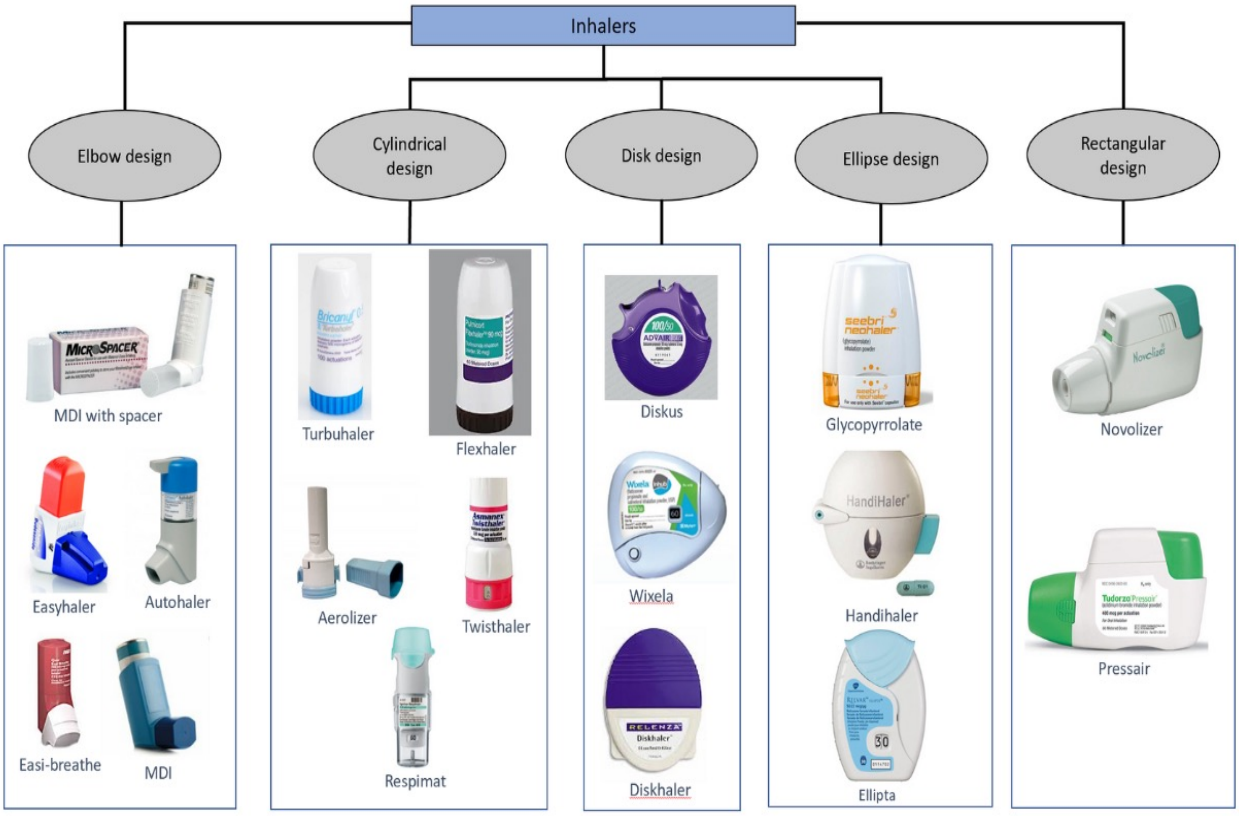


Figure 1. An example of a visual classification library categorizing by design for inhalers.

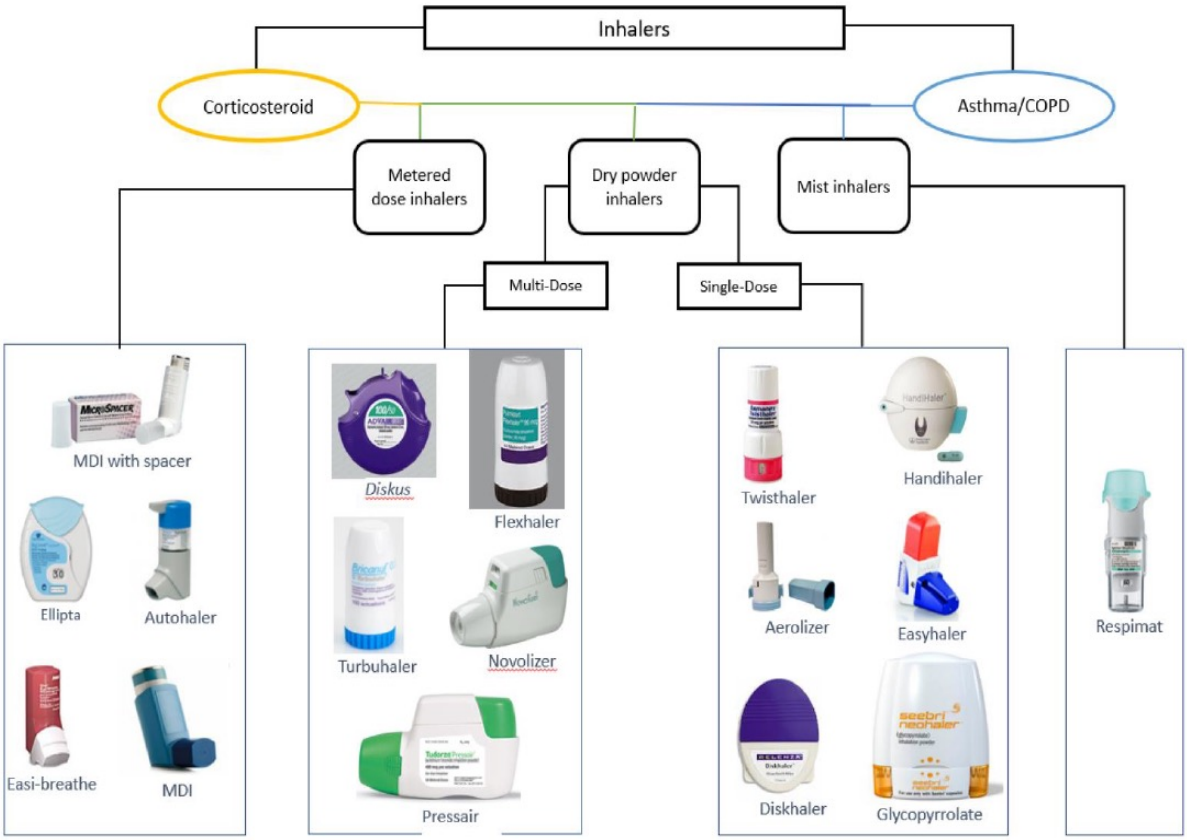


Figure 2. An example of a visual classification library categorizing by type for inhalers.

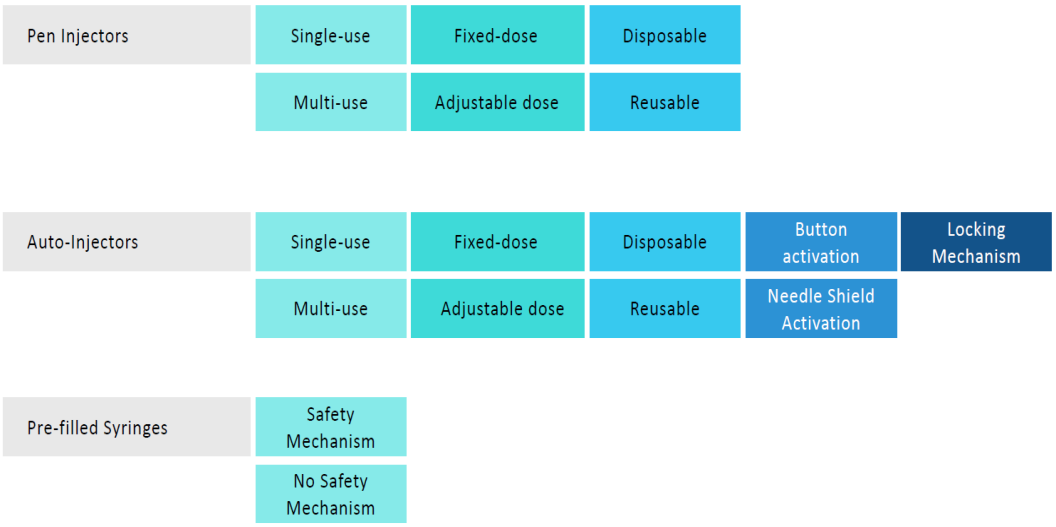


Figure 3. An example of proposed categories to classify injectors using key design features.

This work is expected to help improve the understanding of factors related to UI design differences that may impact substitutability between generic and brand name DDCPs, and to support the development of generic versions of these products that enhance patient access to these critical medicines.

Continuing Grants and Contracts

- Grant (1U01FD007359) *Battelle User Interface Design for Generic vs. RLD Combination Products* with Patrick McCormack at Battelle Memorial Institute.
- Grant (1U01FD007360) *Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA* with Megan O'Meara Conrad at the University of Detroit Mercy.
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at the Imperial College of Science and Technology, London.
- Contract (HHSF223201810113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Monica Scales at RTI International.

Active FDA Research

- *Determining the Accuracy of Peak Inspiratory Flowrate Classifications from the Digihaler Drug Device and Smartphone Application*
- *Developing Clinically Meaningful Disintegration and Dissolution Methods for Teriparatide Loaded Microneedles*
- *Development of new BE methods for Transdermal Irritation and Sensitization*

Product-Specific Guidances

There were 26 new and 5 revised PSGs published in FY 2022 related to *Complex Drug-Device Combination Products*. Among those, PSGs listed below were directly impacted by GDUFA-funded research in this area.

PSG Research Outcomes

- *New Draft Guidance for Aclidinium Bromide; Formoterol Fumarate Inhalation Powder, Metered.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Asenapine Transdermal System.* (May 2022) Link to Posting
- *Revised Draft Guidance for Azelastine Hydrochloride Nasal Spray, Metered.* (NDA 020114) (Aug. 2022) Link to Posting
- *New Draft Guidance for Azelastine Hydrochloride Nasal Spray, Metered.* (NDA 213872) (Aug. 2022) Link to Posting
- *New Draft Guidance for Beclomethasone Dipropionate Monohydrate Nasal Spray, Metered.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Ciclesonide Nasal Spray, Metered.* (Nov. 2021) Link to Posting
- *New Draft Guidance for Cyclosporine Ophthalmic Emulsion.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Dasiglucagon Hydrochloride Subcutaneous Solution.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Doxycycline Hyclate Periodontal System, Extended Release.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Estradiol Transdermal Gel, Metered.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Estradiol Transdermal Spray.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Etonogestrel Implantation Implant.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Exenatide Synthetic Subcutaneous for Suspension, Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Exenatide Synthetic Subcutaneous Suspension, Extended Release.* (May 2022) Link to Posting
- *New Draft Guidance for Flunisolide Nasal Spray, Metered.* (May 2022) Link to Posting
- *New Draft Guidance for Halobetasol Propionate Topical Aerosol, Foam.* (May 2022) Link to Posting
- *New Draft Guidance for Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate Otic Suspension/Drops.* (May 2022) Link to Posting

- *New Draft Guidance for Ibuprofen Oral Suspension/Drops.* (May 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate Subcutaneous Powder.* (NDA 021379 and NDA 021488) (Feb. 2022) Link to Posting
- *New Draft Guidance for Leuprolide Acetate Subcutaneous Powder.* (NDA 021731 and NDA 213150) (Feb. 2022) Link to Posting
- *New Draft Guidance for Loteprednol Etabonate Ophthalmic Suspension/Drops.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Medroxyprogesterone Acetate Injection Injectable.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Minocycline Hydrochloride Topical Aerosol, Foam.* (NDA 212379) (Nov. 2021) Link to Posting
- *New Draft Guidance for Minocycline Hydrochloride Topical Aerosol, Foam.* (NDA 213690) (Nov. 2021) Link to Posting
- *New Draft Guidance for Mometasone Furoate; Olopatadine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Naloxone Hydrochloride Nasal Spray.* (May 2022) Link to Posting
- *Revised Draft Guidance for Nicotine Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Olopatadine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *Revised Draft Guidance for Oxymetazoline Hydrochloride and Tetracaine Hydrochloride Nasal Spray, Metered.* (Aug. 2022) Link to Posting
- *New Draft Guidance for Progesterone Vaginal System.* (Feb. 2022) Link to Posting
- *New Draft Guidance for Risdiplam Oral for Solution.* (May 2022) Link to Posting

Articles

- Ray S, Boudewyns V, Davis C, Tzeng J, Srivastava I, Oguntimein O, Conti D, and Feibus K. *Patient Perceptions of Switching to a Generic Dry Powder Inhaler – Increased Understanding Through Journey Mapping.* International Journal of Chronic Obstructive Pulmonary Disease. (2022) 17: 1751-1768. https://doi.org/10.2147/COPD.S362696. PMID: 35965841.
- Shin S, Yu M, Hammell D, Ghosh P, Raney S, Hassan H, and Stinchcomb A. *Evaluation of In Vitro/In Vivo Correlations for Three Fentanyl Transdermal Delivery Systems Using In Vitro Skin Permeation Testing and Human Pharmacokinetic Studies under the Influence of Transient Heat Application.* Journal of Controlled Release. (2022) 342: 134-147. https://doi.org/10.1016/j.jconrel.2021.11.030. PMID: 34838928.

Posters

- Chakma M, Meah S, Biddiscombe M, Murnane D, Bielski E, Feibus K, Natarajan K, Li K, Kinoj M, Illoh O, Han L, Newman B, and Usmani O. *Dry Powder Inhaler (DPI) Resistance: Human Behaviour and Psychology of Patient Inspiratory Effort.* Poster Presentation at the European Respiratory Society 2022. Virtual Meeting, Sep. 05, 2022.

Presentations

- Ballard B. *Future Challenges: Electronic Devices, PDURS, Impacts on Generic Development and Substitution.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Hartka K. *Comparing Device User Interfaces and Seeking Advice in the Pre-ANDA Period.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Soukup S. *Conducting a Comparative Analysis When the RLD is Not Available.* Presentation at the Small Business and Industry Assistance (SBIA) 2022: Advancing Generic Drug Development Workshop: Translating Science to Approval. Virtual Meeting, Sep. 20, 2022.
- Ballard B. *Pre-ANDA Evaluation of Drug Delivery Device Constituents.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Chan I. *Comparative-Use Human Factors Studies for ANDA Products.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Fehrenbach H. *Opportunities to Leverage Device Functional Assessment for Classifying and Evaluating User Interface Differences.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Feibus K. *Drug-Device Combination Products.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Lemke M. *URRA and Root Cause Analysis: The Secret Ingredients for Effective Comparative Use Human Factors Studies.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Privitera MB. *Building a Taxonomy for Consistent Determination of Design Differences in Combination Products.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.

- VonBriesen T. *Insufficient Published Literature Related to the Usability of Device Constituent Parts.* Presentation at the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop. Virtual Meeting, May 10, 2022.
- Luke M. *Drug Device Combination Products and Similarity.* Presentation at the 2021 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, Nov. 08, 2021.
- Shakleya D. *Analytical Regulatory Considerations for Different Pharmaceutical Drug Matrices.* Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2021. Virtual Meeting, Oct. 17, 2021.

ACKNOWLEDGMENTS

The FY 2022 GDUFA Science and Research Report was prepared through a collaboration between the Office of Research and Standards, Office of Generic Drugs and the Office of Testing and Research, Office of Pharmaceutical Quality:

Lead Writers for Summary and Research Highlight

Andre O'Reilly Beringhs, PhD, ORS/OGD
Andrew Babiskin, PhD, ORS/OGD
Anna Wokovich, PhD, OTR/OPQ
Bin Qin, PhD, ORS/OGD
Bryan Newman, PhD, ORS/OGD
Deyi Zhang, PhD, ORS/OGD
Eleftheria Tsakalozou, PhD, ORS/OGD
Elizabeth Bielski, PhD, ORS/OGD
Fang Wu, PhD, ORS/OGD
Heather Boyce, PhD, ORS/OGD
Ilan Geerlof-Vidavsky, PhD, OTR/OPQ
Jihong Shon, MD, PhD, ORS/OGD
Katherine Feibus, MD, ORS/OGD
Khondoker Alam, PhD, ORS/OGD
Manar Al-Ghabeish, PhD, ORS/OGD
Megan Kelchen, PhD, ORS/OGD
Meng Hu, PhD, ORS/OGD
Mingliang Tan, PhD, ORS/OGD
Miyoung Yoon, PhD, ORS/OGD
Nahid Kamal, PhD, OTR/OPQ
Nathan Reed, PhD, OTR/OPQ
Nicholas Holtgrewe, PhD, OTR/OPQ
Priyanka Ghosh, PhD, ORS/OGD
Ross Walenga, PhD, ORS/OGD
Sam Raney, PhD, ORS/OGD
Wei-Jhe Sun, PhD, ORS/OGD
Wenlei Jiang, PhD, ORS/OGD
Xiaoming Xu, PhD, OTR/OPQ
Xin Feng, PhD, OTR/OPQ
Yan Wang, PhD, ORS/OGD
Yang Yang, PhD, OTR/OPQ
Yi Zhang, PhD, ORS/OGD
Zhong Wang, PhD, ORS/OGD

Contributing Reviewers

Ahmed Zidan, PhD, OTR/OPQ
Barbara Kass, CS/OGD
Changning Guo, PhD, OTR/OPQ
Connie Ruzicka, PhD, OTR/OPQ
Darby Kozak, PhD, ORS/OGD
Iilun Murphy, MD, OGD
Lanyan (Lucy) Fang, PhD, ORS/OGD
Lei Zhang, PhD, ORS/OGD
Liang Zhao, PhD, ORS/OGD
Markham Luke, MD, PhD, ORS/OGD
Melissa Mannion, PharmD, JD, OGDP/OGD
Mitchell Frost, MD, ORS/OGD
Muhammad Ashraf, PhD, OTR/OPQ
Myong-Jin Kim, PharmD, ORS/OGD
Robert Lionberger, PhD, ORS/OGD
Sarah Ibrahim, PhD, OGD
Sarah Rogstad, PhD, OTR/OPQ
Susan Levine, PhD, OGDP/OGD

Contributors to Data for Collaborations and Outcomes

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

Contributors to Report Designing and Editing

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